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THE DIAGNOSIS AND TREATMENT OF ENDOMETRIAL PATHOLOGY IN THE OUTPATIENT SETTING

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ABSTRACT

Hysteroscopy is now the most common gynaecological procedure, where technological advances in endoscopy mean that both diagnostic and operative hysteroscopic procedures can be performed successfully in the outpatient setting. Although the majority of women report excellent care, this thesis aims to improve the care of women who use this service and investigate a novel way in which hysteroscopy can be used to improve outcomes related to miscarriage.

This thesis is split into two halves and has been written in an 'alternative format' as nine of the chapters have either been published or have been submitted for publication. The first half demonstrates the work involved in developing a new evidence-based national 'green-top' guideline for the Royal College of Obstetricians and Gynaecologists and the British Society for Gynaecological Endoscopy on how outpatient hysteroscopy should be provided and how it should be performed, through a series of systematic reviews, followed by the updated guideline itself. The second half determines the feasibility of performing a full-scale, adequately powered, multi-centre randomised controlled trial evaluating the effectiveness of the outpatient hysteroscopic removal of retained pregnancy tissue following a first-trimester miscarriage compared with standard expectant, medical, or surgical management, on the outcomes of fertility and future pregnancy outcome.

Based on the results of this thesis we recommend the following:

1. Patients should be advised to take standard doses of oral non-steroidal anti-inflammatory agents (NSAIDs) one hour before their outpatient hysteroscopy.
2. Local cervical anaesthesia for outpatient hysteroscopy should only be recommended where vaginoscopy fails or where cervical dilatation is anticipated.
3. Vaginoscopy should be the standard technique for hysteroscope insertion in the outpatient setting unless a vaginal speculum is required to dilate the cervix or obtain a blind global endometrial biopsy.
4. Saline is recommended as the best distension medium for outpatient hysteroscopy at the lowest pressure to achieve a satisfactory view.
5. Cervical preparation in order to dilate the cervix and facilitate entry of the hysteroscope should not be routinely administered in the outpatient setting.
6. Conscious sedation should not be routinely used for outpatient hysteroscopy.
7. Mechanical instruments should be preferred over electrical energy in order to remove endometrial pathology in the outpatient setting.
8. A future, full-scale, adequately powered, multi-centre RCT investigating outpatient hysteroscopy against standard treatment for the management of retained pregnancy tissue following a miscarriage is highly feasible, with high numbers of eligible patients, high patient acceptability of proposed interventions and low attrition rates.

DEDICATION

This thesis is dedicated to my wife, Charlotte, who has supported me to no end in producing the research that has contributed to my PhD.

Charlotte, you agreed to marry me when I started this PhD, and three years and four months later, you've supported me through a global pandemic, dislocated shoulder, fractured thumb, membership exams, and as I write the final page of this thesis on a cold, dark, autumn night with Reggie snoring on the floor next to me and nothing but the light of my laptop illuminating Rami's face, I can't quite believe that we now share the joys of parenthood.

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Thank you to Professor Justin Clark for being my primary supervisor over the course of my PhD. It is hard to find the words to express my gratitude to you for the incredible encouragement, guidance and support you have given me since working as your teaching fellow. Your enthusiasm for academia, surgery and education is infectious and I am very lucky to have worked with you to complete this thesis.

Thank you to my parents for your endless love and for the sacrifices you made to ensure that your children had every opportunity in life; thank you Amma, for always striving for me to be better, and thank you Thatha, for sharing your love of surgery with me across the operating table. Thank you Nangi, for always being down the end of the phone and for sharing your woes of being a postgraduate student.

A final thank you must go to the women who, after the traumatic life event of a pregnancy loss, agreed to participate in the HYMMN trial. Without you, we would not be able to make progress in the care we provide other women in your situation.

ABBREVIATIONS

ACN: Ambulatory Care Network

BSGE: British Society for Gynaecological Endoscopy

BWCH: Birmingham Women's & Children's Hospital

CO2 / CO_2: carbon dioxide

D&C: dilatation & curettage

EEC: endometrial echo-complex

EM: endometrial mass

EPAU: Early Pregnancy Assessment Unit

FT: Foundation Trust

GI: gastrointestinal

GPP: 'Good Practice Points'

GTG: green-top guideline

h: hour

He: Hegar

HRA: Health Research Authority

HYMMN: Hysteroscopic Miscarriage Management

ICB: intracervical block

ICOB: intracornual block

IM: intramuscular

IMSR: Institute of Metabolism and Systems Research

IQR: interquartile range

IRAS: Integrated Research Application System

ITT: intention-to-treat

IV: intravenous

IVF: in-vitro fertilisation

l: litres

MD: mean difference

mHTRS: mechanical hysteroscopic tissue retrieval system

microg / μg: microgram(s)

min(s): minute(s)

ml: millilitres

mmHg: millimetres of Mercury

N/A: not applicable

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

NS: normal saline

NSAID: non-steroidal anti-inflammatory drugs

OPH: outpatient hysteroscopy

OR: odds ratio

PCB: paracervical block

PO: oral

PP: per-protocol

PR: per rectum

PV: per vagina

QoL: quality of life

R&D: Research & Development

RCOG: Royal College of Obstetricians & Gynaecologists

RCT: randomised controlled trial

REC: Research Ethics Committee

REDCap: Research Electronic Data Capture

RPOC: retained products of conception

RR: relative risk

SD: standard deviation

SE: standard error

s / sec(s): second(s)

SL: sublingual

SMD: standard mean difference

SMM: surgical management of miscarriage

ST: standard treatment

STOP: surgical termination of pregnancy

TC: transcervical instillation

TENS: transcutaneous electrical nerve stimulation

TOP: topical cervical application

TVU / TVS: transvaginal ultrasound scan

UoB: University of Birmingham

UPT: urinary pregnancy test

VAS: visual analogue scale

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PART 1: INTRODUCTION

CHAPTER 1: BACKGROUND

The term hysteroscopy originates from the Greek words *hystera* or ‘uterus’ and *skopeo* which means ‘to see’ (1). It refers to the insertion of a small endoscope into the female genital tract, allowing for inspection of the vagina, endocervical canal (lining of the neck of the womb, or cervix) and endometrium (lining of the womb) used for the diagnosis and/or treatment of dysfunctional uterine bleeding, uterine factor subfertility and endometrial cancer.

The earliest description of hysteroscopy was in 1807, in Frankfurt, by Phillip Bozzini, a German doctor of Italian descent, who used a mixture of candlelight, apertures and mirrors to direct light into the uterine cavity in order to visualise the endometrium (2). Challenges such as intraoperative bleeding, suboptimal light and inadequate distension within the uterine cavity to allow for adequate inspection of the endometrium hampered clinical progress, until 1925, when Harold Seymour, an English gynaecologist, introduced saline for uterine distension together with suction to allow for the clearance of blood and debris (3). William Norment, the father of operative hysteroscopy, developed the cutting loop in 1957, which meant that endometrial polyps (small, fleshy, outgrowths of the endometrium) and fibroids (benign, muscular growths arising from the myometrium) could be resected and sterilisation could be performed by coagulating the intramural aspect of the fallopian tubes (4).

Fast forward nearly one-hundred years and advances in the miniaturisation of hysteroscopes and refinements in hysteroscopic technique have made it possible to perform diagnostic and operative hysteroscopy in the outpatient setting, with high levels of patient acceptability (5). The forefathers of hysteroscopy may

argue that they were the pioneers of outpatient hysteroscopy, often performing the procedure without any analgesia or anaesthesia at all, despite no record of patient satisfaction and acceptability! The outpatient setting negates the need for a general anaesthetic and the staff and theatre space required for this. In addition, the time spent in hospital is therefore much reduced, contributing to a higher turnover of patients and reduced costs to the healthcare provider. Many operative procedures, originally done under general anaesthesia, are now performed in the outpatient setting, owing not only to advances in the miniaturisation of hysteroscopic equipment, but also the feasibility of operation and faster treatment times, where endometrial polypectomy, endometrial ablation, adhesiolysis, and submucosal fibroid resection are becoming commonplace in the outpatient setting.

The greatest barrier to performing procedures in the outpatient setting, however, is the pain associated with uterine distension and trauma to the genital tract, and vasovagal reactions, which can manifest as palpitations and dizziness due to manipulation of the cervix. It is therefore vital that the practice of outpatient hysteroscopy is performed in a manner that allows for the successful diagnosis and treatment of endometrial/intrauterine pathology whilst minimising pain in order to optimise the patient experience. The first part of the work presented in this thesis adopts a series of systematic reviews in order to identify how outpatient hysteroscopy should be performed and how such services should be organised in order to inform best practice for a national evidence-based guideline.

As researchers, it is important that we do not rest on our laurels but continue to challenge the status quo and look at how we can push the boundaries of medicine in order to improve the care of patients. An area where hysteroscopy still remains in its infancy is in the management of pregnancy tissue that remains inside the womb following either a miscarriage or delivery, known as retained products of conception (RPOC) (6). Current treatments for the removal of RPOC following miscarriage include antibiotics, vaginal prostaglandins and mechanical curettage of the endometrium, neither of which are evidence-based nor without risk. The use of hysteroscopy for this purpose is proposed to be more efficacious and safer, owing to the fact that removal is done under direct vision, therefore reducing the likelihood of incomplete tissue removal and the risk of complications, such as uterine perforation (7). Due to the miniaturisation of hysteroscopes, it may be feasible to do this in the outpatient setting (8). Initial data suggests that hysteroscopic removal of RPOC reduces the time to the next pregnancy (9), an important factor in women who miscarry a planned pregnancy (10). The second part of the work presented in this thesis therefore revolves around a pilot randomised-controlled trial investigating the role of routine ultrasonography and outpatient hysteroscopy in the management of RPOC.

A number of chapters in this thesis have already been published (Part 2: Chapters 3-9) or written up for publication (Part 2: Chapter 10). In these instances, relevant references can be found at the end of each publication, separate from the reference list found at the end of this thesis. Similarly, figures and tables are numbered within their relevant publications apart from those found in the body of the text. Supplemental figures and tables which have not been

displayed within the separate publications can be found in the appendix section at the end of this thesis.

CHAPTER 2: OBJECTIVES

The objectives of my PhD are two-fold, where this thesis is split into two main parts:

1. To investigate the optimal method of undertaking both diagnostic and therapeutic outpatient hysteroscopy in order to provide safe, acceptable and efficacious care for women in order to inform a national evidence-based guideline for the Royal College of Obstetricians & Gynaecologists (RCOG)

2. To investigate the role of routine transvaginal ultrasound and outpatient hysteroscopy for the diagnosis and treatment of retained products of conception (RPOC), following a first-trimester miscarriage, in order to implement a new evidence-based clinical pathway

PART 2: BEST PRACTICE IN OUTPATIENT HYSTEROSCOPY

CHAPTER 1: INTRODUCTION

The Royal College of Obstetricians & Gynaecologists (RCOG) first published a national evidence-based “green-top” guideline in 2011 describing how outpatient hysteroscopy should be delivered in the National Health Service, in the United Kingdom (11). This guideline, jointly written with the British Society for Gynaecological Endoscopy (BSGE), focuses primarily on how this service should be delivered in order to minimise the pain perceived by patients and maximise the patient experience. The other barrier to delivering outpatient hysteroscopy is the incidence of vasovagal episodes, which can manifest as hypotension, palpitations, nausea, vomiting and dizziness. Despite these obstacles, outpatient hysteroscopy remains safe, feasible and acceptable to women, as illustrated by a national survey encompassing over 5000 women who underwent an outpatient hysteroscopy, across 77 units, between October to November 2019 (5). There are, however, a small minority of patients who are dissatisfied with their experience. We must therefore strive to further improve the care we give to the patients who use this service both to optimise clinical outcomes and enhance patient experience.

In order to understand how to minimise pain and the incidence of vasovagal episodes, it is important to understand the innervation to the cervix and uterine body. Pain stimuli from the cervix and vagina are conducted by the pelvic splanchnic nerves (S2-4) whereas pain sensation from the uterus is conducted by the hypogastric nerves (T10-L1). Pain can therefore be caused by genital tract instrumentation, cervical dilatation, uterine cavity distension and trauma to the endometrium e.g. when taking an endometrial biopsy or performing an endometrial polypectomy. It is important to bear in mind that the cervix also

receives parasympathetic innervation from the sacral nerves (S2-4) and so manipulation and dilatation of the cervix can lead to vasovagal reactions.

It is therefore clear that there are three main methods by which pain and the incidence of vasovagal episodes can be reduced;

1) By improving the quality of hysteroscopic equipment (e.g. reducing intrauterine device (hysteroscope, endometrial ablation device) diameters, shortening operative/ablative times etc.)
2) By improving hysteroscopic technique (e.g. minimising genital tract instrumentation)
3) By administering effective adjuncts in order to minimise pain (e.g. analgesia, local anaesthesia etc.)

In order to deliver the highest quality of care to patients, guidance should be clear, consistent and based upon the most up-to-date evidence available as hysteroscopic research, techniques and equipment have evolved significantly over the last decade since the publication of the last green-top guideline.

CHAPTER 2: METHODOLOGY

The new “green-top” guideline sought to answer a set of questions related to a number of topics as displayed in Table 1.1. The structure of this guideline and the questions to be answered were broadly based on the previous green-top guideline, published in 2011 (11). Where possible, recommendations were based on, and directly linked to, the evidence that supported them, which were accrued through the systematic review of randomised controlled trials, and where possible, meta-analysis. Additional questions that encompassed topics that were not present in the previous green-top guideline (as displayed in italics in Table 1.1) were based on areas in hysteroscopy that Professor Justin Clark (primary supervisor), Mr. Paul Smith (secondary supervisor), Dr. Natalie Cooper (first-author of the prior green-top guideline) and I felt required further guidance in light of contemporary technologies, practices and dilemmas that have evolved or arisen since the publication of the last guideline, which were approved by the Royal College for Obstetricians & Gynaecologists (RCOG).

The study selection criteria for the systematic reviews are shown in Table 1.2. The studies primarily investigated the means of reducing the pain associated with outpatient hysteroscopy, but where possible also looked at safety (complications), feasibility (operative time, procedural success), and satisfaction (patient and operator). Appendix 1 outlines the search strategies for the systematic reviews, which utilised the MEDLINE, EMBASE, CINAHL and Cochrane Library databases. All systematic reviews were registered beforehand on the international prospective register of systematic reviews, PROSPERO. All searches were updated (as per the original search terms) on 1st February 2022 before writing the green-top guideline to ensure that the evidence cited was up-

to-date. Where new publications relevant to, but not included in the systematic reviews were found, these were referred to in the supporting text of the relevant section of the green-top guideline. Four additional papers were found with regards to local anaesthesia. These studies were not commented upon in the green-top guideline as their findings did not add any value to the conclusions made regarding local anaesthesia. The findings of these papers, however, have been summarised in the addendum to Chapter 4.

Anticipated topics and associated questions that lacked evidence, as exhibited by the results of scoping searches, were agreed upon by consensus at the 2021 British Society for Gynecological Endoscopy (BSGE) Ambulatory Care Network (ACN) Meeting (12), held on Friday 18th June 2021. The BSGE ACN was conceived by Professor Justin Clark (who at the time was the President of the BSGE) and I in 2019 as I was starting this body of work. We designed the ACN to be a national network that brings together doctors and nurses specialising in ambulatory gynaecology with aims of learning from each other, improving quality, directing research and innovating and managed to heavily subsidise attendance fees for meetings by gaining sponsorship from industry. As a result, the network has grown in popularity over the years where we had c. 90 members that attended the inaugural meeting in 2019, 170 members that attended the 2020 meeting and over 200 members that attended the 2021 meeting, with a variety of participants including nurses, trainee nurse hysteroscopists, trained nurse hysteroscopists, researchers, doctors-in-training and consultants. I have taken the lead for organising the conference and creating the programme for each one of these meetings.

In creating the agenda for the 2021 meeting with Professor Justin Clark and Mr. Paul Smith (secondary supervisor), I was keen to hear delegates share their own experiences regarding practices that improve the provision and practice of outpatient hysteroscopy, provide feedback on the draft guidance that we had written based on the systematic reviews that I had published, and take part in online surveys (Appendix 2) to ensure that the finalised green-top guideline bridged contemporary clinical practice with the up-to-date evidence that I had accrued. I documented minutes from the meeting and analysed results from the online polls (Appendix 2) in order to provide answers to the questions where expert opinion was sought, as outlined in Table 1.1 below.

Table 1.1: An overview of the questions in the new green-top guideline and the anticipated methodology required to answer them

Topic	Questions	Methodology
1. Service Provision	1) What are the requirements for running an effective outpatient hysteroscopy service? *2) What information should be provided prior to outpatient hysteroscopy?* *3) How should consent be obtained prior to outpatient hysteroscopy?* *4) Should a pre-procedural safety checklist be performed prior to outpatient hysteroscopy?* 5) How should care after outpatient hysteroscopy be provided? 6) *How should training and standards in outpatient hysteroscopy be provided and assessed?*	Expert opinion

2. Analgesia	What analgesia should be recommended prior to outpatient hysteroscopy and how should it be given in order to reduce the pain felt by patients during and after their procedure?	Systematic review +/- meta-analysis
3. Cervical preparation	Should cervical preparation be used in order to facilitate outpatient hysteroscopy?	Systematic review +/- meta-analysis
4. Type of hysteroscope	1) What size and angle of hysteroscope should be used in the outpatient setting? 2) Should rigid or flexible hysteroscopes be used routinely in the outpatient setting? *3) What devices should be used for operative procedures in the outpatient setting?*	Systematic review +/- meta-analysis
5. Distension medium	1) Which uterine distension medium should be used during outpatient hysteroscopy? *2) How should uterine distension media be delivered during outpatient hysteroscopy?*	Systematic review +/- meta-analysis
6. Local anaesthesia and cervical dilatation	1) Should routine dilatation of the cervical canal be performed prior to insertion of the hysteroscope in the outpatient setting? 2) Should local anaesthesia be administered prior to outpatient hysteroscopy? 3) Which local anaesthesia should be administered and how should it be given prior to outpatient hysteroscopy?	Systematic review +/- meta-analysis
7. Conscious sedation	Should conscious sedation be used to reduce pain associated with outpatient hysteroscopic procedures?	Systematic review +/- meta-analysis
8. Vaginoscopy	Does a vaginoscopic approach to outpatient hysteroscopy reduce pain and increase the feasibility of the procedure?	Systematic review +/- meta-analysis

9. Prevention of infection	*Should routine antibiotic prophylaxis be employed in outpatient hysteroscopic procedures to reduce the incidence of procedural-related infection?*	Systematic review +/- meta-analysis
10. Documentation	*How should procedural technique and findings at hysteroscopy be recorded?*	Expert opinion

Table 1.2: Study selection criteria for the systematic reviews

Topic	Population	Intervention	Control/Comparator	Outcomes
Analgesia (13)	All women undergoing outpatient diagnostic and therapeutic hysteroscopy	Analgesia (pre, peri- or post procedure)	Any comparator to include none, placebo, alternative type of analgesic regimen (drug type, dose, route, timing of administration, route)	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility, side-effects and complications (including vasovagal episodes / attacks)
Local Anaesthesia (14)	All women undergoing outpatient diagnostic and therapeutic hysteroscopy	Injectable or topical local anaesthetic to the cervix/paracervix/uterus	Any comparator to include none, placebo, alternative type of local anaesthetic regimen (drug type, route (topical (cervical / intrauterine), intracervical, paracervical, fundal ('focal-local'; ICOB – intracornual block)	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility, side-effects and complications (including vasovagal episodes / attacks)

Vaginoscopy (15)	All women undergoing outpatient diagnostic and therapeutic hysteroscopy	Vaginoscopy ('no touch' hysteroscopy)	Use of vaginal instrumentation (speculum, +/- cervical forceps) with or without local anaesthesia	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility, side-effects and complications (including vasovagal episodes / attacks)
Distension Medium (16)	All women undergoing outpatient diagnostic and therapeutic hysteroscopy	i) Type of distention media (e.g. fluid (isotonic – e.g. saline,; hypotonic e.g. sorbitol, glycine), or gas (e.g. CO2); (ii) administration of distension media (e.g. automated vs. non-automated, flow rate, intrauterine pressure etc.)	Alternative type or administration of distension media	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility (including image quality), side-effects and complications (including vasovagal episodes / attacks)
Cervical Preparation (17)	All women undergoing outpatient diagnostic and	Cervical preparation and/or cervical dilatation	Any comparator to include none, placebo, alternative type of cervical	Pain based on visual analogue score (VAS) or numerical rating score (NRS)

	therapeutic hysteroscopy		preparation regimen (prostaglandin, anti-progestogen, oestrogen, osmotic), dose, route (oral / vaginal)	Acceptability (patient and operator), satisfaction (patient and operator), feasibility, side-effects and complications (including vasovagal episodes / attacks)
Conscious Sedation (18)	All women undergoing outpatient diagnostic and therapeutic hysteroscopy	Conscious sedation	Any comparator to include none, placebo, alternative type of analgesia / local anaesthetic / sedative (including anxiolytic) regimen (drug type(s), route (e.g. inhalation, oral etc), timing)	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility, side-effects and complications (including vasovagal episodes / attacks)
Instrumentation for Diagnostic Hysteroscopy (19)	All women undergoing outpatient diagnostic hysteroscopy	Type of hysteroscope (e.g. diameter, single flow / continuous flow, rigid / flexible, angle of lens etc.)	Alternative type of hysteroscope	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility

				(including image quality), side-effects and complications (including vasovagal episodes / attacks)
Instrumentation for Therapeutic Hysteroscopy (20)	All women undergoing outpatient or inpatient operative hysteroscopy (including ablation, morcellation, sterilisation, myomectomy, uteroplasty, tubal cannulation etc)	Specific technology according to procedure / pathology: (polypectomy; myomectomy; uteroplasty (including septoplasty); adhesiolysis; sterilisation; tubal cannulation (salpinography); endometrial ablation	Alternative or identical technology for the same procedure / pathology in an outpatient setting	Pain based on visual analogue score (VAS) or numerical rating score (NRS) Acceptability (patient and operator), satisfaction (patient and operator), feasibility, side-effects and complications (including vasovagal episodes / attacks)
Prevention of Infection (21)	All women undergoing outpatient diagnostic and therapeutic hysteroscopy	Anti-microbial for prophylaxis in all forms of administration (e.g. oral, in vaginal preparation, IV, IM etc.)	None, placebo, alternate anti-microbial, alternative route of administration	Infection, endometritis, pyometra, sepsis rates, hospitalisation, mortality

All systematic reviews were only written in up publishable format if there was additional data since the publication of the former green-top guideline. Published systematic reviews are displayed in this thesis, followed by the new green-top guideline.

The systematic review regarding instrument choice for diagnostic hysteroscopy was discarded due to the fact that a recently published systematic review (22) contained all relevant articles regarding hysteroscope diameter, no further papers had been published regarding the use of flexible hysteroscopes since the last green-top guideline, and no trials investigated the use of an off-set distal lenses against a 0º scope. The planned systematic review investigating the use of antimicrobial prophylaxis for the prevention of infection after hysteroscope was completed but not published because our search only identified a single trial (23), however, this was reported on in the green-top guideline.

CHAPTER 3: ANALGESIA

This work has been published in the Journal of Minimally Invasive Gynecology; De Silva PM, Mahmud A, Smith PP, Clark TJ. Analgesia for Office Hysteroscopy: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2020 Jul-Aug;27(5):1034-1047. doi: 10.1016/j.jmig.2020.01.008. Epub 2020 Jan 23. PMID: 31982584 (24).

My role in this publication is as follows: I carried out the literature search, collected the data, undertook the meta-analysis, and wrote the manuscript.

ELSEVIER

JMIG The Journal of Minimally Invasive Gynecology

Review Article

Analgesia for Office Hysteroscopy: A Systematic Review and Meta-analysis

Prathiba M. De Silva, BSc (Hons), MBBS, Ayesha Mahmud, PhD, MRCOG, Paul P. Smith, PhD, MRCOG, and T. Justin Clark, MD (Hons), FRCOG

From the College of Medical and Dental Sciences (Drs. De Silva and Smith), University of Birmingham, Birmingham, UK, Department of Obstetrics & Gynaecology (Dr. Mahmud), Walsall Manor Hospital, Walsall Healthcare NHS Trust, West Midlands, UK, and Department of Ambulatory Gynaecology (Professor Clark), Birmingham Women's Hospital, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

ABSTRACT **Objective:** To identify the most effective analgesia for women undergoing office hysteroscopy.

Data Sources: We searched Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library from inception until August 2019 for studies that investigated the effect of different analgesics on pain control in office hysteroscopy.

Methods of Study Selection: We included randomized controlled trials that investigated the effect of analgesics on pain experienced by women undergoing diagnostic or operative hysteroscopy in an office setting compared with the control group.

Tabulation, Integration, and Results: The literature search returned 561 records. Twenty-two studies were selected for a systematic review, of which 16 were suitable for meta-analysis. There was a statistically significant reduction in pain during office hysteroscopy associated with preprocedural administration of nonsteroidal anti-inflammatory drugs (NSAIDs) (standardized mean difference [SMD] 0.72; 95% confidence interval [CI] 1.27 to 0.16), opioids (SMD 0.50; 95% CI 0.97 to 0.03), and antispasmodics (SMD 1.48; 95% CI 1.82 to 1.13), as well as with the use of transcutaneous electrical nerve stimulation (TENS) (SMD 0.99; 95% CI 1.67 to 0.31), compared with the control group. Moreover, similar reduction in pain was observed after office hysteroscopy: NSAIDs (SMD 0.55; 95% CI 0.97 to 0.13), opioids (SMD 0.73; 95% CI 1.07 to 0.39), antispasmodics (SMD 1.02; 95% CI 1.34 to 0.69), and TENS (SMD 0.54; 95% CI 0.95 to 0.12). Significantly reduced pain scores with oral NSAID administration during (SMD 0.87; 95% CI 1.59 to 0.15) and after (SMD 0.56; 95% CI 1.02 to 0.10) office hysteroscopy were seen in contrast to other routes. Significantly more adverse effects were reported with the use of opioids ($p < .001$) and antispasmodics ($p < .001$) when compared with the control group, in contrast to NSAIDs ($p = .97$) and TENS ($p = .63$).

Conclusion: Women without contraindications should be advised to take oral NSAIDs before undergoing office hysteroscopy to reduce pain during and after the procedure. TENS should be considered as an alternative analgesic in women with contraindications to NSAIDs. Journal of Minimally Invasive Gynecology (2020) 00, 1 14. © 2020 AAGL. All rights reserved.

Keywords: Ambulatory; Endoscopy; Pain control

Hysteroscopy, one of the most common procedures in gynecology, is used to diagnose and treat intrauterine pathology related to abnormal uterine bleeding and reproductive failure. Performed without general anesthesia or a formal operating theater setting, "office" or "outpatient," hysteroscopy is associated with fewer complications, shorter recovery, and reduced costs [1]. However, there are reports of failure and association with poor patient experience owing to pain [2], which arises from instrumentation of the genital tract, namely vaginal speculum insertion, tenaculum placement, cervical dilatation, uterine cavity distension, and the removal of intrauterine pathology [3].

The authors declare that they have no conflict of interest.

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Previous reviews have consisted of very few studies to provide a meaningful conclusion [1,3] and have focused on local anesthesia, which is becoming less relevant owing to the advent of miniaturized endoscopes. Despite 30% of women experiencing pain with these hysteroscopes [4], the "no touch" vaginoscopic approach obviates the need for genital tract instrumentation and administration of local anesthesia, proving significantly more successful in terms of completion, pain, and complications than the traditional approach [5].

There is a need to review the evidence regarding the administration of analgesia alone to optimize the feasibility, efficiency, and acceptability of office hysteroscopy and improve the overall patient experience. We, therefore, conducted a systematic review and meta-analysis to determine the best analgesia for pain control in office diagnostic and therapeutic hysteroscopy. For the purposes of this study, we defined analgesia as an agent acting on the peripheral and/or central nervous system to reduce pain without affecting sensation.

Materials and Methods

Protocol and Guidance

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [6], with guidance from the Cochrane Handbook for Systematic Reviews of Interventions [7]. This review was conducted on the basis of a protocol registered on the International Prospective Register of Systematic Reviews (CRD42019137351) [8].

Inclusion Criteria

We included randomized controlled trials (RCTs) that investigated women who underwent office diagnostic and/or therapeutic hysteroscopy and were randomized to receive an analgesic agent and a comparator that included no treatment, a placebo, an alternative analgesic regimen (intervention, dose, route, and/or timing of administration), or an alternative method of pain relief (e.g., local anesthesia, conscious sedation) where the outcome was pain. Language restrictions were not applied.

Exclusion Criteria

We excluded conference abstracts, case reports, case series, and observational studies.

Outcomes

The primary outcome was pain. Secondary outcomes included adverse effects (symptoms), acceptability, satisfaction, feasibility, and complications. In addition, information was collected on the use of conscious sedation, vaginoscopy, local anesthesia, cervical preparation, cervical dilatation, distension medium, and instrument size.

Search Strategy

Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature

(CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to August 6, 2019. A combination of the keywords "hysteroscopy," "analgesia," "outpatient," "ambulatory," "office," and their associated medical subject headings were used to search Medline, Embase, and CINAHL through the Healthcare Databases Advanced Search platform of the National Institute for Health and Care Excellence. The keywords "hysteroscopy" and "analgesia" were used to search CENTRAL. No limits or filters were applied. To widen the search, the reference lists of included papers were reviewed, and further studies were included for analysis if deemed appropriate.

Study Selection

After using the Healthcare Databases Advanced Search platform to remove duplicates from the Medline, Embase, and CINAHL databases, 2 researchers (PMDS and AM) independently screened all titles and abstracts. Duplicates from the CENTRAL search were manually excluded. Full texts were screened to select eligible studies. If disagreements were not resolved by consensus, a third researcher (PPS) decided on the eligibility.

Data Collection Process

Two reviewers (PMDS and AM) independently used a standardized data extraction form to extract data from the included trials. Two pain scores were extracted: intraprocedural and postprocedure scores. Some studies scored each of the steps of hysteroscopy separately; if diagnostic, the intraprocedural score related to the score given during the inspection of the uterine cavity, and if therapeutic, it related to the score given during the operative procedure. If multiple postoperative pain scores were recorded, the highest pain score was used. If results were reported graphically, where possible, these data were transcribed and the authors were contacted to clarify the accuracy of derived numeric values [9 12]. Authors of studies that reported medians or failed to clearly report means and standard deviations of pain scores were contacted for their data [9 11,13 17].

Assessment of Risk of Bias

The Cochrane Risk of Bias Tool (version 2) was used by 2 researchers (PMDS and AM) to independently examine the quality of the included trials on an intention-to-treat

basis [18]. If consensus between the 2 researchers could not be reached, a third independent reviewer (PPS) was invited to arbitrate.

Data Synthesis

Statistical analyses were performed using Review Manager (RevMan) [Computer program].(Version 5.3.5; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). [19]. A meta-analysis was conducted on an intention-to-treat basis. Means and standard deviations were used to calculate standardized mean differences (SMD) and their 95% confidence intervals (CI), allowing data from studies using different pain scales to be compared. Inverse-variance weighting was performed to calculate random-effects summary estimates. We considered a p-value less than .05 to be significant. The heterogeneity of the treatment effects was depicted graphically by forest plots and statistically analyzed using the chi-square test on the basis of guidance from the Cochrane Handbook [7]. Data for intraprocedural and postprocedural pain were reported separately. Subgroup analyses were performed on the basis of the risk of bias for each study. For the dichotomous outcome of adverse effects, Peto odds ratios were calculated because of the low incidence of events in each arm of the study.

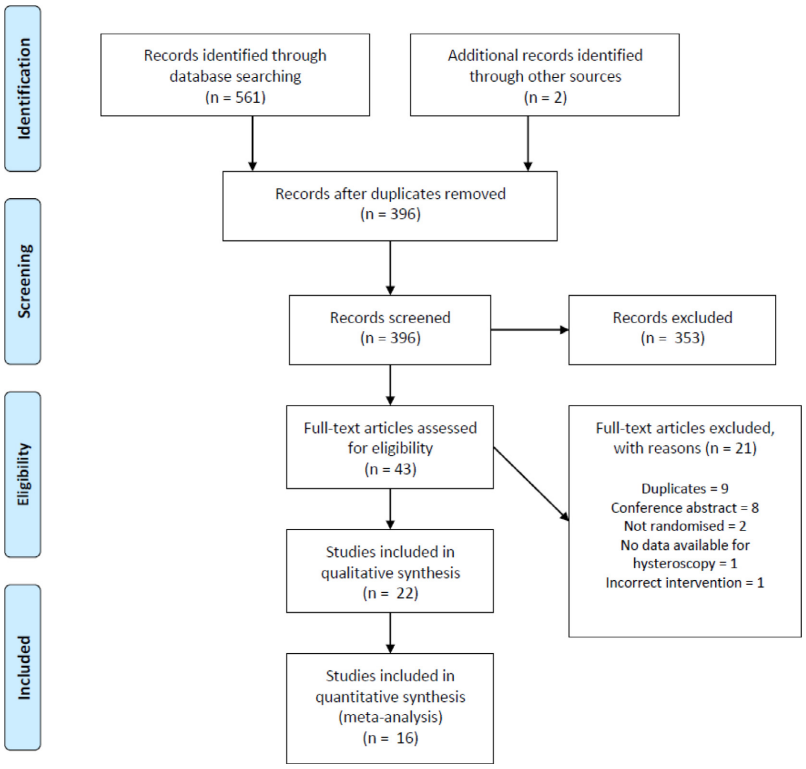
Results

Study Selection

The literature search returned 561 records, of which 167 were duplicates (Fig. 1). The titles and abstracts of these records were screened to leave 43 full-text articles; 22 studies were included for a systematic review [9 17,20 32], of which 16 were suitable for meta-analysis [11,13 15, 17,20 25,27 29,31,32]. Two further studies were included after scanning through the citations of the included articles [10,16].

Fig. 1

PRISMA flow diagram. PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



Study Characteristics

Table 1 shows details of the study population, interventions, control variables, and outcome data for all included studies. All included studies investigated the use of analgesia before office hysteroscopy. Ten of the 22 studies included women of both reproductive and postreproductive age [9,15,17,22 25,27,30,31]. Two studies focused on postmenopausal women [10,20], and a further 9 studies restricted inclusions to premenopausal women [11 14, 16,26,28,29,32], of which 2 included only nulliparous women [14,28] and 1 included only parous women [11]. Sixteen studies examined the role of analgesia in diagnostic hysteroscopy [10,11,13 16,20 25,28,29,31,32], 3 studies looked at therapeutic hysteroscopy [12,26,30], and 3 studies evaluated both diagnostic and therapeutic hysteroscopy [9,17,27]. A variety of hysteroscopes were used, ranging in diameter from 3.1 mm to 5 mm, except for 1 study which used a substantially larger 8-mm hysteroscope [9]. All endoscopes were rigid except for a 3.1-mm flexible hysteroscope used in 1 study [23].

Study Bias

The risk of bias for each study according to each methodological characteristic is detailed in Fig 2. Overall, 36% of the included studies showed a "low risk" of bias, with the rest equally split between showing "some concerns" and a "high risk" of bias. Studies where analgesics were compared with no intervention ("nil") were considered to have a high risk of bias because knowledge of nonreceipt of analgesia in the control group was considered to lead to significant bias in outcome measurement [20,24,27]. Issues related to the randomization process [16,20,24], missing outcome data [9,10], and under-reporting of results [9,10] were the other significant sources of bias.

Effect of the Analgesic

Of the 22 included studies (Table 1), 14 provided mean pain scores [11,12,20,22 32], whereas 7 provided median scores [9,10,13 17]. One study provided raw data that allowed mean pain scores and standard deviations to be calculated [21]. Similarly, 1 study provided standard errors of the mean, which were converted to standard deviations for inclusion in the meta-analysis [20]. Four studies presented pain scores graphically, and 1 study represented this in such a way that the postprocedure standard deviation could not be interpreted [12]. Two studies provided clear graphical presentation, allowing for medians and interquartile ranges to be identified [9,10], and 1 study provided means and standard deviations, allowing us to include this in the meta-analysis [11] (Supplemental Table 1). Conscious sedation was not routinely used, unless specified as an intervention [25,26,30]. Although studies with 2 analgesic agents in an intervention group were included in the meta-analysis [25,27], studies with 3 analgesic agents were excluded because they were considered to produce too much confounding on treatment effect [12,26,30].

Nonsteroidal Anti-inflammatory Drugs

Seven studies, comprising 781 patients [20,22,25,27 29, 32], investigating the administration of a nonsteroidal anti-inflammatory drugs (NSAIDs) against control groups, reported pain scores during office hysteroscopy. A meta-analysis of these studies showed a statistically significant reduction in intraprocedural pain: SMD 0.72; 95% CI 1.27 to 0.16 (Fig. 3A). Six of these studies, which comprised 711 patients [20,22,25,27,29,32], reported post-procedural pain immediately after hysteroscopy [29,32], at 5 minutes [20,27], or at 30 minutes [22,25] after hysteroscopy. As with periprocedural pain, the meta-analysis showed reduced pain scores in association with the use of NSAIDs after office hysteroscopy (SMD 0.55; 95% CI 0.97 to 0.13) (Fig. 3B).

There were high levels of statistical heterogeneity noted, which could not be explained by study quality (Fig. 3B). In 2 studies, the investigated NSAID was combined with the use of another drug; in 1 study, paracetamol was included [27], and in another, an antispasmodic, drotaverine, was included [25]. The preprocedural timing of the NSAID varied between 30 minutes and 81 minutes before the start of the procedure (Supplemental Table 1). Five studies used the oral route [22,25,27,29,32], 1 intramuscular [20], and 1 rectal [28] (Table 1). A subgroup analysis evaluating the route of administration did not change the magnitude or variability of the pooled result but showed significantly reduced pain scores with oral administration during (SMD 0.87; 95% CI 1.59 to 0.15) and after (SMD 0.56; 95% CI 1.02 to 0.10) office hysteroscopy in contrast to other routes (Supplemental Fig. 1A and 1B).

Opioids

Opioids showed a significant reduction in pain against control groups both during (4 studies, 234 patients; SMD 0.50; 95% CI 0.97 to 0.03) (Fig. 4A) [11,21,23,29] and after office hysteroscopy (2 studies, 190 patients; SMD 0.73; 95% CI 1.07 to 0.39) (Fig. 4B) [11,29]. The opioid was given between 40 minutes and 60 minutes before the start of the procedure (Supplemental Table 1). The post-procedural pain scores were recorded immediately after [29] and at 15 minutes [11] after office hysteroscopy. Each study investigated a different route of administration, including intravenous [11], intramuscular [21], sublingual [23], and oral [29] (Table 1). A significant reduction in mean pain during office hysteroscopy remained when data aggregation was restricted to studies with a lower risk of bias, but the degree of variation was much reduced (Fig. 4A).

Table 1

Individual study data

Study	Patient demographics	Type	Group 1	Group 2	Group 3	Cervical preparation	Cervical dilatation	Vaginoscopy	Local anesthesia	Distension medium	Instrument size	Adverse effects	Feasibility/ Complications	Satisfaction
Caligiani et al, 1994 [20]	Postmenopausal women	Diagnostic	Nil	30 mg IM ketorolak (NSAID)	N/A	Not reported	Yes	No	4 mL of 3% intracervical mepivacaine	Not reported	Not reported	Not reported	Not reported	All group 2 patients satisfied
Nagele et al, 1997 [9]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic and therapeutic (biopsy and polypectomy)	500 mg PO mefenamic acid (NSAID)	Placebo	N/A	No	Not routinely	Not reported	10 mL of 1% intracervical lignocaine and 1:200 000 adrenaline, if required	CO_2 at 45 mL/min and <100 mm Hg	5-mm diagnostic, 8-mm therapeutic	Not reported	Unsuccessful in 2 patients in each group (anxiety (2), pain (2))	Not reported
Bellati et al, 1998 [21]	Not reported	Diagnostic	100 mg IM tramadol (opioid)	4 mL of 2% intracervical mepivicaine	Nil†	No	Not reported	No	Yes, in Group 2	CO_2 at 40 mL/min and 50 mm Hg	5 mm	Not reported	Not reported	Not reported
Tam et al, 2001 [22]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic	50 mg PO diclofenac (NSAID)	Placebo	N/A	No	No	No	No	CO_2 at 70 mL/min and 100 −150 mm Hg	5-mm	Group 1: vasovagal (4), epigastric pain (1), skin rash (1). Group 2: vasovagal (5)	Unsuccessful in 2 patients (1 in each group) owing to pain and failure to insert hysteroscope	Not reported
Mercorio et al, 2002 [10]	Postmenopausal women	Diagnostic	25 mg PO dexketoprofen (NSAID)	5 mL of 2% intracervical mepivacaine	N/A	200 μg PV misoprostol 2 −3 h prior	Not routinely	No	Yes, in Group 2	CO_2 at 45 mL/min and <100 mm Hg	5 mm	Not reported	Unsuccessful in 13 women owing to pain (5 in each group) and unsatisfactory view (3 in Group 1)	Not reported
De Angelis et al, 2003 [24]	Nulliparous, parous, pre- and postmenopausal women but Group 1 had more nulliparous women (p <.05)	Diagnostic	TENS	Nil	N/A	No	Not routinely	Yes	No	CO_2 at 30 −35 mL/min and <100 mm Hg	5 mm	Group 1: nausea (8.5%) shoulder pain (3%), dizziness (8.5%). Group 2: nausea (11.3%), bradycardia (2.8%), dizziness (10%)	Nil	Not reported
Lin et al, 2005 [23]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic	0.2 mg SL buprenorphine (opioid)	Placebo	N/A	No	No	No	No	5% dextrose hung 60 cm above table	3.1 mm	Group 1: nausea or vomiting (4), drowsiness (2), both (25). Group 2: nil	Nil	30 women in group 1 were unsatisfied (p <.0001)
Floris et al, 2007 [11]	Perimenopausal and parous women	Diagnostic	100 mg IV tramadol (opioid)	Placebo	N/A	No	Not routinely	Not specified	Not specified	CO_2	3.8 mm	Group 1: nausea (3), vomiting (1), bradycardia (4). Group 2: nausea (2), bradycardia (3)	Nil	Not reported
Sharma et al 2009 [25]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic	80 mg PO drotaverine (antispasmodic) and 250 mg PO mefenamic acid (NSAID)	10 mL of 1% paracervical lignocaine	IV sedation†	No	Not routinely	No	Yes, in Group 2	Normal saline using a pressure bag was hung at about 6 feet and inflated to <300 mm Hg	5mm	Group 1: gastritis (1)	Nil	Not reported

Table 1

Continued

Study	Patient demographics	Type	Group 1	Group 2	Group 3	Cervical preparation	Cervical dilatation	Vaginoscopy	Local anesthesia	Distension medium	Instrument size	Adverse effects	Feasibility/ Complications	Satisfaction
Thiel et al, 2011 [26]	Reproductive age	Therapeutic (sterilization only)	IV sedation and PO placebo	5 mg PO oxycodone (opioid) and 500 mg PO naproxen (NSAID) and IV placebo	N/A	No	No	Yes	8 mL of 1% intracervical lidocaine	Normal saline at lowest pressure necessary	5 mm	Not reported	Not reported	Not reported
Hassa et al, 2013 [14]	Premenopausal nulliparous women only	Diagnostic	200 μg misoprostol PV and PR placebo[†]	PV placebo and 100 mg PR diclofenac (NSAID)	PV placebo and PR placebo	Yes, in Group 1	No	Yes	No	Normal saline at 100–120 mm Hg	4 mm	Group 1: vasovagal symptoms (3). Group 2: vasovagal symptoms (2). Group 3: vasovagal symptoms (4)	Unsuccessful in 4 women owing to failure to pass hysteroscope through cervix	5 point Likert scale for acceptance; 3.13 (misoprostol) vs 2.91 (diclofenac) vs 2.69 (placebo) ($p = .67$)
Issat et al, 2014 [17]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic and therapeutic (myomectomy, polypectomy)	PV placebo and IV placebo	PV placebo and IV ketoprofen (NSAID)	400 μg				PV misoprostol and IV placebo[†]	Yes, in Group 3	No	Yes	No	Distension fluid pressure set at 120 mm Hg
3.2 mm	Nil	Unsuccessful in 2 women owing to closed cervical os	Not reported											
Teran-Alonso et al, 2014 [27]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic and therapeutic (sterilization, polypectomy)	1 g PO paracetamol and 600 mg PO ibuprofen (NSAID)	Nil	N/A	No	Yes	Yes	No	Normal saline <80 mm Hg at 200 mL/min	5 mm	Group 1: nausea and hypotension (5), other (1)	Unsuccessful in 7 women in Group 1 and 13 in Group 2. Pain, cervical stenosis and patient fear cited as reasons for failure	Not reported
Mohammadi et al, 2015 [28]	Premenopausal nulliparous women	Diagnostic	5 mL of 2% transcervical intrauterine lidocaine	100 mg PR diclofenac (NSAID) and 5 mL of transcervical intrauterine normal saline	N/A	No	N/A	No	Yes, 1 mL of 2% intracervical lidocaine for tenaculum	Not reported	3.5 mm	Not reported	Unsuccessful in 9 women in Group 1 and 5 women in Group 2 owing to pain	Not reported
Kadiroğulları et al, 2016 [16]	Premenopausal women	Diagnostic	100 mg PO tramadol (opioid)	Placebo	N/A	No	No	No	No	Physiological saline	5 mm	Not reported	Nil	Not reported
Senturk et al, 2016 [15]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic	PR and intrauterine placebo	1000 mL intrauterine distension medium containing 18 mL lidocaine per 250 mL (20 mg at 2%)[‡]	100 mg PR indomethacin (NSAID) and intrauterine placebo	No	No	Yes	Yes, in Group 2	0.09% sodium chloride at room temperature and 70–80 mm Hg	3.5mm	Group 1: vasovagal (3). Group 2: vasovagal (4). Group 3: vasovagal (4)	Not reported	Not reported
Hassan et al, 2016 (a) [29]	Premenopausal women	Diagnostic	100 mg PO tramadol (opioid)	200 mg PO celecoxib (NSAID)	PO placebo	No	No	Yes	No	Saline with pressure <100 mm Hg	3.8 mm	Group 1: nausea (4)	Unsuccessful in 1 woman in Group 3 owing to pain	Not reported

Table 1

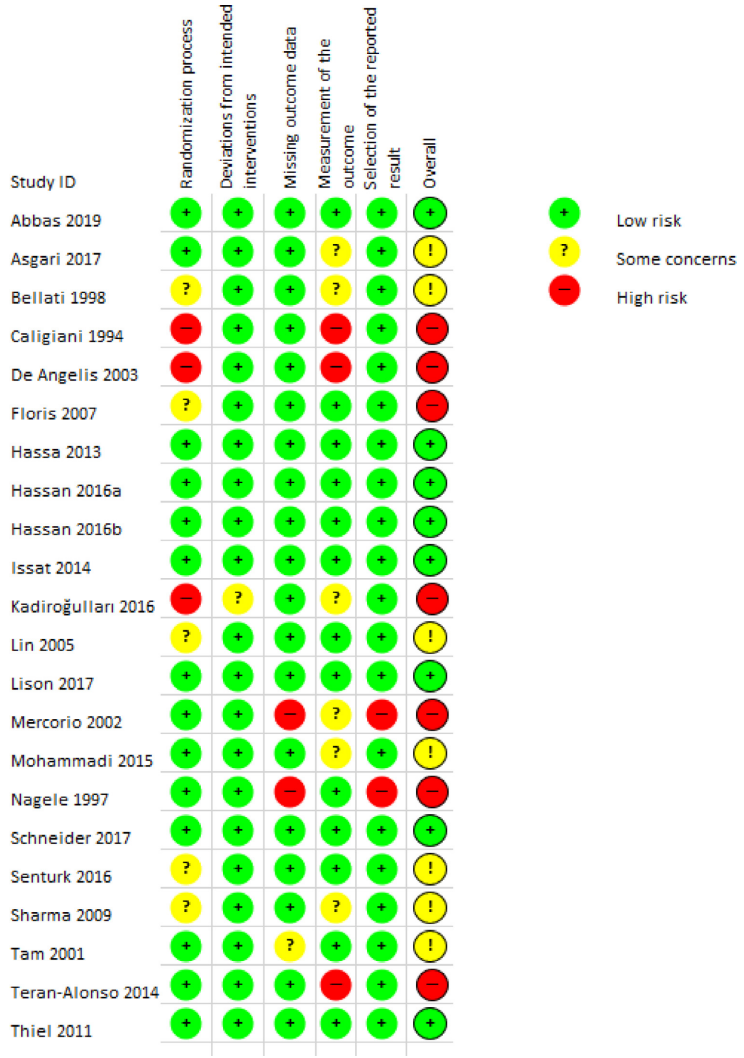
Continued

Study	Patient demographics	Type	Group 1	Group 2	Group 3	Cervical preparation	Cervical dilatation	Vaginoscopy	Local anesthesia	Distension medium	Instrument size	Adverse effects	Feasibility/ Complications	Satisfaction
Hassan et al, 2016 (b) [13]	Women of reproductive age	Diagnostic	50 mg PO tramadol (opioid)	Placebo	N/A	No	No	Yes	No	Saline with pressure <100 mm Hg	3.8 mm	Group 1: nausea (2)	Unsuccessful in 1 woman in Group 2 owing to pain	Not reported
Asgari et al, 2017 [30]	Nulliparous, parous, pre- and postmenopausal women	Therapeutic (D&C and polypectomy only)	General anesthesia†	PO diazepam 10 mg and 100 mg diclofenac PR (NSAID) and paracervical 10 cc 2% lidocaine	IV sedation	No	Yes	No	Yes, in Group 2	0.9% normal saline at <0.1 bar	4 mm	Nil	Not reported	Not reported
Schneider et al, 2017 [12]	Reproductive age	Therapeutic (sterilization only)	Placebo pills and inhalational N_2O/O2 to max conc 70%/30%	5/325 mg PO hydrocodone/ acetaminophen (opioid) and 1 mg PO lorazepam and inhaled O2	N/A	No	Yes, 8 in Group 1 and 12 in Group 2	No	Yes, paracervical block with 18 mL of 1% lidocaine	Normal saline	5 mm	Not reported	Group 1: uterine perforation (1), device malfunction (1). Group 2: poor visualization obscuring placement (4), device malfunction (2)	81.3% of women were satisfied regardless of study group
Lisón et al, 2017 [31]	Nulliparous, parous, pre- and postmenopausal women	Diagnostic	Nil†	Placebo TENS	Active TENS	No	No	Yes	No	Saline solution at 80 mL/min at 100 mm Hg	5 mm	Group 1: dizziness (6), nausea (5), vomiting (1), vertigo (1), sweating (5). Group 2: dizziness (3), nausea (2), shoulder pain (1), vertigo (1), sweating (2). Group 3: dizziness (3), nausea (2), vertigo (1), sweating (3).	Not reported	For active TENS vs placebo, satisfaction index score difference of 1.3 (95% CI 0.5–2.2; p = .001)
Abbas et al, 2019 [32]	Premenopausal women	Diagnostic	50 mg PO diclofenac (NSAID)	20 mg PO hyoscine butyl-bromide [buscopan] (antispasmodic)	PO placebo	No	No	Yes	No	Normal saline to 50 mm Hg	4 mm	Group 1: dizziness (4), vomiting (2). Group 2: dizziness (14), nausea (2).	Nil	Not reported

CI = confidence interval; CO_2 = carbon dioxide; D&C = dilatation & curettage; IM = intramuscular; IV = intravenous; N/A = not applicable; N_2O = nitrous oxide; NSAIDs = nonsteroidal anti-inflammatory drug; O_2 = oxygen; PO = oral; PR = rectal; PV = vaginal; SL = sublingual; TENS = transcutaneous electrical nerve stimulation.
Values are given in mean [95% CI], median {range}, or number (%).
† group not used as control.

Fig. 2

Individual risk of bias.

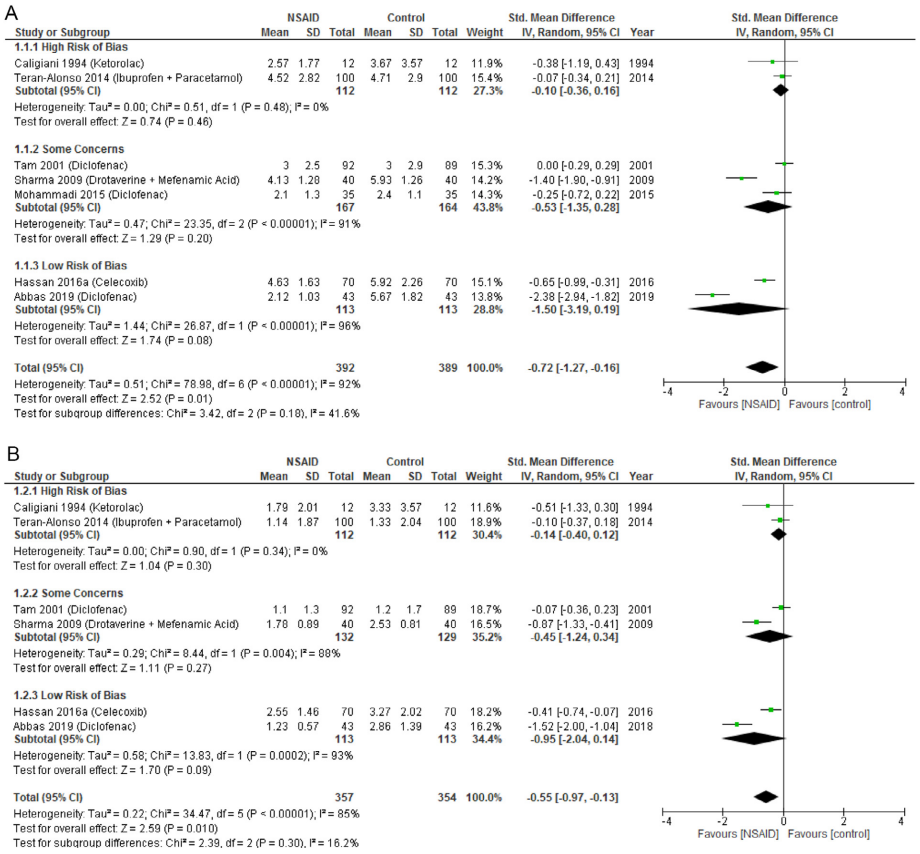


Antispasmodics

A meta-analysis of the 2 studies (166 patients) investigating the use of an oral antispasmodic against control groups [25,32] showed a significant reduction in pain (SMD 1.48; 95% CI 1.82 to 1.13, and SMD 1.02; 95% CI 1.34 to 0.69) both during (Fig. 5A) and after (Fig. 5B) office hysteroscopy, respectively. The antispasmodic was given 1 hour before the procedure in both studies (Supplemental Table 1). No significant statistical heterogeneity was observed. One of the 2 studies involved the combination of an antispasmodic with an NSAID [25].

Fig. 3

(A) Effect of NSAIDs on pain control during office hysteroscopy (*arrow*). (B). Effect of NSAIDs on pain control after office hysteroscopy. NSAIDs nonsteroidal anti-inflammatory drugs. NSAIDs nonsteroidal anti-inflammatory drugs.



However, both studies individually showed statistically significant reductions in procedural pain. The postprocedural pain score was recorded immediately after [32] and at 30 minutes [25] after hysteroscopy.

Transcutaneous Electrical Nerve Stimulation

A meta-analysis of the studies investigating the use of transcutaneous electrical nerve stimulation (TENS) against control groups for pain relief during office hysteroscopy includes 2 studies and 234 patients (Fig. 6A) [24,31] and after office hysteroscopy includes 1 study and 92 patients (Fig. 6B) [31]. A significant reduction in pain scores during (SMD 0.99; 95% CI 1.67 to 0.31) [24,31] and 5 minutes after (SMD 0.54; 95% CI 0.95 to 0.12) [31] office hysteroscopy was seen.

Acceptability and Satisfaction

Only 5 studies reported acceptability or satisfaction (Table 1) [12,14,20,23,31]. Women were more satisfied with NSAIDs compared with "nil" or placebo in 1 study, although no clear superiority was reported in 2 other studies evaluating NSAIDs [14]. One study found that 37.5% of women receiving an opioid were dissatisfied because of adverse effects ($p < .001$) [23]. TENS, in contrast, showed a significantly higher satisfaction index score when compared with placebo in another study ($p = .001$) [31].

Fig. 4

(A) Effect of opioids on pain control during office hysteroscopy (*arrow*). (B) Effect of opioids on pain control after office hysteroscopy.

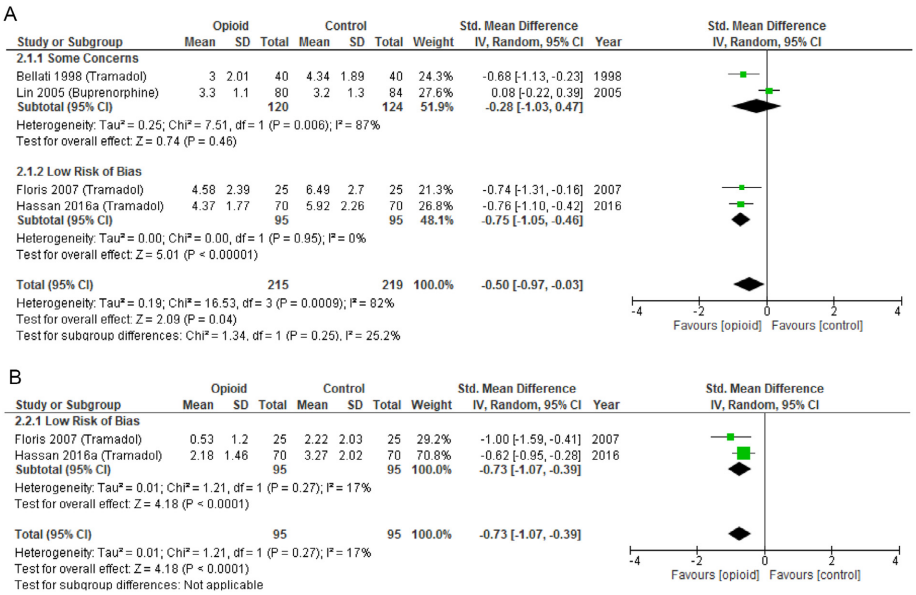


Fig. 5

(A) Effect of antispasmodics on pain control during office hysteroscopy (*arrow*). (B) Effect of antispasmodics on pain control after office hysteroscopy.

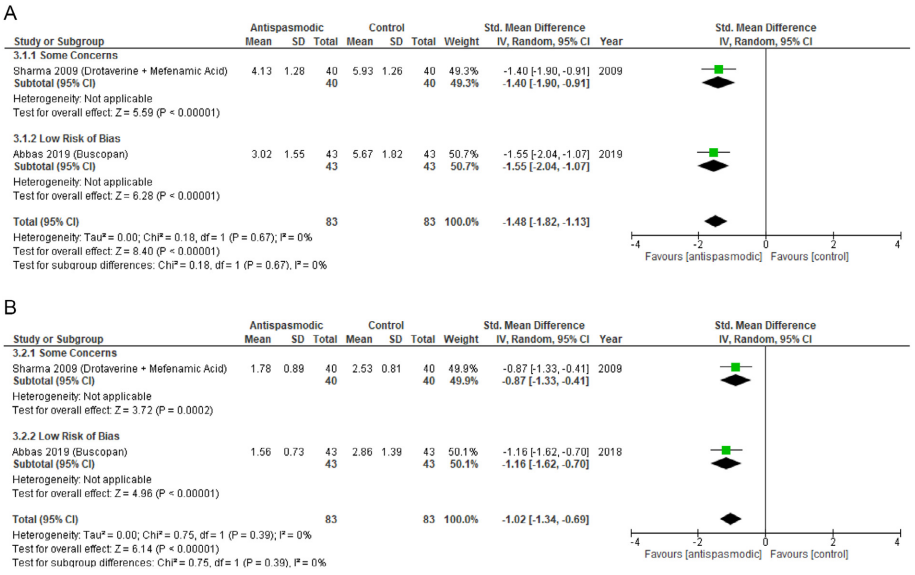
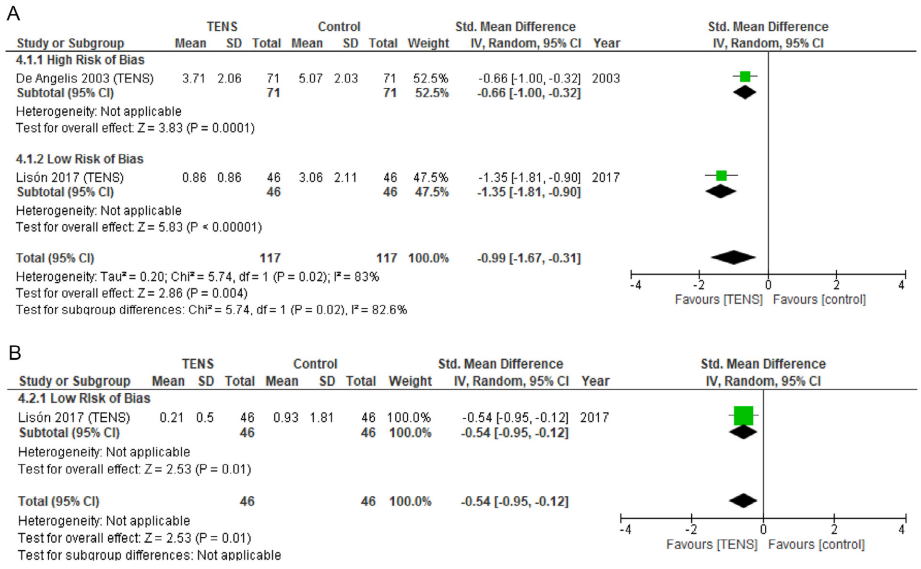


Fig. 6

(A) Effect of TENS on pain control during office hysteroscopy (*arrow*). (B) Effect of TENS on pain control after office hysteroscopy. TENS transcutaneous electrical nerve stimulation.



Adverse Effects

Fourteen studies reported adverse effects (Table 1) [11,13 15,17,22 25,27,29 32]. Fig. 7 shows a meta-analysis of the adverse effects of analgesic interventions used for office hysteroscopy. Studies spanning more than 1 class of analgesia could not be included [25,30]. Vasovagal adverse effects (i.e., symptoms including nausea, vomiting, dizziness, sweating, vertigo, bradycardia, and hypotension) were reported in all studies. However, drowsiness was only reported with the use of opioids [23]; shoulder pain with TENS [24]; and 1 case each of skin rash [22], epigastric pain [22], and gastritis [25] with NSAIDs. Although there was no significant difference in the incidence of adverse effects between NSAIDs versus the control group ($p = .97$) and between TENS versus the control group ($p = .63$), there was a significantly increased incidence of adverse effects with opioids ($p < .001$) and antispasmodics ($p < .001$).

Feasibility and Complications

Feasibility and complication rates were reported in 16 studies (Table 1) [9 14,16,17,22 25,27 29,32]. However, technical failure rates (only 61/2215 office hysteroscopies failed because of pain, anxiety, and/or cervical stenosis across all studies) and the incidence of complications (1/1139) were too low to determine an association between a specific analgesic and feasibility or the risk of developing a complication. A subgroup analysis of pain scores in patients who underwent the vaginoscopic approach (5 studies; 886 patients) showed a statistically significant reduction only if a hysteroscope with a diameter ≤4 mm was employed (SMD 1.31; 95% CI 2.01 to 0.61) (Supplemental Fig. 2).

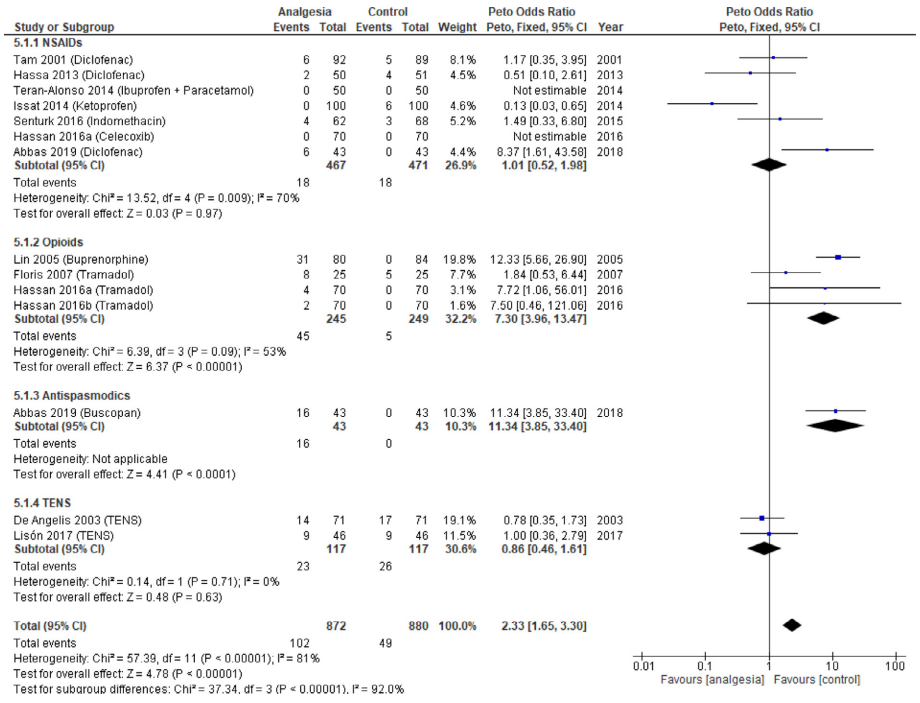
Discussion

Principal Findings

Preprocedural analgesia using pharmacological agents, NSAIDs, opiates, and antispasmodics reduces pain both during and after office hysteroscopy. Electroanalgesia using TENS is also associated with a significant reduction in periprocedural and postprocedural pain. The magnitude of average pain reduction was similar across analgesic classes. In contrast to opiates and antispasmodic drugs, NSAIDs and TENS were not associated with an increased risk of adverse effects. Therefore, NSAIDs and TENS seem to be the safest and most effective methods of analgesia for combating pain, both during and after office hysteroscopy. In most

Fig. 7

Incidence of adverse effects according to class of analgesia.



studies, NSAIDs were administered orally 1 hour before the procedure and this method of administration was associated with a greater reduction in pain compared with other routes.

Comparison with Other Studies

The only previous systematic review and meta-analysis evaluating analgesia in office hysteroscopy, developed by Cochrane, also included local anesthesia [1]. Our review focused on the use of analgesia alone, in keeping with contemporary vaginoscopic office hysteroscopy. In widening our search (to include nonpharmaceutical methods of analgesia, e.g., TENS, and current practices, e.g., conscious sedation) and in including foreign-language studies, we expanded on the previous Cochrane review by including 12 additional RCTs. In contrast to Cochrane, with the addition of these studies, we were able to identify evidence supporting the effectiveness of analgesia when compared with control groups. Of note, our findings are supported by a recent network meta-analysis that found that naproxen, an NSAID, was associated with the greatest, statistically significant reduction in pain score during endometrial biopsy after office hysteroscopy, when compared with other analgesics and local anesthetics [33].

Strengths and Weaknesses

By formulating a clinically focused question, using comprehensive searches of multiple databases, not applying language restrictions, and searching reference lists for additional studies, our search strategy was performed adequately to reduce the risk of selection bias.

The main limitations of this study relate to the heterogeneity associated with data pooling and methodological weaknesses within included primary studies. However, heterogeneity was not always attributable to methodological weaknesses but was explained by clinical differences in the patient population, approach (e.g., vaginoscopy), type of distension media, and instrument diameter.

Implications for Clinical Practice

Preprocedural analgesia reduces pain both during and after office hysteroscopy. Alleviating pain should enhance

tolerance and experience of the procedure, with the average reduction in pain scores being consistent with a medium to large clinical effect [34]. Regarding the choice of the analgesic, women should be advised to take an oral NSAID 1 hour before office hysteroscopy and this recommendation should be incorporated into evidence-based guidance [35]. The justification for this advice is based on the greater body of evidence supporting the use of NSAIDs, in addition to their wider availability, compared with TENS. In situations where NSAIDs are contraindicated, the use of TENS to reduce peri- and postoperative pain should be considered. Opiates or antispasmodics can be used to reduce pain during and after office hysteroscopy in women with contraindications to NSAIDs, but they should be made aware of the increased adverse effects. Where the vaginoscopic approach is used, a small diameter hysteroscope should be used to achieve the full benefit of preprocedural analgesia. In 2011, only 27% of UK gynecologists offered oral analgesia before office hysteroscopy [36]. The findings supporting the use of preoperative analgesia from this study should be disseminated to practitioners.

Implications for Future Research

In conclusion, there is a need for further research into the optimal route, dose, and timing of NSAID administration before office hysteroscopy. Large-scale RCTs are required to understand better the potential of antispasmodics and TENS as analgesic agents. All but one study [27] included in our meta-analysis evaluated analgesia for diagnostic hysteroscopy. We need more data to determine the optimal analgesic agents or regimes for operative office hysteroscopy procedures such as polypectomy [37] and endometrial ablation [38], which are being increasingly performed in this setting. These studies should take into account advances in instrumentation (miniaturization) and techniques (vaginoscopy). Furthermore, they should be adequately powered and robustly designed and pay particular attention to minimizing confounding because of operator proficiency.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jmig.2020.01.008.

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Addendum to Chapter 3

Pain in all studies were measured on either a visual analogue scale (VAS) or numerical rating scale (NRS). All studies utilised a 10-point/10cm/100mm scale apart from one which used a 20cm scale (which was scaled down to a 10cm scale for the purposes of meta-analysis) (21) and another which did not specify the range of the scale used (22), however, it is likely that a 10-point/10cm/100mm scale was used based on the information given.

CHAPTER 4: LOCAL ANAESTHESIA

This work has been published in the European Journal of Obstetrics & Gynecology and Reproductive Biology; De Silva PM, Carnegy A, Smith PP, Clark TJ. Local anaesthesia for office hysteroscopy: A systematic review & meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020 Sep;252:70-81. doi: 10.1016/j.ejogrb.2020.05.062. Epub 2020 Jun 2. PMID: 325701 (25).

My role in this publication is as follows: I carried out the literature search, collected the data, undertook the meta-analysis, and wrote the manuscript.

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Local anaesthesia for office hysteroscopy: A systematic review & meta-analysis

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ABSTRACT

Objective: To compare the effects of different types and routes of administration of local anaesthetic for pain control during and after office hysteroscopy.
Methods: Medline, Embase, CINAHL and the Cochrane library were searched from inception until October 2019, in order to perform a systematic review and meta-analysis of all randomised controlled trials investigating the use of a local anaesthetic compared to a control, for pain relief in women undergoing diagnostic or operative office hysteroscopy. Average pain scores and data regarding side-effects, feasibility, complications, acceptability and satisfaction were collected.
Results: The literature search yielded 612 citations. A total of 37 studies were included for systematic review, of which data from 20 studies were used for meta-analysis. Local anaesthesia was associated with significantly reduced pain during (SMD -0.57, 95 % CI -0.79 to -0.34) and after (SMD -0.30, 95 % CI -0.54 to -0.06) office hysteroscopy but did not reduce vasovagal episodes (OR 0.73, 95 % CI 0.50–1.09). A reduction in intra-procedural pain was observed regardless of type or route of administration. Local anaesthesia did not significantly reduce the risk of procedural failure (OR 0.72, 95 % CI 0.47–1.11). Insufficient data regarding complications, acceptability and satisfaction were available for meta-analysis.
Conclusion: Local anaesthesia via any route of genital tract administration, should be considered when undertaking office diagnostic or operative hysteroscopy to reduce pain during and after the procedure. Further research is needed to understand whether the pain control benefits of local anaesthesia remain apparent with vaginoscopic approaches to office hysteroscopy that avoid genital tract instrumentation.

Contents

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Introduction

Hysteroscopy is used in the investigation and treatment of abnormal uterine bleeding and uterine factor infertility. Compared to a formal operating theatre, the 'office' or 'outpatient' setting carries a shorter recovery time, less complications and economic benefits [1]. Nevertheless, patient experience and tolerance of office hysteroscopy is adversely affected by pain and vasovagal episodes [2], which arise from genital tract manipulation, uterine cavity distension and trauma to the endometrium [3].

Previous reviews have demonstrated a reduction in pain associated with pre-procedural local anaesthesia for diagnostic office hysteroscopy. However, questions remain regarding the optimal type and route of local anaesthetic for both diagnostic and operative office hysteroscopy [1,3–5]. Furthermore, there is additional uncertainty regarding the benefits of local anaesthetic on procedural pain in contemporary hysteroscopy, where miniaturisation of endoscopes has diminished the requirement for vaginal instrumentation and cervical dilatation [6]. In addition, more data are likely to have accumulated since publication of earlier reviews in light of the wider adoption of the office setting for hysteroscopy and the introduction of novel administration methods such as intracornual blocks [7].

We therefore conducted a systematic review and meta-analysis to determine the best local anaesthesia types and routes of administration to control pain and reduce side-effects, including vasovagal episodes, in diagnostic and therapeutic hysteroscopy conducted in an office setting, i.e. without general or regional anaesthesia.

Materials and methods

Protocol and guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance was adopted for the design of this systematic review [8], with support from the Cochrane Handbook for Systematic Reviews of Interventions [9]. An initial protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42019138142) [10].

Inclusion criteria

Randomised controlled trials investigating all women undergoing office diagnostic and/or therapeutic hysteroscopy who were randomised to receive either a local anaesthetic or a control that included no treatment, placebo, an alternate local anaesthetic regimen (intervention, dose, route and/or timing of administration) or an alternate method of pain relief (e.g. analgesia, conscious sedation) where the outcome was pain, were included. There were no language restrictions.

Exclusion criteria

Case reports, case series, conference abstracts (where no full text was available) and observational studies were excluded.

Outcomes

The primary outcome was pain. Secondary outcomes included side-effects (symptoms), acceptability, satisfaction, feasibility and complications. Information was also collected on the use of analgesia, additional local anaesthesia (e.g. for tenaculum placement), conscious sedation, vaginoscopy, cervical preparation, cervical dilatation, distension medium and instrument size.

Search strategy

The National Institute for Health and Care Excellence (NICE) Healthcare Databases Advanced Search (HDAS) platform was used to search Medline, Embase, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to October 2019. A combination of the keywords "hysteroscopy", "local an(a)esthesia", "outpatient", "ambulatory", "office" and their associated medical subject headings (MeSH) were used to search the databases associated with HDAS. The key words "hysteroscopy" and "an(a)esthesia" were used to search CENTRAL. Filters or limits were not applied. In order to widen the search, the reference lists of included papers were reviewed, and further studies were included for analysis if deemed appropriate.

Study selection

The HDAS platform was used to remove duplicates, after which two researchers (PDS and AC) independently screened all titles and abstracts. Duplicates from CENTRAL were manually rejected. Full texts were reviewed to select eligible studies. An additional independent researcher (PS) decided on eligibility if consensus was not met.

Data collection process

Two reviewers (PDS and AC) independently extracted data from the included trials into a piloted data extraction form, using

Microsoft Excel. Intra-procedural and post-procedural pain scores were extracted. If the intra-procedural pain score was broken down according to specific points during hysteroscopy, the following rules were applied; if diagnostic, the score related to the level of pain during uterine inspection and if therapeutic, the score related to the level of pain during the given operative procedure. Where multiple post-operative pain scores were documented, the highest score was used. Mean pain scores and associated standard deviations were calculated for studies that provided raw data [11] and standard errors of the mean [12]. They were also calculated for grouped pain scores [13,14] and descriptive scales [15] to which numerical values were assigned.

The authors of the grouped pain scores [13,14] were contacted for their raw pain scores to increase the quality of data entered for meta-analysis. Authors of the ten studies that did not report means and associated standard deviations (i.e. reported median pain scores [16–21], means without standard deviations [22–24] and dichotomous outcomes [25]) were contacted for their data to increase the number of trials that could be meta-analysed.

Assessment of risk of bias

Independent assessment of individual study quality was assessed using the Cochrane Collaboration Risk of Bias 2 tool by two researchers (PDS and AC) in an intention-to-treat basis [26]. Again, if consensus was not reached, a third independent reviewer (PS) was asked to intercede.

Data synthesis

Statistical analyses were performed using RevMan (version 5.3.5) [27], where meta-analysis was performed on an intention-to-treat basis. To allow for comparison between different pain scales, standard mean differences (SMD) and their 95 % confidence intervals were calculated. Studies were weighted according to the inverse of their variance to calculate random-effects summary estimates. A p-value less than 0.05 was deemed significant. Heterogeneity of treatment effects based on appropriate subgroup analyses were depicted graphically by forest plots and statistically analysed using the chi-squared test. Peto odds ratios were calculated in order to graphically present the association of side effects to different treatments due to the low incidences of such events amongst randomised groups.

Results

Study selection

The literature search yielded 612 citations (Fig. 1). Four other studies were included identified through other sources [12,21,28,29]. After excluding 184 duplicate articles, 432 titles and abstracts were screened, leaving 54 full-text articles which were assessed for eligibility. After excluding 17 trials, reasons for which are given in Fig. 1, 37 studies were included for systematic review, of which data from 20 studies were used for meta-analysis.

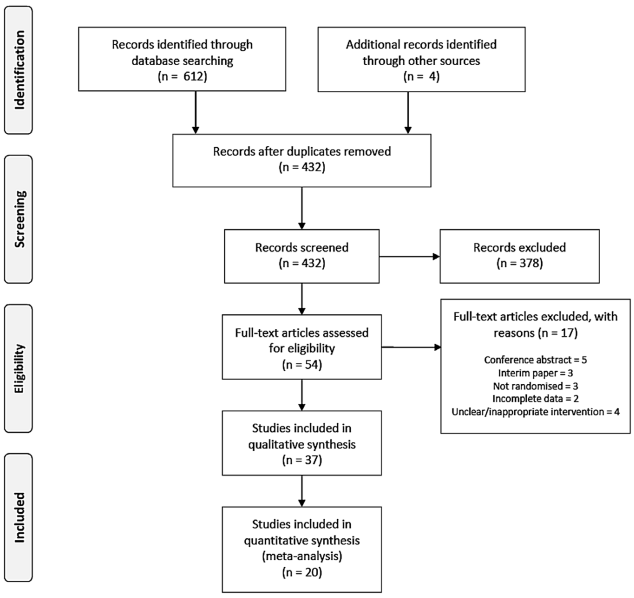

Fig. 1. PRISMA (Preferred Reporting Items of Systematic Reviews and Meta Analyses) flow diagram. A flow diagram of the study selection process.

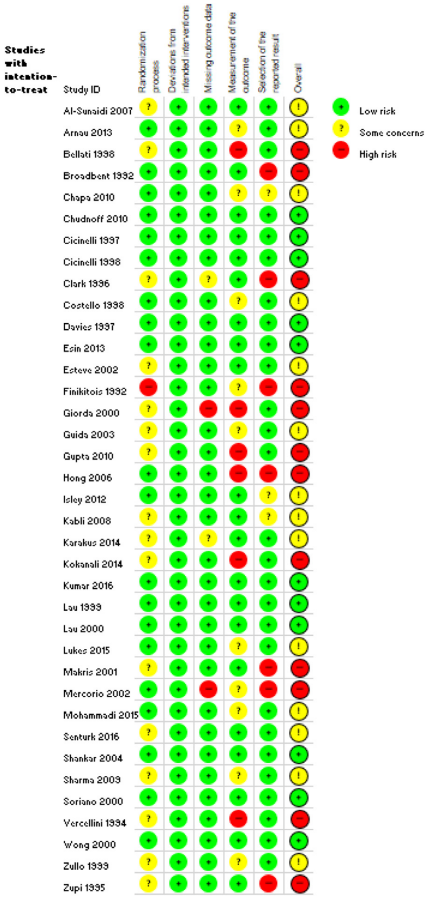

Fig. 2. Risk of Bias.
Assessment of risk of bias for each trial.

Study characteristics

Supplementary Table 1 shows details of the interventions, data presented and control variables for all included studies. Of the 37 studies included, 17 had women of both reproductive and post-reproductive age [14–16,20,23–25,30–39]. Four studies consisted entirely of postmenopausal women [12,17,40,41] and 13 studies solely investigated premenopausal women [7,18,19,21,28,42–49], of which one restricted inclusion to nulliparous women only [42]. Three studies did not report menopausal status or parity [11,13,22]. 28 studies examined the role of local anaesthesia in diagnostic hysteroscopy only [11–18,20,22,23,25,30–37,39–43,45,46,49], two which performed diagnostic and therapeutic hysteroscopy [38,48], and seven where only operative procedures were undertaken (polypectomy [24], endometrial ablation [7,21], sterilisation [19,47], mixed [28,44]). All studies utilised rigid hysteroscopes. Studies restricted to diagnostic hysteroscopy ranged from outer diameters of 2.7 mm–5.5 mm (including sheath) and those including operative hysteroscopy used hysteroscopes up to 8.5 mm.

Mean pain scores and standard deviations were provided in 22 studies [7,28,30–49] and calculated from scores provided by five studies [11–15]. Of these 27 studies, 20 trials compared a local anaesthetic against placebo or nil, for meta-analysis of pain scores [7,11,12,14,30–36,38–41,43,45–47,49]. The remaining seven studies consisted of control groups including different local anaesthetics [13,15,28], analgesia [37,42], sedation [37,44] and cervical preparation [48], which was felt to produce too much confounding on treatment effect if included in the meta-analysis. Five studies comprised of more than two groups to which patients could be randomised; in four of these, a more suitable group was used for comparison [11,20,36,37], however in one study [49], each intervention group, consisting of a different method of administration of lidocaine, was repeatedly compared against the same placebo group in the meta-analysis. Six studies reported median pain scores [16–21], three studies presented means without standard deviations [22–24] and one study displayed pain scores as a dichotomous outcome [25]. Contacted authors either did not respond or were unable to provide appropriate data.

Study bias

The risk of bias for all included studies according to their methodological characteristics is detailed in Fig. 2. Overall, 30 % of studies showed a 'low risk' of bias, with 38 % showing 'some concerns' and 32 % depicting a 'high risk' of bias. Underreporting of the randomization process [13], poor clarity of whether pain scores were included where hysteroscopy failed [12,17], participant awareness of the intervention received [11,12,39,43,46], significant differences in methodology between randomised groups [24] and unsatisfactory reporting of results [13,14,17,22–25] were the significant sources of bias amongst included studies.

Effect of local anaesthetic

Meta-analysis of 20 studies [7,11,12,14,30–36,38–41,43,45–47,49], including 2610 patients, showed that administration of local anaesthesia achieved a statistically significant reduction in pain during office hysteroscopy; standard mean difference (SMD) -0.57, 95 % CI -0.79 to -0.34 (Figs. 3 & 4). A significant reduction in mean pain during office hysteroscopy remained when data aggregation was restricted to studies with lower risk of bias (Fig. 5). Post-procedural pain was also significantly reduced following office hysteroscopy in 12 studies [7,14,31,32,35,39,40,41,45–47,49], inclusive of 1103 patients; SMD -0.30, 95 % CI -0.54 to -0.06, for pain scores observed at 5 min [47], 10 min [45], 15 min [40,41,46], 30 min [14,31,32,35,39,49] and 60 min [7] post-hysteroscopy (Figs. 6 & 7). High levels of statistical heterogeneity were noted in these meta-analyses depicting intra-procedural and post-procedural pain, with I^2 values of 87 % and 76 %, respectively.

The majority of studies included for meta-analysis administered local anaesthesia 5 min prior to office hysteroscopy [11,12,14,31–33,40,43,45,47,49]. Hysteroscopy was otherwise performed approximately two minutes [30,46], three minutes [7], or 10 min [38,41] after administering local anaesthesia, unless given

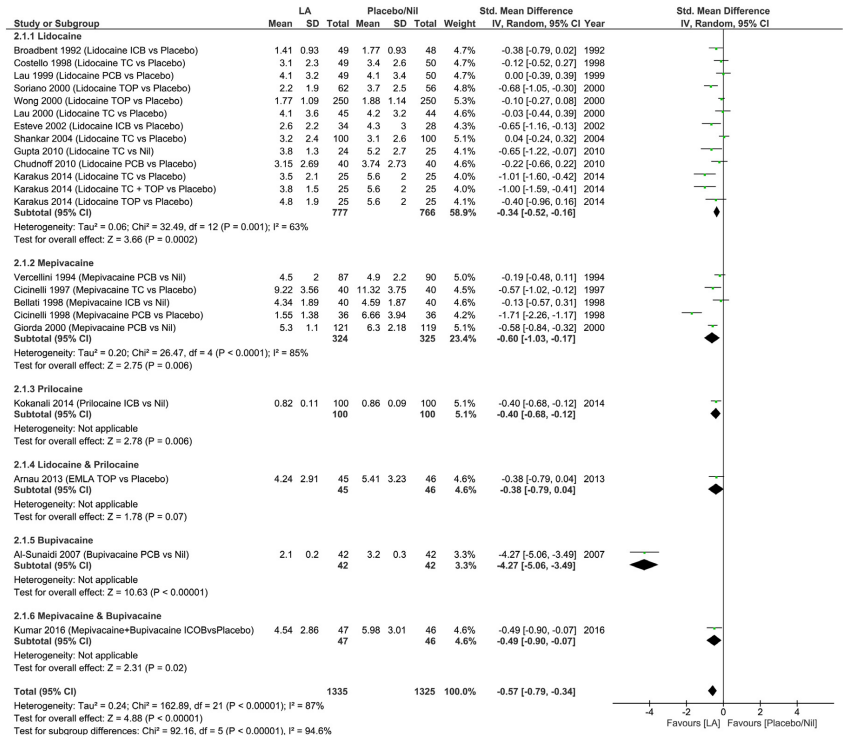

Fig. 3. Intra Procedural Pain Score According to Local Anaesthetic.
A forest plot depicting the intra procedural pain scores according to the local anaesthetic administered.
LA: local anaesthetic, SD: standard deviation, IV: inverse variance, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

within the distension medium, when it was given during the procedure [36].

Choice of local anaesthesia

Included studies were divided into subgroups according to the local anaesthetic administered, independent of route (Fig. 3). Lidocaine was investigated in 11 studies (1493 patients) and was found to produce a statistically significant reduction in intra-procedural pain; SMD -0.34, 95 % CI -0.52 to -0.16 [14,30–36,46,47,49]. Mepivacaine (5 studies [11,12,40,41,43], 649 patients) and prilocaine (1 study [39], 200 patients) also significantly reduced pain scores during office hysteroscopy; SMD -0.60, 95 % CI -1.03 to -0.17 and SMD -0.40, 95 % CI -0.68 to -0.12, respectively. Giving bupivacaine (1 study [45], 84 patients) produced the greatest statistically significant reduction in intra-procedural pain; SMD -4.27, 95 % CI -5.06 to -3.49. Two trials investigated combinations of local anaesthesia; lidocaine plus prilocaine (1 study [38], 91 patients) did not significantly reduce pain scores during office hysteroscopy (SMD -0.38, 95 % CI -0.79 to 0.04), whereas combining mepivacaine and bupivacaine (1 study [7], 93 patients), did (SMD -0.49, 95 % CI of -0.90 to -0.07).

In contrast, the only specific local anaesthetics that produced a statistically significant reduction in post-procedural pain scores were mepivacaine (2 studies [40,41], 152 patients) with a SMD of -0.66 (95 % CI -1.19 to -0.14), and bupivacaine (1 study [45], 84 patients) with a SMD of -1.55 (95 % CI -2.05 to -1.06) (Fig. 6).

Route of administration

Included studies were divided into subgroups according to the route that local anaesthesia was given. All routes of administration including topical application (to the ectocervix and / or trans-cervical instillation) and injection (intracervical, paracervical and intracornual blocks) reduced peri-operative significantly reduced pain during hysteroscopy (Fig. 4). Statistical heterogeneity was observed within all subgroups, except for data aggregated from 4 studies inclusive of 439 patients, evaluating intracervical blocks [11,14,35,39]; SMD -0.38, 95 % CI -0.57 to -0.19, I^2 0%). The paracervical route of administration was most frequently

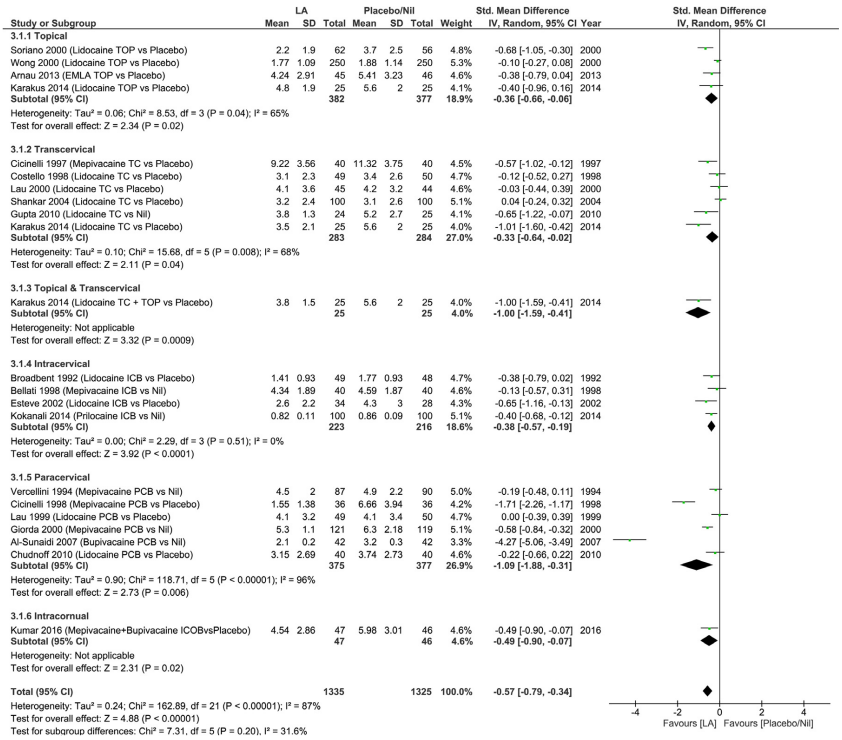

Fig. 4. Intra Procedural Pain Score According to Route of Administration.
A forest plot depicting the intra procedural pain scores according to the route of local anaesthetic administered.
LA: local anaesthetic, SD: standard deviation, IV: inverse variance, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

evaluated (6 studies, 752 patients) [12,31,41,43,45,47]; SMD -1.09, 95 % CI -1.88 to -0.31, I^2 96 %. Statistical significance remained when an outlier was removed [45], however the degree of heterogeneity was not substantially reduced; SMD -0.51, 95 % CI -0.96 to -0.06, I^2 87 %. An intracornual block was evaluated in one trial involving 93 patients undergoing office endometrial ablation [7], and showed a statistically significant reduction in pain; SMD -0.49, 95 % CI -0.90 to -0.07. In contrast, no particular route of local anaesthesia was found to achieve a significant reduction in pain following office hysteroscopy (Fig. 7).

Side effects

A total of 161 side effects occurred in 19 studies [7,12,14,16,19,20,22–24,31–34,38,40,41,45,46,49], where 2381 patients were randomised to either local anaesthesia or placebo/nil for pain control in office hysteroscopy. Vasovagal side-effects (i.e. symptoms including nausea, vomiting, dizziness, sweating, vertigo, bradycardia and hypotension) were reported 117 times in 17 studies [7,12,16,20,22–24,31–34,38,40,41,45,46,49]. Shoulder pain (n = 35) [14,24,31], headache (n = 2) [24], temporary voiding dysfunction (n = 1) [24] and symptoms of lidocaine exposure e.g. numbness, tingling, ear ringing (n = 6) [19] were the only non-vagal side-effects reported in 4/19 studies.

Whilst meta-analysis did not show a significant reduction in vagal episodes when local anaesthesia was given (17 studies, 2156 patients; OR 0.73, 95 % CI 0.50–1.09) [7,12,16,20,22–24,31–34,38,40,41,45,46,49], when subgroup analysis was performed according to the local anaesthetic given, a statistically significant reduction in vasovagal episodes was observed with the administration of mepivacaine only (5 studies, 619 patients) [12,22,23,40,41]; OR 0.33, 95 % CI 0.19 to 0.60 (Fig. 8). When subgroup analysis was performed according to route of local anaesthesia, a statistically significant reduction in vagal effects was observed only when given through the transcervical route (6 studies, 439 patients) [20,22,32,40,46,49]; OR 0.39, 95 % CI 0.18 to 0.83 (Fig. 9).

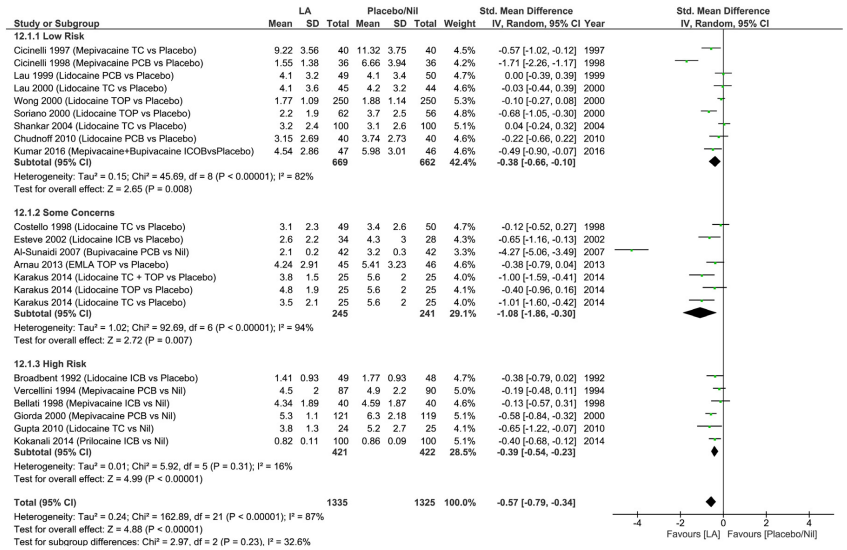

Fig. 5. Intra Procedural Pain Score According to Risk of Bias.
A forest plot depicting the intra procedural pain scores according to the risk of bias of included studies.
LA: local anaesthetic, SD: standard deviation, IV: inverse variance, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

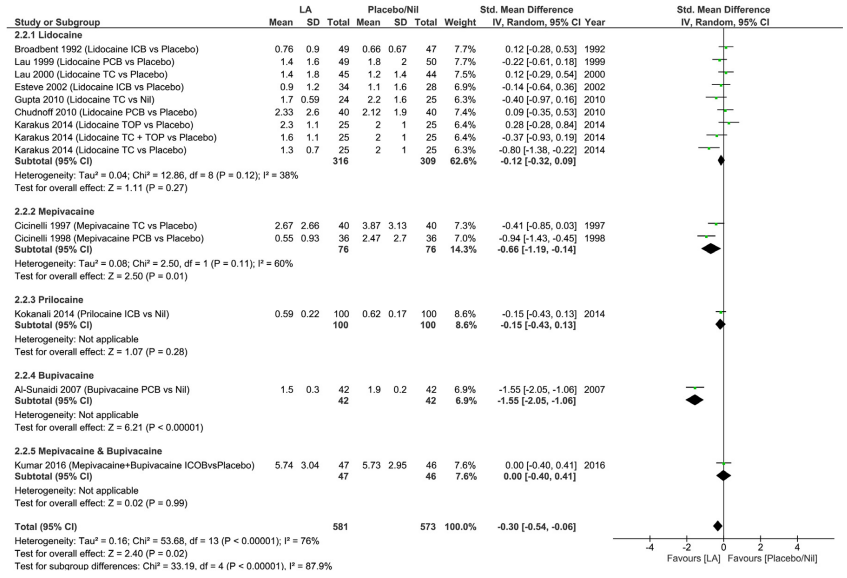

Fig. 6. Post Procedural Pain Score According to Local Anaesthetic.
A forest plot depicting the post procedural pain scores according to the local anaesthetic administered.
LA: local anaesthetic, SD: standard deviation, IV: inverse variance, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

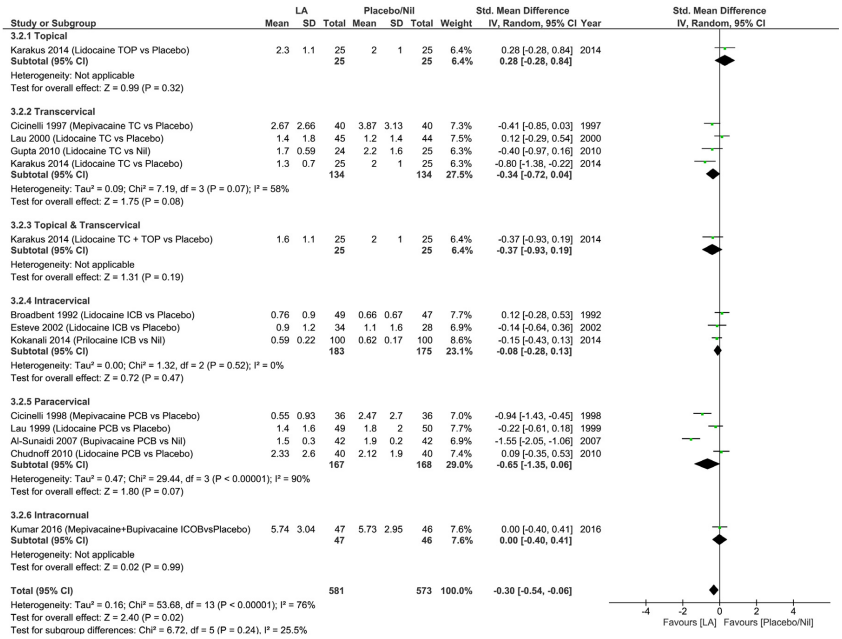

Fig. 7. Post Procedural Pain Score According to Route of Administration.
A forest plot depicting the post procedural pain scores according to the route of local anaesthetic administered.
LA: local anaesthetic, SD: standard deviation, IV: inverse variance, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

Feasibility & complications

42 procedures failed in the 1292 women randomised to local anaesthesia and 55 procedures failed in the 1221 women randomised to nil or placebo, as reported by 20 studies [7,12,14,16,23–25,30–35,38,40,41,43,46,47,49]. Meta-analysis of these data showed no significant reduction in failure rates were observed with the administration of local anaesthesia against nil or placebo; OR 0.72, 95 % CI 0.47–1.11 (Fig. 10). The incidence of complications (reported by only two studies) were too low to determine an association between a specific type and/or route of local anaesthesia on the risk of developing a complication; one study described four patients that were bleeding from the injection site [12], and the other reported four cases of post-procedural infection [28].

Acceptability & satisfaction

Eleven studies commented on acceptability or satisfaction [13,14,19,21,25,28,30,36,38,44,46]. Five studies performed statistical analysis on rates of acceptability and/or satisfaction between local anaesthesia and placebo [19,30,36,38,46], where data were presented in such a way that did not allow for aggregation for meta-analysis. These studies did not demonstrate a preference towards either intervention apart from one study [46], which showed a significantly lower proportion of patients in the group randomised to receive a local anaesthetic who wished for a general anaesthetic if hysteroscopy was to be repeated ($p = 0.001$).

Discussion

Principal findings

Administration of a local anaesthetic to the genital tract reduces pain during and after office hysteroscopy, regardless of the site or method of application. These effects were apparent if the agent was administered within two to 10 min of the procedure or during the procedure if incorporated within the fluid distension media. However, local anaesthesia did not reduce the incidence of vasovagal episodes, one of the commonest adverse effects of hysteroscopy conducted in conscious women. Thus, local anaesthetic administered topically or parenterally to the genital tract, should be considered in all women undergoing office based hysteroscopic procedures.

Considerable heterogeneity existed between studies included in all meta-analyses evaluating pain control during and after office hysteroscopy. Subgroup analyses showed that all short acting (lidocaine, prilocaine, and mepivacaine) and long acting (bupivacaine) anaesthetic agents were effective in reducing pain during office hysteroscopic procedures. However, only the anaesthetic agents, mepivacaine and bupivacaine, reduced post-procedural pain, although the data were limited to two trials and one trial respectively. Whilst vasovagal episodes were unaffected by local, genital tract anaesthesia overall, subgroup analyses showed that the pharmacological agent, mepivacaine, and the transcervical route of administration, were associated with reductions in the likelihood of these fainting episodes, although moderate heterogeneity across included trials was observed.

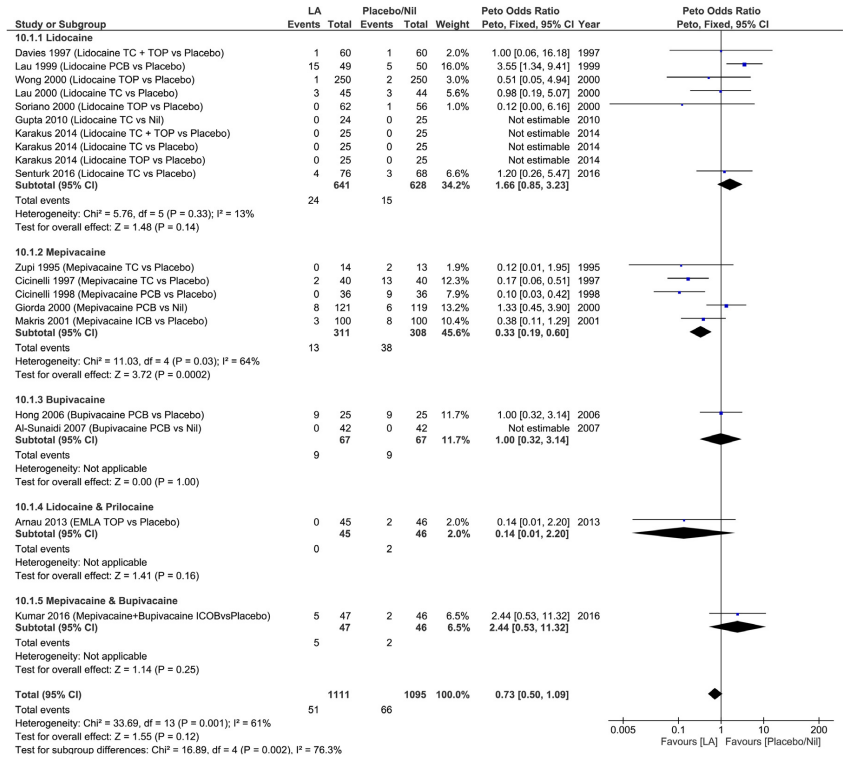

Fig. 8. Incidence of Vasovagal According to Local Anaesthetic.
A forest plot depicting the incidence of vasovagal episodes according to the local anaesthetic administered.
LA: local anaesthetic, SD: standard deviation, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

Comparison with other studies

Whilst a number of systematic reviews have evaluated the use of local anaesthesia for office hysteroscopy [1,3–5], only two have meta-analysed pain scores [1,5]. The former systematic quantitative review found that only intracervical and paracervical routes of administration produced a significant decrease in pain during office hysteroscopy but did not investigate post-procedural pain [5]. A more recent Cochrane review, also showed a statistically significant reduction in pain both during and within 30 min of hysteroscopy, but exploratory analyses were not performed to illustrate the effect of specific local anaesthetics or routes of administration [1]. We were able to expand on this previous Cochrane review by including 13 more trials within our systematic review and eight more studies eligible for meta-analysis of pain scores during and after office hysteroscopy. The greater amount of data available enabled subgroup analyses to be conducted regarding the effect on pain control and the likelihood of vasovagal episodes for specific types of local anaesthetic agent, in addition to the route of administration.

Strengths and weaknesses

In formulating a clinically focused question and performing broad, yet comprehensive searches using a variety of databases, where language restrictions were not applied and reference lists of relevant papers were searched, we are confident that we have effectively minimised the risk of selection bias.

The main limitation of our review relates to the statistical heterogeneity arising from data pooling. By restricting study inclusion to randomised controlled trials, we minimised confounding within trials. However, the observed variation in direction and magnitude of effect between studies is likely to relate to methodological differences in how data were assessed and collected. Sensitivity analyses based upon study quality did not, however, change the overall message. Clinical disparities may also explain the observed heterogeneity and these inconsistencies include populations studied, operative techniques (vaginoscopy, choice of distension media, diagnostic versus operative procedures), concomitant interventions to control pain (e.g. concurrent analgesia, use of cervical preparation), equipment (e.g. endoscope diameter) and operator proficiency.

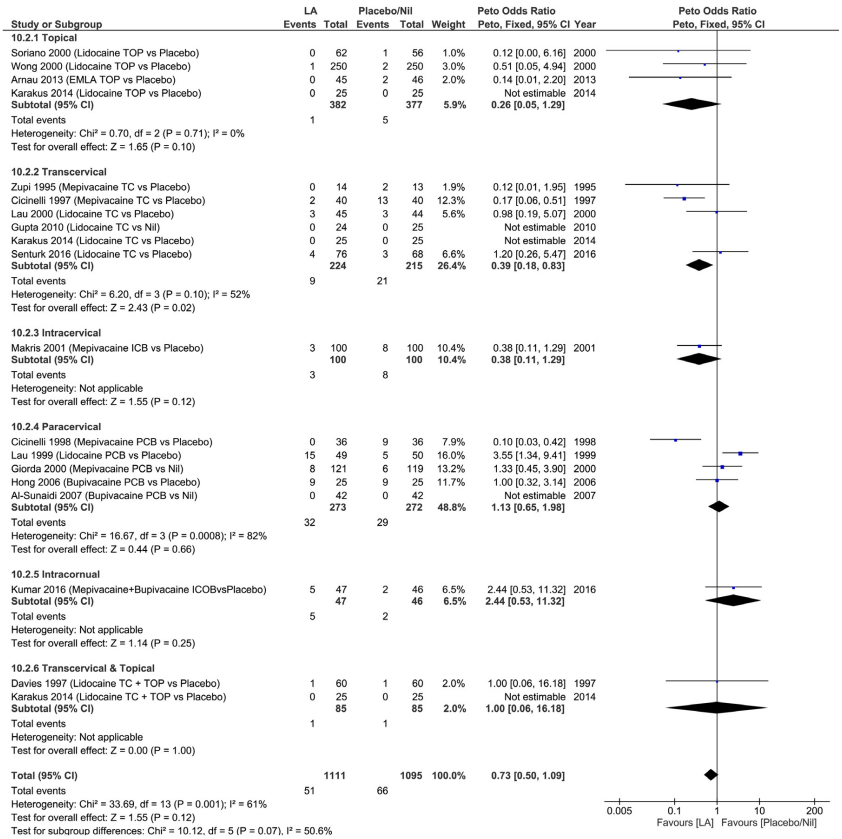

Fig. 9. Incidence of Vasovagal According to Route of Administration.
A forest plot depicting the incidence of vasovagal episodes according to the route of local anaesthetic administered.
LA: local anaesthetic, SD: standard deviation, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

Implications for clinical practice

Local anaesthesia reduces pain both during and after office hysteroscopy. However, the clinical significance of the observed reductions in average pain remain unclear. This is because too few studies evaluated the impact of this pain reduction upon procedure satisfaction / acceptability and no clear improvement in these qualitative parameters were observed. Furthermore, the miniaturisation of hysteroscopes has facilitated 'vaginoscopic' approaches to office hysteroscopy, where genital tract instrumentation is avoided. A recent large randomised controlled trial comparing vaginoscopy with a standard approach to office hysteroscopy (routine insertion of vaginal specula +/- cervical forceps), showed that vaginoscopy was associated with reduced pain and increased acceptability [6]. With the exception of transcervical instillation of local anaesthetic added to fluid distension media (and possibly intracornual blocks), all topical and injectable routes of local anaesthetic administration require passage of a vaginal speculum as a minimum. Thus, any potential benefits of local anaesthesia administration may be offset by the use of smaller diameter hysteroscopes utilising a 'no touch' vaginoscopic technique. The potential benefits, as well as the uncertainties, of local, genital tract anaesthesia on pain reduction, especially if a vaginoscopic approach is to be adopted, should be discussed with women undergoing office hysteroscopic procedures to allow informed decision making.

Implications for future research

There exist a multitude of factors in office hysteroscopy that contribute towards pain; whilst we can attempt to minimise pain caused by procedural factors (e.g. hysteroscope diameter, distension media pressures / temperature etc.), we cannot control for patient factors (e.g. cervical stenosis due to nulliparity and/or menopausal status). Further research is required into the optimal route, dose and timing of local anaesthesia for office hysteroscopy in addition to the particular patient groups who will benefit from its administration. Only seven studies investigated the impact of

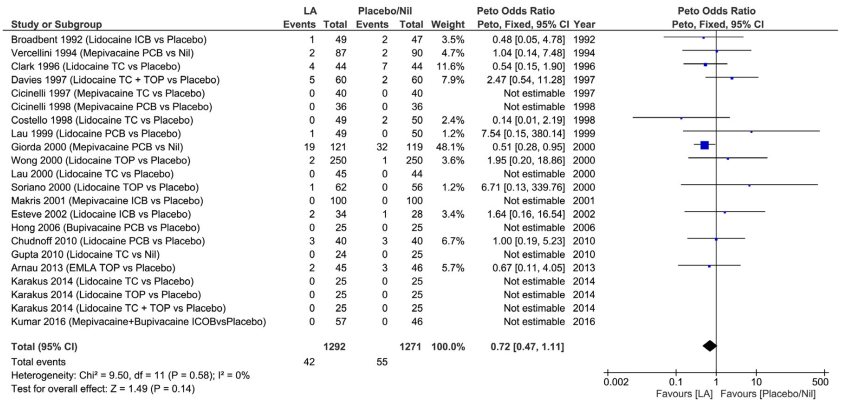

Fig. 10. Incidence of Failure.
A forest plot depicting the incidence of failure amongst all included individual studies.
LA: local anaesthetic, SD: standard deviation, CI: confidence interval, ICB: intracervical block, TC: transcervical instillation, PCB: paracervical block, TOP: topical application, ICOB: intracornual block.

local anaesthesia on pain control for therapeutic procedures alone. More data are therefore required to determine the optimal practice protocols and use of local anaesthesia for operative office hysteroscopic procedures such as polypectomy [50], and endometrial ablation [51], which are being increasingly performed in this setting. More trials are needed to better delineate the type and route of local anaesthesia for these specific office hysteroscopic procedures. Finally, further research is required to understand whether the pain control benefits of local anaesthesia remain apparent with vaginoscopic approaches to office hysteroscopy that avoid genital tract instrumentation

Conclusion

Administration of a local anaesthetic to the genital tract for office hysteroscopy is associated with a reduction in intra- and post-procedural pain, although it does not impact upon the likelihood of vasovagal reactions. The use of local anaesthetic should be discussed with women prior to undergoing office diagnostic and operative hysteroscopic procedures. The benefits of local anaesthesia prior to office hysteroscopy when a vaginoscopic approach is routinely adopted remain unclear. Further research is required to evaluate the effect of local anaesthesia on pain experienced by women undergoing office hysteroscopy to better identify specific patient populations that may benefit most, understand the relative advantages when used for operative as opposed to simply diagnostic procedures, and determine whether the benefits of local anaesthesia remain apparent with vaginoscopy.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest and nothing to disclose. This research has not been presented or published elsewhere. Dr. De Silva is pursuing a funded PhD through the Ambulatory Gynaecology department at Birmingham Women's Hospital, UK. Dr. Smith is funded as a post-doctoral lecturer through the National Institute for Health Research.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.05.062.

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Addendum to Chapter 4

Three additional randomised-controlled trials have been published from this publication of this paper until February 2022.

The first (26) randomised 100 patients undergoing outpatient diagnostic hysteroscopy to either 10ml 2% lidocaine instilled within 1000ml saline given as the distension medium or to placebo (1000ml saline without lidocaine). Although intraprocedural pain scores were not recorded, there was no significant difference between mean pain scores after hysteroscopy (2.6±2.5 vs 3.4±3.1) between the two groups (p=0.75). The proportion of patients who had a satisfaction score >7/10 was higher in the group randomised to intrauterine lidocaine (98% vs 92%) as were the rates of success (96% vs 94%), however, these differences were not significant (p=0.17 and p=0.65, respectively).

The second trial (27) which was a non-inferiority trial evaluating the impact of intracornual/fundal anaesthesia randomised 96 women undergoing outpatient Novasure® endometrial ablation to either a 40ml (2mg/ml) ropivacaine paracervical and 4ml intracornual/fundal block or a 40ml (2mg/ml) ropivacaine paracervical block and 4ml intracornual/fundal saline placebo. There was a significant reduction in intraprocedural pain scores between the two groups when a Faces Pain Score (ruler with a series of faces on scale of 0–10) was used (5.4 vs 4.8 (mean difference -0.6; 95% CI -0.3 to -1.5)) but not when a Numerical Rating Scale was utilised (5.0 vs 3.9 (MD -1.2 ;95% CI 0.1 to -2.2)). Post-

procedural pain at 1 (p=0.159), 6 (p=0.605), and 24 hours (p=0.451) rates of satisfaction, and side-effects (p=0.293) were comparable between groups.

The third trial (28) randomised 260 women undergoing diagnostic outpatient hysteroscopy to either 5ml 2% lidocaine diluted in 15ml saline given transcervically through an embryo transfer catheter by using a posterior vaginal retractor or placebo (20ml saline given the same way). This study found that transcervical lidocaine significantly reduced pain intraprocedurally (1.77±1.088 vs 5.23±1.832; p<0.001), 10 minutes (1.31±1.152 vs 4.27±2.060; p<0.001) and 30 minutes (0.76±0.925 vs 2.98±1.960; p<0.001) after. Transcervical instillation of local anaesthesia also reduced the incidence of vasovagal episodes (p=0.001).

The final trial (29) randomised 156 postmenopausal women undergoing diagnostic hysteroscopy to either a 1000 ml distension medium containing 5ml 2% lidocaine per 250 ml or oral tramadol or placebo. When comparing the lidocaine group against placebo, there was a significant reduction in pain during (MD -1.8 (95%CI -2.9 to -0.7); p<0.001) and 10 minutes (MD -1.8 (95%CI -2.8 to -0.9); p<0.001) after hysteroscopy. Patients randomised to lidocaine were significantly more satisfied (p<0.001). No side-effects with the use of lidocaine were reported.

The findings of these papers do not change our overall conclusions and clinical implications for the use of local anaesthesia for the reduction of pain for outpatient hysteroscopy.

CHAPTER 5: VAGINOSCOPY

This work has been published in the European Journal of Obstetrics & Gynecology and Reproductive Biology; De Silva PM, Carnegy A, Smith PP, Clark TJ. Vaginoscopy for office hysteroscopy: A systematic review & meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020 Sep;252:278-285. doi: 10.1016/j.ejogrb.2020.06.045. Epub 2020 Jun 23. PMID: 32645643 (30).

My role in this publication is as follows: I carried out the literature search, collected the data, undertook the meta-analysis, and wrote the manuscript.

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Full length article

Vaginoscopy for office hysteroscopy: A systematic review & meta-analysis

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ABSTRACT

Objective: To investigate the effect of the vaginoscopic approach to office hysteroscopy on patients' experience of pain, when compared with the traditional approach where a vaginal speculum is used.
Methods: Medline, Embase, CINAHL and the Cochrane library were searched from inception until December 2019, in order to perform a systematic review and meta-analysis of all randomised controlled trials investigating vaginoscopy compared to traditional hysteroscopy on pain experienced by women undergoing diagnostic or operative hysteroscopy in an office setting. Data regarding procedural time, feasibility, incidence of vasovagal reactions and complications, acceptability and satisfaction were also recorded.
Results: The literature search returned 363 results of which seven were selected for systematic review, and six for meta-analysis. The vaginoscopic approach was associated with a statistically significant reduction in pain (4 studies including 2214 patients; SMD -0.27, 95 % CI -0.48 to -0.06), procedural time (6 studies including 2443 patients; SMD -0.25, 95 % CI -0.43 to -0.08) and the incidence of vasovagal episodes (3 studies including 2127 patients; OR 0.35; 95 % CI 0.15 to 0.82). Failure rates between the two techniques were similar (p = .90). No study reported significant differences in complications or patient or clinician acceptability or satisfaction.
Conclusion: Clinicians performing office hysteroscopy should use the vaginoscopic technique because it makes office hysteroscopy quicker, less painful and reduces the likelihood of inducing a vasovagal reaction. The traditional approach should only be used when vaginoscopy fails or when the need for cervical dilatation is anticipated.

Introduction

Hysteroscopy is increasingly being performed in conscious women in an office setting due to its lower complication rate, quicker recovery and greater cost-effectiveness compared to the formal theatre setting under general anaesthesia [1]. Induced pain is the greatest barrier to successfully performing hysteroscopic procedures in an office setting because it can lead to poor patient experience or procedural failure [2]. Pain arises from genital tract instrumentation (vaginal speculum insertion +/- cervical instrumentation +/- cervical dilatation), uterine cavity distension and disruption to the endometrium caused by the removal of intrauterine pathology [3]. Minimizing pain is of paramount importance in improving the acceptability, feasibility and efficiency of office hysteroscopy.

Vaginoscopy is an alternative method for performing hysteroscopy. The technique negates the need for the traditional approach which employs the routine use of a vaginal speculum with or without instruments applied to the cervix. Vaginoscopy involves inserting the hysteroscope into the lower vagina, which is then hydro-distended with the distension medium. The hysteroscope can then be manipulated to identify the external cervical os, to allow for passage into the cervical canal and uterine cavity through gentle movements.

A previous systematic review investigating the impact of vaginoscopy against routine speculum use for diagnostic office hysteroscopy was published a decade ago [4]. In light of the wider adoption of office hysteroscopy and increasing operative interventions in this setting [5,6], we undertook an updated systematic quantitative review to investigate the relative effect of vaginoscopy on pain, feasibility, safety and acceptability compared to conventional approaches.

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Methods

Protocol and guidance

The protocol for this study was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42019138156) [7]. Guidance was provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [8], and the Cochrane Handbook for Systematic Reviews of Interventions [9].

Inclusion criteria

We included trials investigating women undergoing office diagnostic and/or therapeutic hysteroscopy who were randomized to undergo hysteroscopy performed with the vaginoscopic technique or the traditional technique, using a vaginal speculum, where a pain outcome was collected.

Exclusion criteria

We excluded conference abstracts (where no full text was available), case reports, case series and observational studies.

Outcomes

The primary outcome was pain. Secondary outcomes included side-effects (symptoms), complications (trauma or adverse procedural events), failure rates, procedural time, and the acceptability and/or satisfaction of patients and clinicians performing hysteroscopy. Data were also extracted regarding the use of conscious sedation, analgesia, local anaesthesia, cervical preparation, cervical dilatation, distension medium and instrument size to account for differences between studies.

Search strategy

A combination of the keywords “hysteroscopy”, “vaginoscopy”, “no*touch”, “outpatient”, “ambulatory”, “office” and their associated medical subject headings (MeSH) were used to search Medline, Embase and CINAHL from inception to December 2019, through the National Institute for Health and Care Excellence (NICE) Healthcare Databases Advanced Search (HDAS) platform. The key words “hysteroscopy”, “vaginoscopy” and “no*touch” were used to search the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to December 2019. Limits or filters were not applied. The bibliographies of included papers were scanned and additional studies were included for review if deemed appropriate, in order to widen our search.

Study selection

Two reviewers (PD and AC) independently screened all titles and abstracts after using the HDAS platform to remove duplicates from the citations received from the Medline, Embase and CINAHL databases. Duplicates from the CENTRAL search were manually excluded. After the exclusion of irrelevant titles and abstracts, the remaining full texts were reviewed in order to select final eligible studies. A third reviewer (PS) was invited to arbitrate where there were discrepancies that were not resolved by consensus.

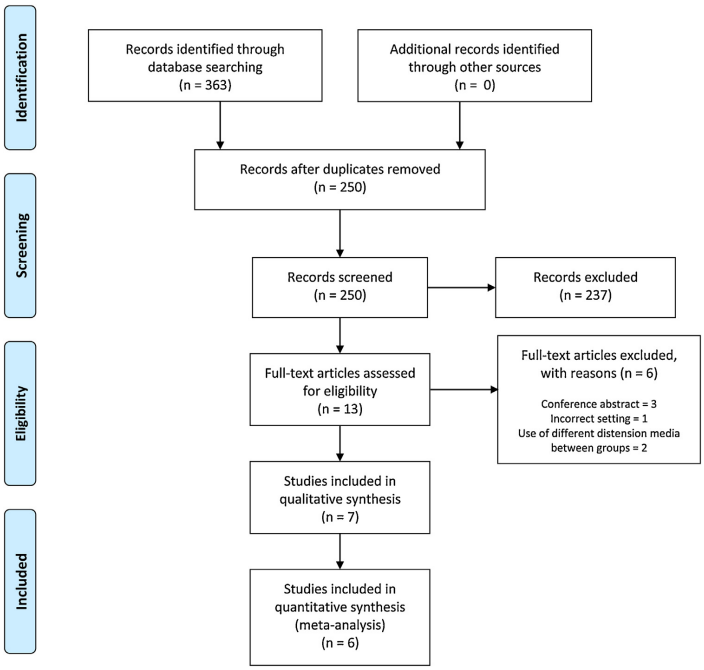

Fig. 1. PRISMA (Preferred Reporting Items of Systematic Reviews and Meta Analyses) flow diagram.

Data collection process

Two reviewers (PDS and AC) independently extracted data from all included trials using a standardised data extraction form created on Microsoft Excel. Intra-procedural and post-procedural pain scores were obtained, in addition to procedural time and data regarding side-effects, complications, technical failure, and the acceptability and/or satisfaction of the procedure to both patients and clinicians. Failure and complications were only recorded if directly related to the technique used e.g. bleeding from the cervix during the traditional approach would count whereas tubal spasm at sterilization would not. Some studies scored pain according to each of the phases of hysteroscopy separately; if diagnostic, the intra-procedural score related to the score given during inspection of the uterine cavity and if operative, it related to the score given during the given procedure e.g. pain score during endometrial polyp removal. The post-procedural score related to the pain score recorded after the end of hysteroscopy; if multiple post-operative pain scores were reported, then the highest pain score was used. Authors of studies that failed to report means and standard deviations of pain scores [10–12] and procedural time [11,13] were contacted for their data in order to increase the number of studies that could be entered into the meta-analysis.

Assessment of risk of bias

Two independent reviewers (PDS and AM) used the Cochrane Collaboration Risk of Bias 2 tool to examine the risk of bias of the included trials on an intention-to-treat basis [14]. Again, a third independent reviewer (PS) was involved if disagreements were not resolved by consensus.

Data synthesis

RevMan (version 5.3.5) was used to perform all statistical analyses [15]. Meta-analysis was conducted on an intention-to-treat basis. Means and standard deviations were used to calculate standardised mean differences (SMD) and their 95 % confidence intervals for the continuous outcomes of pain and procedural time. Random-effects summary estimates were calculated from inverse-variance weighting. For the dichotomous outcomes of failure and side-effects, Peto odds ratios were calculated because of the low incidence of events in each arm of the studies. A P-value less than 0.05 was considered significant. Heterogeneity of the treatment effects were displayed graphically by forest plots and statistically analysed using the chi-squared test, in consistency with the Cochrane Handbook [9].

Table 1
Hysteroscopic Technique in Vaginoscopic and Traditional Approaches.

Year	Author	Group 1 (Vaginoscopy)	Group 2 (Traditional)	Method of Recording Pain Score
2005	Sharma et al	Vaginoscopy	Speculum Routine cervical instrumentation Cervical dilatation only if required Intracervical prilocaine/felypressin only if requested by patient	Patients were asked to complete a postprocedure questionnaire immediately following the investigation scoring their discomfort at various phases of the hysteroscopy on a 10 cm VAS.
2006	Garbin et al	Routine vaginal and cervical disinfectant with swab forceps, Vaginoscopy	Speculum Routine cervical disinfectant with swab forceps Routine cervical instrumentation	Immediately after the procedure, patients rated their pain on a 10 point VAS in an interview with the nurse outside the doctor's presence.
2006	Sagiv et al	Routine vaginal disinfectant with swab forceps, Vaginoscopy	Speculum Unclear regarding the use of disinfectant Routine cervical instrumentation Routine intracervical mepivacaine	A 10 cm VAS score was used to quantify the intensity of pain experienced during and after the procedure.
2006	Guida et al	Vaginoscopy	Speculum Cervical instrumentation only if required	During the different phases of hysteroscopy, patients were asked to record their degree of pain with a 5 point VAS. A second operator, next to the patient, quizzed the patient during the procedure.
2012	Ngu et al	Vaginoscopy	Speculum Routine cervical instrumentation Cervical dilatation only if required	Women were asked to give pain scores on a 10 point VAS immediately after the procedure to a nurse who scored their degree of pain during hysteroscopy; during endometrial biopsy, if performed, and overall pain during the procedure.
2015	Chapa et al	Vaginoscopy	Speculum Routine cervical instrumentation Routine paracervical mepivacaine	Patient were asked to rate their pain score via a 10 cm VAS. The discomfort in each stage and overall was rated after the procedure by the patient but recorded by an independent research assistant.
2019	Smith et al	Vaginoscopy	Speculum Routine cervical disinfectant Cervical instrumentation only if required Intracervical mepivacaine only if required	Procedural pain was collected on an iPad mini™ (Apple™, Cupertino, CA, USA) device. A novel system was designed, programming the iPad mini™ device to allow easy patient input. Pain was assessed using a slider on a 10 cm VAS.

Results

Study selection

The literature search returned 363 records, of which 113 were duplicates (Fig. 1). The titles and abstracts of the remaining 250 studies were screened to leave 13 full-text articles which were assessed for eligibility. Due to reasons listed in Fig. 1, six studies were excluded, leaving seven studies suitable for systematic review and meta-analysis.

Study characteristics

Whilst six studies investigated a mixture of both women in reproductive and post-reproductive age [10,12,13,16–18], only one study included women of reproductive age only [11]. Six studies examined the role of vaginoscopy in diagnostic hysteroscopy [10,12,13,16–18], with only one investigating its use in therapeutic hysteroscopy for hysteroscopic sterilisation [11]. All hysteroscopes were rigid, ranging in diameter (including the outer sheath) from 2 mm to 5 mm. All studies adopted the use of normal saline as a distension medium and none used conscious sedation or cervical preparation. Only one study administered a preprocedural analgesic to patients randomized to both intervention groups [11].

Table 1 outlines the techniques adopted for both vaginoscopic and traditional approaches amongst included studies. Three studies preceded hysteroscopy with vaginal and/or cervical disinfectant in patients; whilst one study performed this for patients randomized to both vaginoscopic and traditional approaches [16], the other two only performed this for patients randomized to either the vaginoscopic approach [17], or the traditional approach [13]. Whilst all studies employed the use of a vaginal speculum in the traditional technique, five studies routinely used cervical instrumentation (e.g. tenaculum, Littlewood's forceps etc) [11,12,16–18], and two only used this if required [10,13]. Two studies incorporated the administration of a parenteral local anaesthetic into their traditional technique as standard [11,17]. Cervical dilatation and the use of parenteral local anaesthesia was only performed, if required, in three [12,13,18] and two [12,13] studies, respectively.

Four studies performed statistical analysis according to the intention-to-treat principle where all patients were analysed according to the group they were randomized to [12,13,16,17], even if conversion to the use of the other technique proved successful [12,13,17]. In the other three studies, patients where clinicians failed to perform hysteroscopy using their allocated approach successfully were excluded from analysis [10,11,18].

Study bias

The risk of bias for each study according to each methodological characteristic is displayed in Fig. 2. Only one study was of 'high risk' of bias [10], due to the exclusion of patients who failed any form of hysteroscopy from the final analysis and the failure to clearly report their results. Three studies showed 'some concern' [11,12,18], due to inconsistencies in the results displayed [11,12] and/or the exclusion of patients allocated to vaginoscopy due to failure [11,18].

Effect on pain

All studies asked patients to score their pain according to a visual analogue score (VAS); in five studies this was on a 10 cm/10-point scale [11–13,16–18], and in one a 5-point scale was used [10]. All studies reported pain scores either as means with standard deviations [13,16–18], medians with ranges [11,12,16], or as medians with 95 % confidence intervals [10]. One paper depicted pain scores graphically, which were transcribed for the purpose of data collection [10]. The authors of the papers that presented pain scores as medians either did not reply [10,12], or no longer had the required data available [11].

Meta-analysis of the four studies that reported pain scores as means and standard deviations [13,16–18], including 2214 patients, showed a statistically significant reduction in intra-

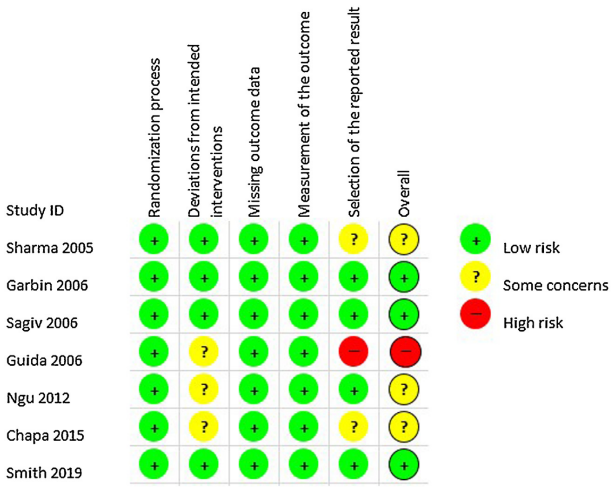

Fig. 2. Risk of Bias of Individual Studies.

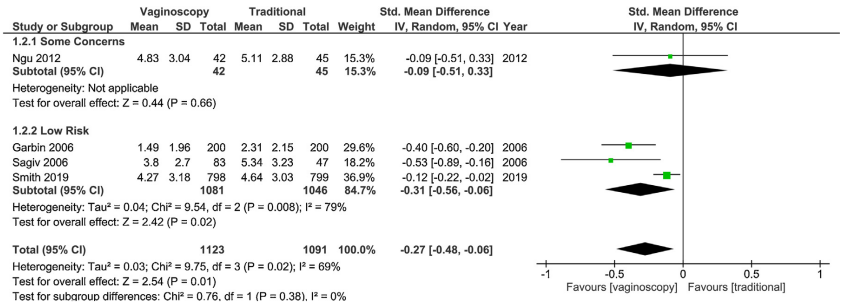

Fig. 3. Intra Procedural Pain Scores According to Hysteroscopic Approach.

procedural pain; standard mean difference (SMD) -0.27, 95 % confidence interval (CI) -0.48 to -0.06 (Fig. 3). Substantial statistical heterogeneity was observed as per the I^2 value of 69 %. However, whilst stratifying meta-analysis to studies with a 'low risk' of bias increased the magnitude of effect (SMD -0.31) [13,16,17], it did not reduce the degree of inconsistency (95 % CI -0.56 to -0.06). Only one study, inclusive of 130 patients, reported post-procedural pain scores suitable for analysis [17]; this also showed a statistically significant reduction in pain recorded 15 min after hysteroscopy in favour of vaginoscopy; SMD -0.55, 95 % CI -0.91 to -0.18.

Procedural time

All included studies reported procedural time. Four studies provided means with associated standard deviations [10,16–18], and one study provided means and standard errors of the mean (SEM) [12], from which standard deviations could be calculated. Two studies presented procedural times in a format not suitable for meta-analysis; the first providing ranges instead of standard deviations [11], and the second providing medians and interquartile ranges [13]; authors of both papers were contacted for means and standard deviation, of which the latter replied. Six studies, inclusive of 2443 patients, showed that vaginoscopy was associated with a significant reduction in procedural time [10,12,13,16–18]; SMD -0.25, 95 % CI -0.43 to -0.08 (Fig. 4).

Side effects & complications

Meta-analysis of the three studies reporting the incidence of side-effects [13,16,17], inclusive of 2127 patients, showed a statistically significant reduction associated with vaginoscopy; OR 0.35, 95 % CI 0.15 to 0.82 (Fig. 5). All reported side-effects were vasovagal episodes (i.e. signs and symptoms including nausea, vomiting, sweating, dizziness, vertigo, bradycardia, hypotension). Of the six studies that reported complications [10,11,13,16–18], one study reported their presence [13]. Post-procedural infection was reported in 27/798 patients who had vaginoscopy compared with 31/799 patients who underwent the traditional approach (p = .60). All other complications occurred in patients randomized to the traditional technique (cervical trauma (n = 2), admission for analgesia (n = 2) and post-procedural haemorrhage (n = 1)).

Failure rates

Meta-analysis of all studies [10–13,16–18], inclusive of 2727 patients, did not show a clear benefit of either vaginoscopy or the traditional approach in reducing technical failure rates; OR 0.98, 95 % CI 0.69–1.38 (Fig. 6). Cervical stenosis (n = 51), pain (n = 7) and the inability to gain access to the cervical canal (n = 5; reasons given including uterine retroversion and vaginal prolapse) were cited as reasons for failure in vaginoscopy. Pain (n = 31), inability to gain access to the cervical canal (n = 20), cervical stenosis (n = 9), vaginism (n = 2) and haemorrhage (n = 2) were cited for reasons for failure in the traditional approach. In the six studies [10–13,17,18], where when the procedure failed with the allocated treatment, the other technique was used, leading to the procedure being ultimately successful in the majority of cases; 95/127 (75 %).

Acceptability & satisfaction

Only four studies reported on patient acceptability and/or satisfaction [12,13,17,18], of which three studies performed

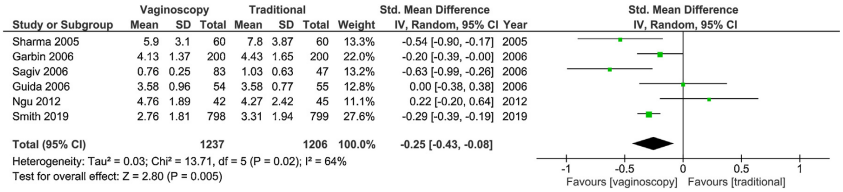

Fig. 4. Procedural Time According to Hysteroscopic Approach.

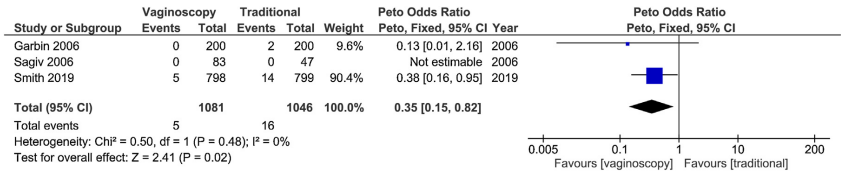

Fig. 5. Incidence of Side Effects According to Hysteroscopic Approach.

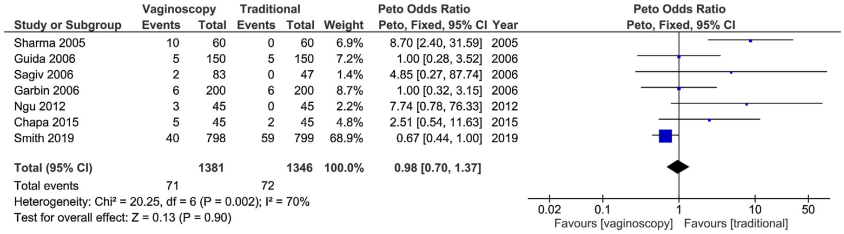

Fig. 6. Incidence of Failure According to Hysteroscopic Approach.

individual statistical analyses revealing no significant difference in levels of patient satisfaction and/or acceptability between either vaginoscopy or the traditional approach [12,13,17]. Data was provided in a heterogeneous manner which did not allow meta-analysis of results. Hysteroscopist acceptability and/or satisfaction was only commented upon in one study [16], which found no significant difference in the ease of cervical passage or the quality of hysteroscopic examination.

Discussion

Principal findings

The vaginoscopic approach is associated with a reduction in pain, procedural time and side-effects, when compared to the traditional approach to office hysteroscopy, which employs the use of a vaginal speculum. Only one study reported the incidence of complications between these two techniques, where the chance of post-procedural infection did not differ; otherwise all other complications were attributed to the traditional approach. Procedural success (i.e. feasibility) was comparable between techniques, and where one technique failed, the other proved successful in 75 % of cases. No superiority between techniques could be found with regards to patient and clinician acceptability or satisfaction.

Comparison with other studies

The only previous systematic-review and meta-analysis investigating the impact of the vaginoscopic approach to office hysteroscopy was published a decade ago [4]. In this updated meta-analysis, we excluded two of their studies (due to differences in distension media between randomized groups [19] and the inclusion of a conference abstract [20]) and included three more studies [11,13,18]. Our updated findings agree with the previous systematic review regarding vaginoscopy being associated with a significant reduction in intra-procedural pain with no significant difference found regarding procedural feasibility. We, however, were able to meta-analyse more data with regards to post-procedural pain, side-effects and procedural time.

Strengths and weaknesses

The search strategy was performed to reduce the risk of selection bias by devising a clinically focused question, by using broad search terms without applying filters or limits and by scanning reference lists of included studies for further potential sources of data. Minor procedural differences existed in patients randomized to traditional hysteroscopy using a vaginal speculum, where cervical instrumentation and occasionally, parenteral local anaesthesia, were sometimes applied. We felt that rather being a limitation, the inclusion of these additional steps reflects differences in practice of the traditional approach amongst hysteroscopists globally.

The main limitations of this study correlate to heterogeneity associated with the pooling of data and methodological flaws within included primary studies. In reporting separate subgroups according to risk of bias, we were unable to reduce statistical heterogeneity when restricting data pooling to studies with low risk of bias. Heterogeneity, however, was not always attributable to methodological weaknesses but, instead, explained by clinical differences in the study population, use of analgesia and/or local anaesthesia, instrument diameter and operator proficiency.

Implications for clinical practice

Clinicians should be advised to adopt the vaginoscopic approach to office hysteroscopy and this recommendation should be incorporated into evidence-based guidance [21]. Vaginoscopy may minimise pain and facilitate hysteroscopic

procedures because it allows greater manoeuvrability of the hysteroscope within the uterine cavity because there is no vaginal speculum restricting movement. This greater manoeuvrability is highly advantageous in women who are unable to lie supine due to medical comorbidities (e.g. heart failure, respiratory disease and obesity), where such procedures can only be performed in an ambulatory setting due to the risks of a general anaesthetic, and in women with restricted hip flexion/abduction or acutely flexed uteri. Additionally, nulliparous women, those suffering from vaginismus, those who have not had sexual intercourse and those with genital tract atrophy will also likely benefit the most from the vaginoscopic approach, where vaginal distension is minimized.

Traditional hysteroscopy, involving the use of a vaginal speculum and possible cervical instrumentation should be reserved for patients where vaginoscopy fails, either because visualising the cervical canal is difficult (e.g. previous cone biopsy) or because cervical stenosis is present. In the case of the latter, a speculum will also allow for the administration of local cervical anaesthesia prior to cervical dilatation. Some studies have reported routinely removing the speculum after applying local anaesthesia [22–25] in an attempt to invoke the benefits of the vaginoscopic approach.

Implications for future research

All studies that contributed to the meta-analysis of pain scores during office hysteroscopy evaluated vaginoscopy for diagnostic procedures only. More research is therefore required to identify the role of the vaginoscopic approach in reducing pain for operative office hysteroscopy. Such procedures invariably require the use of larger diameter hysteroscopic systems, where traversing the narrow cervical canal can be harder and the requirement for local cervical anaesthesia and cervical dilatation is more likely. Thus, the advantages of vaginoscopy may be negated if a substantial proportion of operative office procedures require passage of a vaginal speculum, even if genital tract instrumentation is removed following cervical dilatation. Randomized controlled trials that investigate the use of the vaginoscopic approach for flexible hysteroscopy are required, as all included studies used rigid hysteroscopes. In addition, further research is needed which reports on post-procedural pain, complications, acceptability and satisfaction in a standardized manner, as the proportion of existing studies reporting these outcomes is limited.

Conclusion

The vaginoscopic approach to office hysteroscopy is quicker, less painful and reduces the likelihood of inducing a vasovagal reaction, when compared to the traditional approach, which employs the use of a vaginal speculum and/or cervical instrumentation and/or local anaesthesia. A vaginal speculum should only be used either when vaginoscopy fails or when the need for cervical dilatation is anticipated. Further research is required in order to draw conclusions on the effect of vaginoscopy when using flexible hysteroscopes as well as on post-procedural pain, complications, acceptability and satisfaction.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest and nothing to disclose. This research has not been presented or published elsewhere.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.06.045.

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CHAPTER 6: DISTENSION MEDIUM TYPE, PRESSURE AND TEMPERATURE

This work has been published in the Journal of Minimally Invasive Gynecology; De Silva PM, Stevenson H, Smith PP, Justin Clark T. A Systematic Review of the Effect of Type, Pressure, and Temperature of the Distension Medium on Pain During Office Hysteroscopy. J Minim Invasive Gynecol. 2021 Jun;28(6):1148-1159.e2. doi: 10.1016/j.jmig.2021.01.003. Epub 2021 Jan 11. PMID: 33444792 (31).

My role in this publication is as follows: I carried out the literature search, collected the data, undertook the meta-analysis, and wrote the manuscript.

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Review

A Systematic Review of the Effect of Type, Pressure, and Temperature of the Distension Medium on Pain During Office Hysteroscopy

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ABSTRACT **Objective:** To identify the optimal distension medium type, pressure, and temperature to minimize pain during office hysteroscopy.

Data Sources: MEDLINE, EMBASE, CINAHL, and CENTRAL were searched from inception to January 29, 2020.

Methods of Study Selection: We included randomized controlled trials in which women undergoing office hysteroscopy were randomized to either a distension medium type, pressure, or temperature against a suitable control, where pain was an outcome. Data regarding feasibility, visualization, complications, and satisfaction were also collected.

Tabulation, Integration, and Results: The literature search returned 847 studies, of which 18 were included for systematic review and 17 for meta-analysis. There was no significant difference in intraprocedural pain when comparing the use of normal saline against carbon dioxide (standardized mean difference [SMD], 0.12; 95% confidence interval [CI], 0.36 to 0.13). Subgroup analysis of high-quality studies revealed a statistically significant reduction in postprocedural pain with normal saline (SMD, 0.65; 95% CI, 1.14 to 0.16). Side effects were less frequent (Peto odds ratio, 0.29; 95% CI, 0.20 0.40) and patient satisfaction was higher (SMD, 1.39; 95% CI, 0.51 2.28) with normal saline compared with carbon dioxide. Pressures of ≤40 mm Hg reduced intraprocedural pain (SMD, 0.67; 95% CI, 1.09 to 0.26) at the expense of a higher proportion of unsatisfactory views (81% 89% at ≤40 mm Hg vs 95% 99% at ≥50 mm Hg). Postprocedural pain was reduced with lower filling pressures. Warming saline did not reduce intraprocedural pain (SMD, 0.59; 95% CI, 0.14 to 1.33).

Conclusion: Normal saline, instilled at the lowest pressure to acquire a satisfactory view, should be used for uterine distension during office hysteroscopy to minimize pain. Journal of Minimally Invasive Gynecology (2021) 00, 1 12. © 2021 AAGL. All rights reserved.

Keywords: Outpatient hysteroscopy; Surgery; Saline; Carbon dioxide

Office hysteroscopy is widely used for the investigation and treatment of uterine factor subfertility and abnormal uterine bleeding. This setting negates the need for a formal operating room and general anesthesia, reducing the time spent in hospital and thus increasing efficiency and reducing overall healthcare costs [1]. Instillation of a distension medium from the hysteroscope is required to visualize the uterine cavity. This, however, causes pain from T10 to L1 nerve roots, and passage of distension media into the peritoneal cavity through the fallopian tubes may be associated with shoulder tip pain. In addition, cervical stimulation may cause vasovagal side effects mediated by parasympathetic nerve roots S2-4 [2].

The greatest barrier to delivering office hysteroscopy is pain [3,4]; however, conflicting evidence exists with regard to the optimal distension medium for the reduction of pain during office hysteroscopy [5,6]. Questions also remain regarding the optimal uterine distension pressure to minimize pain while ensuring a satisfactory view and the role of warming distension media above room temperature [7]. We

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therefore performed a systematic review and meta-analysis investigating the impact of distension medium type, pressure, and temperature for both diagnostic and operative office hysteroscopy, primarily on pain, but also on procedural success and duration, image quality, complications, and satisfaction and/or acceptability from both the patient's and operator's perspectives.

Material and Methods

Protocol and Guidance

The study protocol was registered on PROSPERO (CRD42019138160) [8], with guidance from Cochrane [9].

Inclusion Criteria

Randomized controlled trials investigating women undergoing diagnostic and/or operative office hysteroscopy randomized to either different types of distension media (e.g., fluid or gas) or different methods of administration (e.g., flow rates, pressures, and temperatures) against a suitable control were included for review.

Exclusion Criteria

Conference abstracts, case reports, case series, and observational studies were excluded.

Outcomes

The primary outcome was pain. Secondary outcomes included data regarding hysteroscopic view, procedural time, side effects, complications, failure rates, and the acceptability and/or satisfaction of patients and hysteroscopists.

Search Strategy

MEDLINE, EMBASE, and CINAHL were searched from inception to January 29, 2020, using the keywords "hysteroscopy," "distension medi*," "saline," "sodium chloride," "carbon dioxide," "glycine," "dextrans," "mannitol," "sorbitol," "dextrose," "glucose," "outpatient," "ambulatory," and "office" and associated medical subject headings through the National Institute for Health and Care Excellence Healthcare Databases Advanced Search (HDAS) platform. CENTRAL was searched from inception to January 29, 2020, using the keywords "hysteroscopy," "distension," "saline," "carbon," "glucose," "mannitol," "sorbitol," and "dextr*." No restrictions were applied. Bibliographies of included papers were scanned to include appropriate additional studies.

Study Selection

Duplicates from MEDLINE, EMBASE, and CINAHL were removed using HDAS. Duplicates from the CENTRAL database were manually excluded by 2 independent reviewers (PDS and HS). The same reviewers removed irrelevant titles and abstracts of the remaining papers through HDAS and CENTRAL. Finally, the remaining full texts were reviewed to select eligible studies for systematic review. A third independent reviewer (PS) was invited to arbitrate any disagreements.

Data Collection

Data from the included trials were extracted by 2 independent reviewers (PDS and PS) into a standardized data extraction form. Intraprocedural and postprocedural pain scores, hysteroscopic view, procedural time, side effects, complications, failure, and the acceptability and/or satisfaction of patients and hysteroscopists were recorded. Some studies scored intraprocedural pain according to separate phases of hysteroscopy; if diagnostic, the score given during uterine cavity inspection was recorded and, if operative, the score given during the operative phase was recorded (e.g., at endometrial polypectomy). The postprocedural score was recorded for studies scoring pain felt after the end of hysteroscopy; where multiple pain scores were given at different timings after hysteroscopy, the highest set of pain scores was recorded. Authors of studies in which means and standard deviations for continuous outcomes were not clearly presented were contacted for their data for meta-analysis [10,11], with no success. Data were also extracted regarding the use of conscious sedation, analgesia, cervical preparation, cervical dilatation, local anesthesia, hysteroscopic approach, and instrument diameter to identify differences in individual study methodology.

Assessment of Risk of Bias

Two independent reviewers (PDS and PS) examined the risk of bias of all included trials on an intention-to-treat basis using the Cochrane Risk of Bias 2 tool [12]. A third independent (TJC) reviewer was involved if differences in bias assessment could not be resolved by consensus.

Data Synthesis

RevMan (version 5.3.5) was used to perform all statistical analyses on an intention-to-treat basis [13]. Continuous outcomes were evaluated using standardized mean differences (SMDs) and their 95% confidence intervals (CIs). Random-effects summary estimates were calculated from inverse-variance weighting. Peto odds ratios (ORs) were calculated to display dichotomous outcomes because of the low incidence of events in each arm of the studies. A p value $<.05$ was considered significant. Heterogeneity of

treatment effects was displayed graphically using forest plots and statistically analyzed using the chi-square test.

Results

Study Selection

Fig. 1 summarizes the study selection process.

Study Characteristics

Table 1 summarizes the study characteristics of all included studies.

Study Bias

The risk of bias for each study is depicted in Fig. 2. Issues with the "randomization process" produced the most bias within the included studies. In the 3 studies in which this was categorized as "high risk of bias," there was no random element used in generating the allocation sequence [11,14,15]. In the 3 other trials that had "some concerns," one did not comment on their method of randomization [16], another did not provide baseline characteristics between groups, nor explain the differences in group sizes [17], and the other did not clearly document the actual distension pressures that patients were randomized to [18]. Failure to analyze patients who were randomized to their allocated group resulted in 3 studies having "some concerns" with regard to "deviations from intended interventions" [16,17,19]. Misallocation of failed hysteroscopies to a randomized group led to "some concerns" in "missing outcome data" [14,17]. Poor clarity over the proportion of women receiving analgesia between groups caused "some concerns" in "measurement of the outcome" [20].

Impact on Pain

A total of 15 studies reported pain scores as means and standard deviations [10,11,15 18,20 29], one provided raw data by which these could be calculated [19], one displayed medians and interquartile ranges [10], and one study which reported means mistakenly reported standard

Fig. 1

Preferred reporting items for systematic reviews and meta-analyses flow diagram of the study selection process.

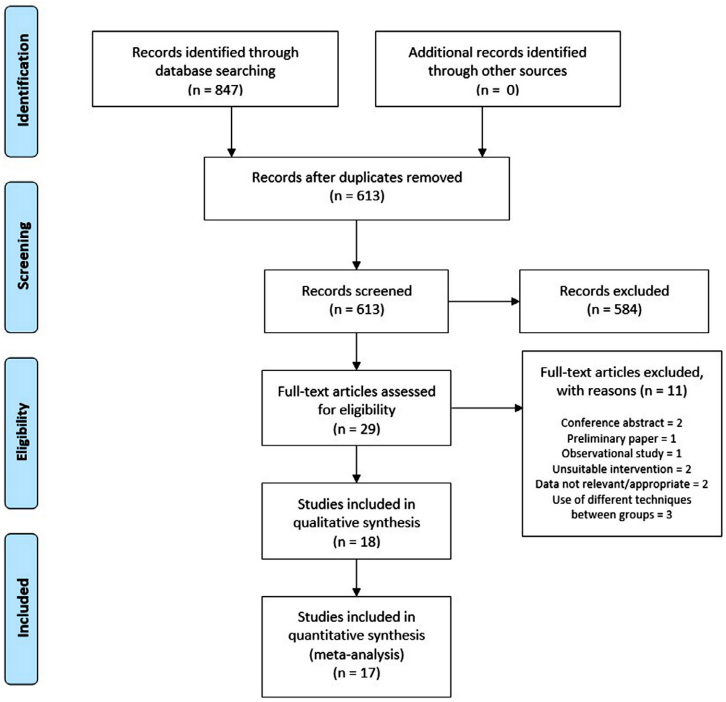


Table 1

Study characteristics of included studies

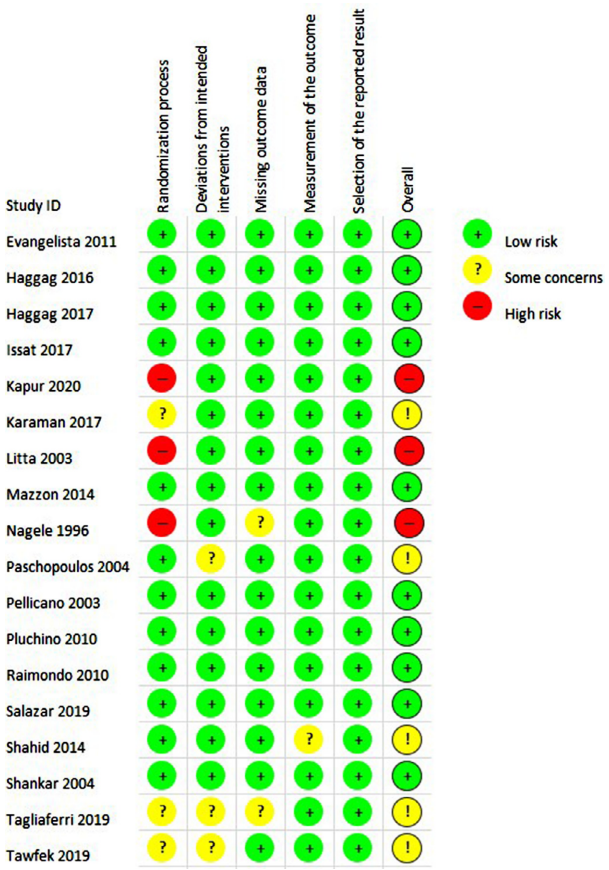
Year	Lead author	Comparison	Population	Procedure type	Group 1	Group 2	Group 3	Cervical preparation	Conscious sedation	Analgesia	Local anesthesia	Cervical dilatation	Approach	Instrument diameter
1996	Nagele [14]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic and therapeutic	NaCl at 150−250 mm Hg	CO_2 ≤ 120 mL/min at 100 mm Hg		N	N	N	Y, lidocaine with adrenaline ICB, if required	Y, if required to 5 mm to 6 mm	Speculum	5.5-mm diagnostic, 7-mm operative
2003	Litta [15]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 100 mm Hg	CO_2 at 40 mL/min ≤ 100 mm Hg		N	N	N	N	N	Speculum	2.9 mm
2003	Pellicano [21]	Media type	Premenopausal women with primary infertility	Diagnostic	NaCl at 80 mm Hg −120 mm Hg	CO_2 ≤ 50 mL/min ≤ 100 mm Hg		N	N	N	N	N	Vaginoscopy	5 mm
2004	Paschopoulos [19]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 40 mm Hg to 80 mm Hg	CO_2 at 25 mL/min at 40 mm Hg−100 mm Hg		N	N	N	N	Y, if required	Vaginoscopy	2.8 mm
2004	Shankar [22]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 150 mm Hg −20 mm Hg	CO_2 ≤ 100 mL/min ≤ 100 mm Hg	500 mL NaCl with 2% lignocaine (20 mL/mL)*	N	N	N	Y, 0.2 to 0.5 mL 4% prilocaine ICB for vulsellum	Y to 4-mm Hegar	Speculum	3.5 mm
2010	Pluchino [23]	Media type	Premenopausal women with primary infertility	Diagnostic	NaCl at 100 mm Hg	CO_2 ≤ 50 mL/min ≤ 100 mm Hg		N	N	N	N	N	Vaginoscopy	3.5 mm (A) 5 mm (B)
2010	Raimondo [24]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl ≤ 100 mm Hg	CO_2 at 80 mL/min ≤ 100 mm Hg		N	N	N	N	N	Vaginoscopy	5.1 mm
2014	Mazzon [25]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 80 mm Hg	CO_2 at 30 mL/min ≤ 75 mm Hg		N	N	N	N	N	Vaginoscopy	5.1 mm
2019	Tagliaferri [17]	Media type	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 100 mm Hg	CO_2 ≤ 60 mL/min ≤ 100 mm Hg		N	N	N	N	N	Vaginoscopy	3.5 mm or 5 mm
2014	Shahid [20]	Pressure	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 40 mm Hg	NaCl at 70 mm Hg	NaCl at 100 mm Hg	N	N	Y, most given 500-mg PO mefenamic acid ≥ 1 h before, unless contraindicated	N	N	Speculum	3.5 mm
2016	Haggag [26]	Pressure	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 30 mm Hg	NaCl at 50 mm Hg	NaCl at 80 mm Hg	N	N	Y, 100 mg PO diclofenac 1 h before	N	N	Vaginoscopy	3.8 mm
2017	Haggag [27]	Pressure	Premenopausal, postmenopausal, nulliparous and parous women	Therapeutic	NaCl at 40 mm Hg	NaCl at 60 mm Hg	NaCl at 80 mm Hg	N	N	Y, 100 mg PO diclofenac 1 h before	N	N	Vaginoscopy	5 mm
2017	Karaman [18]	Pressure	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at lower pressures (30 mm Hg, 40 mm Hg, 50 mm Hg)	NaCl at higher pressures (70, 80, 100 mm Hg)		N	N	Y, 500 mg PO mefenamic acid > 30 min before	N	N	Vaginoscopy	5 mm
2011	Evangelista [28]	Temperature	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic	NaCl at 28°C, gravity-fed at 1 5 m	NaCl at 37 5°C, gravity-fed at 1.5-m		N	N	N	N	N	Vaginoscopy	2.9 mm
2019	Tawfek [16]	Temperature	Women between 20 and 40 years old, nulliparous and parous women	Diagnostic	NaCl at 28°C, at 100 mm Hg −120mmHg	NaCl at 37 5°C, at 100 −120mmHg		N	N	N	N	N	Vaginoscopy	4 mm
2020	Kapur [11]	Temperature	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic and therapeutic	NaCl at 25°C, gravity-fed at 1 5 to 200 mm Hg	NaCl at 37°C, gravity-fed at 1.5 to 200 mm Hg		N	N	Y, Ibuprofen 100 mg PO 60 min before	N	N	Vaginoscopy	3.5 mm
2017	Issat [10]	Temperature	Premenopausal, postmenopausal, nulliparous and parous women	Diagnostic and therapeutic	NaCl at 25°C to 120 mm Hg	NaCl at 36°C to 120 mm Hg		N	N	N	N	N	Vaginoscopy	3.2 mm
2019	Salazar [29]	Temperature	Premenopausal and postmenopausal women	Therapeutic	NaCl at 20.5°C−22°C to mean pressure of 72.7 mm Hg	NaCl at 40°C from warming cabinet to a mean pressure of 76.1 mm Hg	NaCl continuously warmed at 40°C to a mean pressure of 71.1 mm Hg*	N	Y	N	N	N	Not reported	Not reported

CO_2 = carbon dioxide; ICB = intracervical block; m = meter; mm Hg = millimeters of mercury; mm = millimeters; NaCl = sodium chloride or normal saline; N = no; PO = oral; Y = yes.

* Excluded as comparator.

Fig. 2

Risk of bias assessment of included studies.



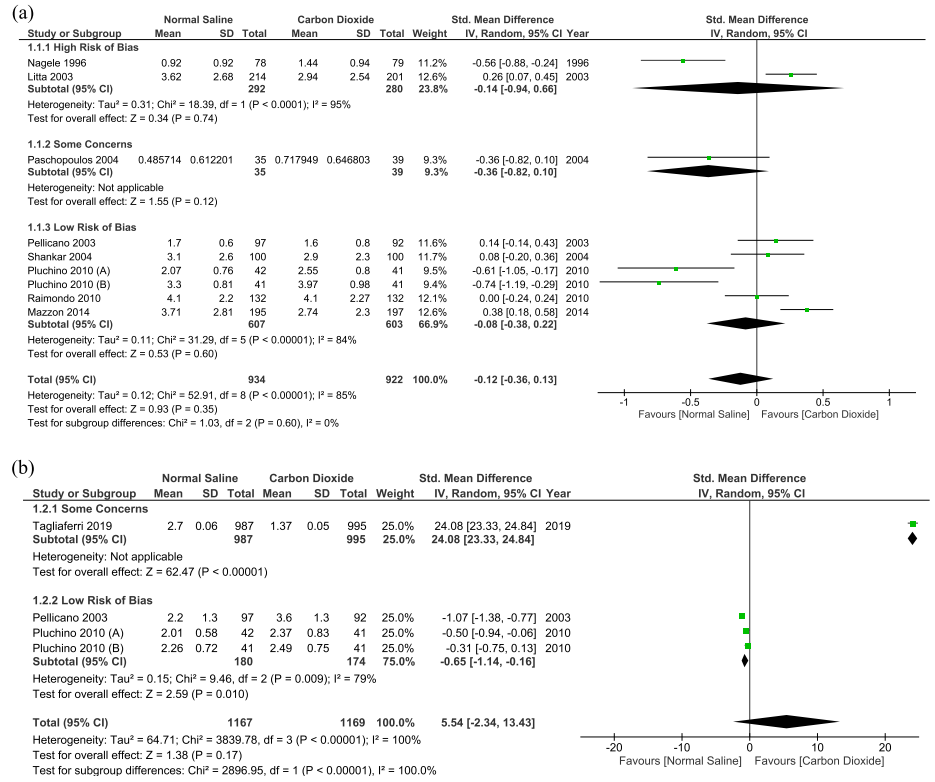
deviations as standard errors that were therefore meta-analyzed as standard deviations [11]. All patients self-reported pain scores. In most studies, a 10-point or 10-cm visual analog scale (VAS) was used [10,11,15 18,20 29]. However, in 2 studies, either a 4-point [19] or 5-point [14] scale was used. Seven studies reported intraprocedural pain [14,15,19,20,22,24,25], 2 reported postprocedural pain [17,29], and 9 reported both [10,11,16,18,21,23,26 28].

Distension Media Type

Meta-analysis of the eight studies (including 1856 patients) that reported pain during office hysteroscopy [14,15,19,21 25], when investigating the use of normal saline against carbon dioxide as a distension medium, revealed no significant difference in intraprocedural pain; SMD, 0.12; 95% CI, 0.36 to 0.13 (Fig. 3A). Subgroup analysis of studies according to study quality did not show any difference in treatment effect but reduced the degree of heterogeneity from an I^2 of 95% to 84%. Meta-analysis of the three studies (including 2336 patients) reporting pain scores immediately after [21], 1 minute after [17], and 15 minutes after [23] office hysteroscopy, also revealed no difference between the 2 distension media; SMD, 5.54; 95% CI, 2.34 to 13.43 (Fig. 3B). When subgroup analysis of these data

Fig. 3

Forest plots of intraprocedural (A) and postprocedural (B) pain scores for studies randomizing women according to distension media type. CI confidence interval; IV inverse-variance; SD standard deviation.



was performed according to risk of bias, the low-risk studies [21,23] had a statistically significant reduction in postprocedural pain when using normal saline (2 studies, 354 patients); SMD, 0.65; 95% CI, 1.14 to 0.16.

Pressure

Four studies provided pain scores for meta-analysis [18,20,26,27], of which three studies compared more than one pressure threshold [20,26,27]. For clarity of comparison and to ease clinical interpretation, we categorized the comparisons into six categories of distension media pressure (≤30 mm Hg vs >30 mm Hg, ≤40 mm Hg vs >40 mm Hg, ≤50 mm Hg vs >50 mm Hg, ≤60 mm Hg vs >60 mm Hg, ≤70 mm Hg vs >70 mm Hg, ≤80 mm Hg vs >80 mm Hg) (Figs. 4A and 4B) [18,20,26,27]. The pain scores that were closest in relation to their category were analyzed, for example, for the study reporting ≤30 mm Hg vs >30 mm Hg [26]; pain scores at 30 mm Hg were meta-analyzed against 50 mm Hg rather than 80 mm Hg to reduce the bias from using a greater pressure that would result in a disproportionate difference in pain. A significant reduction in pain was found with pressures of ≤40 mm Hg (3 studies [20,26,27], 475 patients; SMD, 0.67; 95% CI, 1.09 to 0.26); however, no significant difference in pain scores could be found when the pressure was increased above this threshold (Fig. 4A). With regard to postprocedural pain, any reduction in distension media pressure resulted in a statistically significant reduction in pain, from a SMD of 1.07 (95% CI, 1.31 to 0.84) when decreasing pressure from >70 mm Hg to ≤70 mm Hg (2 studies [26,27], 320 patients), to a SMD of 0.59 (95% CI, 0.91 to 0.28) when decreasing pressure from >30 mm Hg to ≤30 mm Hg (1 study [26], 160 patients) (Fig. 4B).

Temperature

Four studies provided data for the meta-analysis of pain scores of women randomized to either normal saline at room temperature or warmed normal saline, in which three reported intraprocedural pain [11,16,28] and four reported postprocedural pain [11,16,28,29]. There was no statistically significant reduction in pain during hysteroscopy in patients randomized to warmed saline compared with saline at room temperature; SMD, 0.59; 95% CI, 0.14 to 1.33 (3 studies, 241 patients) (Fig. 5A) [11,16,28]. The same effect was also apparent in pain following hysteroscopy, reported immediately after [29], and at 1 [28], 5 [11], and 15 minutes [16] post-procedure; SMD, 0.22; 95% CI, 0.35 to 0.79 (4 studies, 301 patients) (Fig. 5B). In the one study that provided postprocedural pain scores for continuously warmed saline, the differences in pain scores still remained non-significant (p = .21), when compared with room temperature and cabinet-warmed saline [29].

Hysteroscopic View

Distension Media Type

Hysteroscopic view was commented on in seven studies investigating women randomized to normal saline or carbon dioxide [14,19,21 25]. One study revealed a statistically significant improvement in the quality of hysteroscopic view (using a 10-cm VAS) with the use of carbon dioxide (p <.001) [24]; however, another study found that while both distension media were similar with regard to

Fig. 4

Forest plots of intraprocedural (A) and postprocedural (B) pain scores for studies randomizing women according to distension media pressure. CI confidence interval; IV inverse-variance; SD standard deviation.

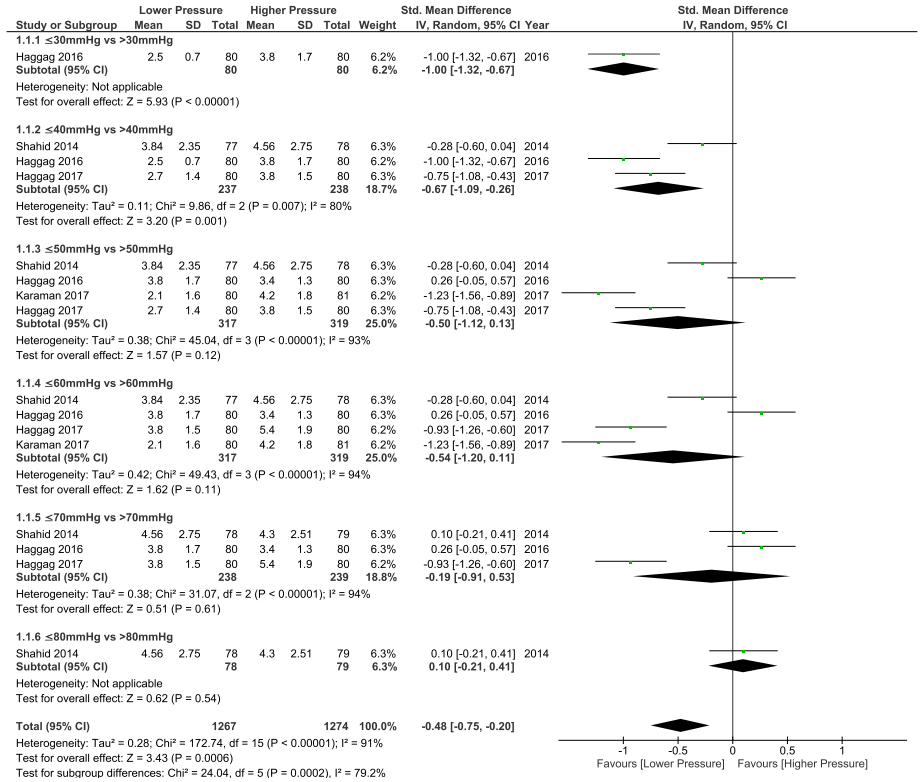


Fig. 4

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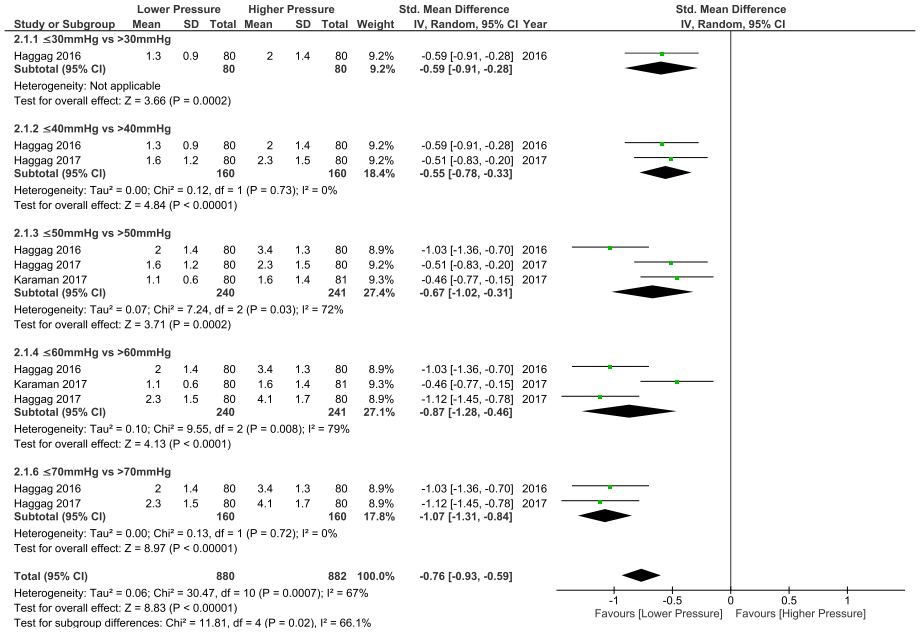


diagnosing major pathology (e.g., large polyps, myomas), with subtle endometrial lesions (e.g., small polyps, hypervascularization), saline had a significantly higher diagnostic accuracy (85.4% vs 64.6%) [19]. The other five studies provided data that allowed for meta-analysis of unsatisfactory hysteroscopies (Supplemental Fig. 1) [14,21 23,25], revealing a statistically significant reduction in hysteroscopies with an unsatisfactory view when normal saline was used (Peto OR, 0.38; 95% CI, 0.22 0.66 [5 studies, 1103 patients]). Reasons for poor view owing to carbon dioxide were cervical leakage (5 of 11) and bleeding (3 of 11) in 1 study [14] and bubbles (9 of 19), bleeding (4 of 19), poor distension (4 of 19), and excess mucus (1 of 19) in another [22]. Reasons for poor vision using saline were only given in 1 study, in which bleeding (1 of 4), inadequate light (1 of 4), and inadequate distension (1 of 4) were cited [22].

Pressure

Supplemental Fig. 2 reveals a graph of the proportion of satisfactory hysteroscopic examinations according to distension media pressure, as provided by data from three studies [20,26,27]. At pressures of 30 mm Hg to 40 mm Hg, this value ranged from 81.25% to 88.75%, whereas at pressures of 50 mm Hg to 100 mm Hg, this range was much higher at 94.87% to 98.75%.

Temperature

No studies explored the role of distension media temperature on image quality at hysteroscopy.

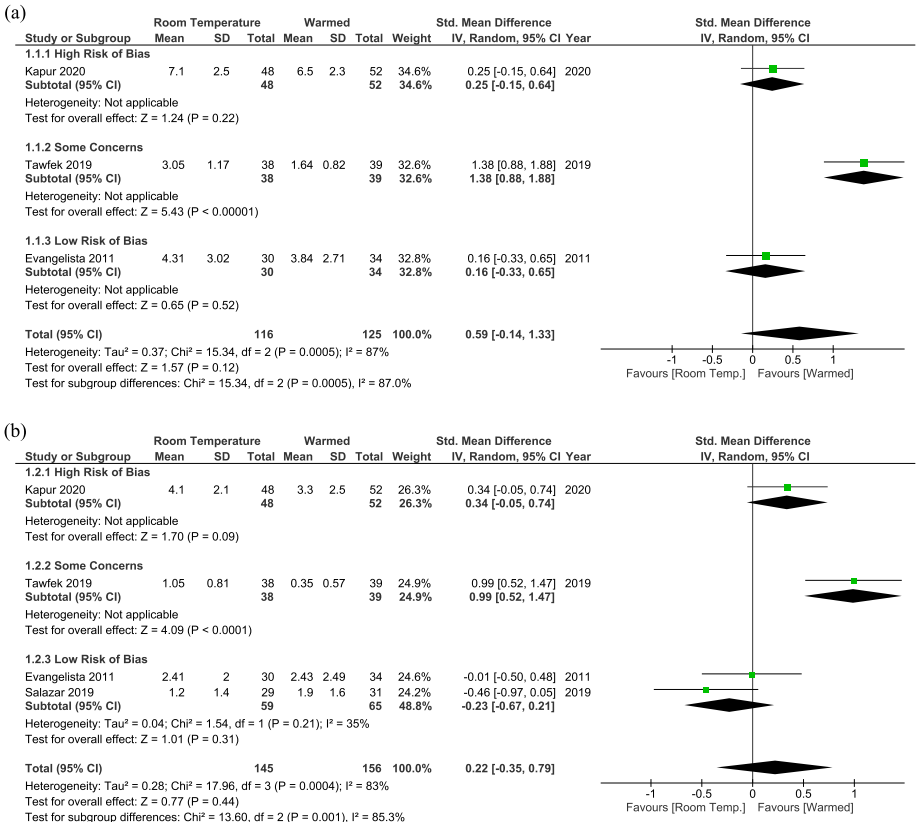
Procedural Time

Distension Media Type

Five studies (3007 patients) provided data for the meta-analysis of procedural time according to distension media type, as depicted in Supplemental Fig. 3 [14,15,17,21,24]. This revealed a statistically significant reduction in time taken for hysteroscopy with the use of carbon dioxide as a distension medium (SMD, 5.46; 95% CI, 0.96 9.96). When performing subgroup analyses according to risk of bias, studies of higher quality revealed a statistically significant reduction in procedural time with normal saline; SMD, 0.40; 95% CI, 0.74 to 0.05 (2 studies, 453 patients) [21,24].

Fig. 5

Forest plots of intraprocedural (A) and postprocedural (B) pain scores for studies randomizing women according to distension media temperature. CI confidence interval; IV inverse-variance; SD standard deviation.



Pressure

Only two studies reported procedural times with regard to distension media pressure, in which one reported timings for diagnostic hysteroscopy [26] and the other for operative hysteroscopy [27] and so were not suitable for meta-analysis. The timings between the groups in the individual studies were not significant ($p > .05$).

Temperature

No significant difference in procedural timing could be found in the four studies (301 patients) that randomized women to warmed or room temperature saline; SMD, 0.17; 95% CI, 0.47 to 0.13 (Supplemental Fig. 4) [11,16,28,29].

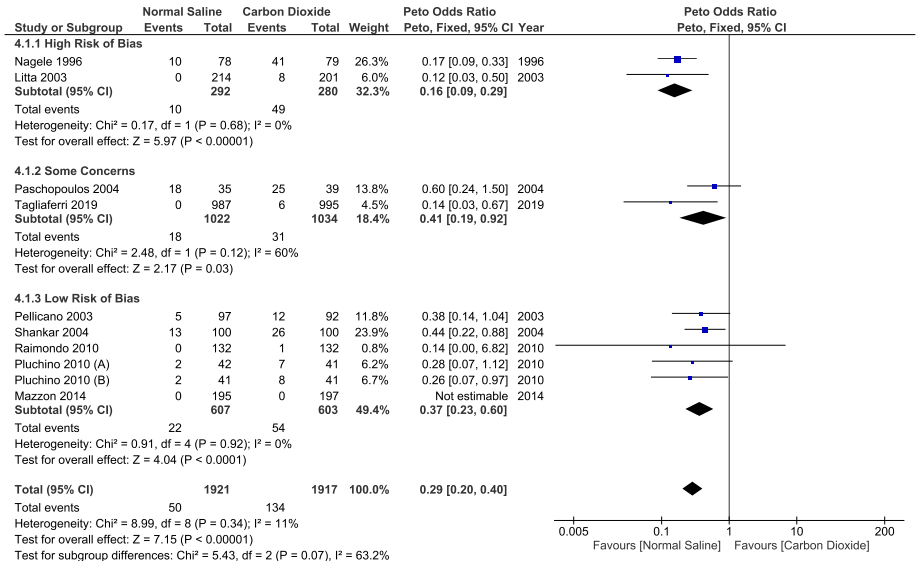
Side Effects, Complications, and Failure

Distension Media Type

Meta-analysis of the nine studies (3838 patients) that provided data regarding side effects is depicted in Fig. 6, which shows a statistically significant reduction in side effects with the use of normal saline when compared with carbon dioxide; Peto OR, 0.29; 95% CI, 0.20 0.40 [14,15,17,19,21 25]. Side effects from normal saline were predominantly vasovagal (38 of 50, 76%), exhibiting symptoms such as nausea, vomiting, dizziness, and fainting, but also included shoulder pain (8 of 50, 16%) and bleeding (4 of 50, 8%). Side effects from carbon dioxide were also predominantly vasovagal (71 of 134, 53%) but also owing to

Fig. 6

Forest plot of the incidence of side effects for studies randomizing women according to distension media type. CI confidence interval; IV inverse-variance; SD standard deviation.



shoulder pain (59 of 134, 44%) and bleeding (4 of 134, 3%). Complications either did not occur [14,17,21 23] or were not reported [15,19,24,25]. Technical failures owing to the use of distension media were reported in five studies and were invariably because of view and/or vasovagal episodes, which have been meta-analyzed already [14,17,19,21,22].

Pressure

Vasovagal episodes (6 of 7 patients) and hypertension (1 of 7 patients) were the only side effects reported in three studies and therefore too small for meta-analysis [18,26,27]. No complications were reported. Failures at different pressures were always related to hysteroscopic view, pain, and the side effects reported previously, and so meta-analysis was not performed.

Temperature

Side effects, complications, and/or technical failures related to the use of distension media either did not occur or were not reported [11,16,28,29].

Acceptability and Satisfaction

Distension Media Type

Patient satisfaction was recorded on a 5-point scale in two studies, involving 604 patients [15,21]; these data were meta-analyzed, as found in Supplemental Fig. 5, to reveal a statistically significant increase in patient satisfaction scores with the use of normal saline (SMD, 1.39; 95% CI, 0.51 2.28). Two studies reported on the impression made on the hysteroscopist; in the first, the mean VAS score for confidence in hysteroscopic diagnosis was significantly higher for normal saline (9.6 ± 1.1) compared with carbon dioxide (8.3 ± 2.1) [22], and in the second, which recorded the degree of hysteroscopic difficulty on a 10-point VAS, did not report the data, but stated that "the degree of difficulty did not differ between groups" [24].

Pressure

Acceptability and/or satisfaction of either the patient or the hysteroscopist was not commented on in any study investigating different distension media pressures for office hysteroscopy.

Temperature

Three studies commented on patient satisfaction [11,16,28]; however, only one found a significant difference in rates of patient satisfaction, with patients having warmed saline reporting a higher satisfaction rate ($p = .04$) [16]. With regard to hysteroscopist acceptability/satisfaction, a 10-cm VAS was used to report the ease of hysteroscopic entry in one study, however, no significant difference was found between room temperature and warmed saline ($p = .20$) [11].

Discussion

Principal Findings

Pain during office hysteroscopy was not affected by using either normal saline or carbon dioxide. However, higher quality trials suggested that postprocedural pain was reduced if normal saline was used. Although a satisfactory view was obtained in the vast majority of procedures, normal saline was associated with less unsatisfactory images. Procedure times were short but higher quality studies found that the duration of office hysteroscopy was less when normal saline was used. Side effects, generally limited to vasovagal reactions and shoulder tip pain, were uncommon, but noted to be lower when using normal saline. Qualitatively, normal saline was associated with higher patient satisfaction and instilled greater confidence in the ability to diagnose intrauterine pathology among hysteroscopists. Pain associated with office hysteroscopy was lower with lower distension media pressures but at the expense of a higher proportion of unsatisfactory images. Heating saline to approximate body temperature did not reduce pain associated with office hysteroscopy.

Strengths and Limitations

This systematic review was performed using a clinically focused question. The search strategy was comprehensive, using multiple databases and scanning bibliographies of included papers. Two reviewers independently selected studies, extracted data, and assessed bias to reduce misjudgment. Only randomized controlled trials were included to minimize selection bias.

The main limitation of this systematic review was that of heterogeneity arising from methodological weaknesses and differences in conduct between included studies. Subgroup analyses were performed according to risk of bias, where possible; however, such variation was not always explained by study quality. Studies also had differences in the composition of their patient population, pain relief interventions, technique, procedures performed, equipment used, and operator experience.

Comparison with Existing Literature

This is the first systematic review exploring the roles of distension media pressure and temperature on pain during office hysteroscopy and the first systematic review to investigate the role of distension media type on postprocedural pain. Although there have been two previous systematic reviews investigating the optimal distension media type for intraprocedural pain, their results were conflicting [5,6].

Clinical Application

Normal saline should be the preferred distension medium for office hysteroscopy. It allows for the efficient practice of "see and treat" services, in which diagnosis can be immediately followed by treatment [2]. It is isotonic, minimizing risks associated with fluid overload, and is able to conduct electricity, essential for the operation of modern, miniature bipolar electrosurgical electrodes [30] and works optimally with modern mechanical tissue removal systems [31]. Data comparing the effect of pressure on pain associated with office hysteroscopy involved the use of normal saline and should be interpreted with caution; unless using modern fluid management systems [18], which themselves are not perfectly reliable owing to dynamic fluid losses (e.g., through the fallopian tubes, cervix, intravascularly), then intrauterine pressures are not being accurately measured. In addition, the flow rate through the hysteroscope, and resultant intrauterine pressure, will depend on hysteroscope diameter and fluid reservoir height. Considering this and our findings, we recommend using the minimal distension medium filling pressure possible to achieve the best visibility. Finally, warming saline to approximate body temperature does not reduce pain but may leave women feeling more satisfied with their office hysteroscopic procedure.

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Addendum to Chapter 6

Figure 4 on page 7 of the manuscript refers to figure 4A and figure 4 on page 8 of the manuscript refers to figure 4B.

CHAPTER 7: CERVICAL DILATATION AND PREPARATION

This work has been published in the British Journal of Obstetrics & Gynaecology; De Silva PM, Wilson L, Carnegy A, Smith PP, Clark TJ. Cervical dilatation and preparation prior to outpatient hysteroscopy: a systematic review and meta-analysis. BJOG. 2021 Jun;128(7):1112-1123. doi: 10.1111/1471-0528.16604. Epub 2020 Dec 6. PMID: 33219606 (32).

My role in this publication is as follows: I carried out the literature search, collected the data, undertook the meta-analysis, and wrote the manuscript.

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Systematic reviews

Cervical dilatation and preparation prior to outpatient hysteroscopy: a systematic review and meta-analysis

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Background There are uncertainties about the benefit of routine cervical preparation and/or cervical dilatation before outpatient hysteroscopy.

Objective To determine if cervical preparation and/or routine mechanical dilatation reduces pain during outpatient hysteroscopy.

Search strategy MEDLINE, EMBASE, CINAHL and CENTRAL were searched on 19 October 2020, using keywords 'hysteroscopy', 'cervical preparation', 'cervical ripening', 'cervical dilatation', 'outpatient', 'office' and/or 'ambulatory' and associated medical subject headings.

Selection criteria Randomised controlled trials investigating the benefit of cervical preparation and/or cervical dilatation on pain in women undergoing outpatient hysteroscopy were included.

Data collection and analysis Two independent reviewers selected eligible trials and extracted data on pain, feasibility, adverse events and satisfaction/acceptability for meta-analysis.

Main results The literature search yielded 807 records, of which 24 were included for review and 19 provided data for meta-analysis. No trials investigated the role of routine mechanical cervical dilatation. Cervical preparation significantly reduced pain during outpatient hysteroscopy; standard mean difference (SMD) –0.67, 95% confidence interval (CI) –1.05 to –0.29. Feasibility also improved as priming provided significantly easier hysteroscopic entry (SMD 0.89, 95% CI 0.32–1.46), greater cervical dilatation (SMD 0.81, 95% CI 0.08–1.53) and shorter procedural times (SMD –0.51, 95% CI –0.88 to –0.13). Cervical preparation, however, incurred significantly more adverse effects, mainly comprising genital tract bleeding, abdominal pain and gastrointestinal symptoms (odds ratio 2.94, 95% CI 1.58–5.47). There were limited data regarding satisfaction, acceptability and complications.

Conclusions Cervical preparation reduces pain and improves feasibility associated with outpatient hysteroscopy but increases the risk of adverse effects.

Keywords Carboprost, dinoprostone, mifepristone, misoprostol, outpatient hysteroscopy, pain.

Tweetable abstract Cervical preparation before outpatient hysteroscopy reduces pain, enhances feasibility but increases adverse effects.

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Introduction

Outpatient hysteroscopy is used in the investigation and management of menstrual abnormalities, uterine factor subfertility and postmenopausal bleeding. The outpatient setting negates the need for general anaesthesia, therefore carrying benefits of requiring fewer staff and equipment, a shorter recovery time and fewer complications, all leading to a reduced economic burden to the healthcare sector.[1] Although generally well accepted,[2] the greatest barriers to patient experience are pain and vasovagal episodes,[3] which arise from cervical manipulation (instrumentation, dilatation, hysteroscope insertion), uterine cavity distension and operative procedures that disrupt the endometrium.[4]

The use of cervical preparation, namely prostaglandins, for cervical dilatation, has been widely recognised in inducing labour, medical abortion and managing pregnancy loss. Previous systematic reviews have focused on the use of a

specific prostaglandin, misoprostol, before hysteroscopy, regardless of the setting in which it was delivered (i.e. under general anaesthesia or in the outpatient setting).[5 9] The only systematic review performed investigating the impact of pain during outpatient hysteroscopy following the administration of any type of cervical preparation accrued insufficient data for the meta-analysis of pain scores.[10] No data exist to recommend routine cervical dilatation before outpatient hysteroscopy.[11]

With the advent of miniaturised hysteroscopes, the wider adoption of the vaginoscopic approach and an increase in therapeutic procedures (e.g. endometrial ablation, polypectomy) performed in the outpatient setting,[12,13] we performed a systematic review and meta-analysis to determine if cervical preparation and/or routine cervical dilatation decreases the pain experienced in outpatient hysteroscopy in light of additional data available since the last review.

Methods

Protocol and guidance

The study protocol was registered on PROSPERO (CRD42019138146).[14] Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance and the Cochrane Handbook for Systematic Reviews of Interventions were used to design this systematic review.[15,16] Patients were not involved in developing this study and there is no applicable core outcome set. No funding was received for this study.

Inclusion criteria

Randomised controlled trials investigating all women undergoing diagnostic and/or therapeutic hysteroscopy randomised to receive an intervention including cervical preparation or dilatation, and a control that included no treatment, placebo or an alternative intervention (type of preparation, dose, route, timing of administration) where the outcome was pain, were included.

Exclusion criteria

Observational studies, case reports, case series, conference abstracts and brief communications (where no full text was available) were excluded.

Outcomes

The primary outcome was pain. Secondary outcomes included adverse effects, complications, failure rate, procedural time, ease of hysteroscopic entry, cervical dilatation achieved, the need for additional cervical dilatation and acceptability/satisfaction.

Search strategy

The National Institute for Health and Care Excellence (NICE) Healthcare Databases Advanced Search (HDAS) platform was used to search the Medline, Embase, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception until 19 October 2020 (see Supplementary material, Appendix S1). Keywords including 'hysteroscopy', 'cervical preparation', 'cervical ripening', 'cervical dilatation', 'outpatient', 'office' and 'ambulatory' and their associated medical subject headings (MeSH) were used to search the HDAS databases. The keywords 'hysteroscopy', 'cervical preparation', 'cervical ripening' and 'cervical dilatation' were used to search CENTRAL. No restrictions were applied.

Study selection

Two independent researchers (PDS and AC) screened all returned titles and abstracts. Duplicates from HDAS were automatically excluded whereas duplicates from CENTRAL were manually rejected. Eligible studies were selected after reviewing the manuscripts of studies where titles and abstracts met the inclusion criteria. A further independent reviewer (TJC) determined eligibility if consensus was not met. The reference lists of included papers were screened, and further studies were included for review if eligible.

Data collection

A piloted data extraction form was created in Microsoft Excel, which two reviewers (PDS and LW) populated with data from the included studies. In addition to the outcomes listed above, data were also collected on the use of sedation, analgesia, local anaesthesia, approach (e.g. speculum or vaginoscopy), distension medium and instrument size, to explain any study heterogeneity that may arise. Adverse effects reported within 24 hours were recorded to avoid recording outcomes unrelated to the intervention given. Where multiple pain scores were documented, the highest score was recorded whether that was during passage of the hysteroscope through the cervical canal or during inspection of the uterine cavity. This rule was applied to post-procedural pain scores, which invariably meant that the pain score recorded after hysteroscopy was the one given closest to the end of the procedure. Where multiple scales were used to record pain, either visual analogue scale or numerical rating scale measurements were recorded to reduce heterogeneity between studies. Authors of studies where pain scores were not reported as means and standard deviations were contacted for their data for meta-analysis.

Assessment of risk of bias

Two independent reviewers (PDS and LW) assessed the quality of included studies using the Cochrane Collaboration Risk of Bias 2 tool on an intention-to-treat basis.[17] If consensus was not met, then a third independent researcher (PS) was asked for mediation.

Data synthesis

Only trials where a cervical preparation was compared against nil or placebo were eligible for meta-analysis to allow for fair comparison of treatment effects between studies. In studies where there were three groups to which women could be randomised,[18 21] either the two most suitable groups were used for comparison (i.e. cervical preparation versus placebo),[19 22] or each intervention group was repeatedly compared against the same placebo group.[18]

Statistical analyses were carried out on an intention-to-treat basis using RevMan (version 5.3.5).[23] Standard mean differences (SMD) and their 95% confidence intervals (CI) were calculated for continuous outcomes (e.g. pain), where inverse-variance weighting was used to calculate random-effects summary estimates. Odds ratios (OR) were calculated for dichotomous outcomes (e.g. incidence of adverse effects) and Peto odds ratios were calculated where there were low incidences of outcomes between randomised groups. A value of P less than 0.05 was considered significant. Heterogeneity of treatment effects based on appropriately selected subgroup analyses was statistically analysed using the chi-square test and depicted graphically using forest plots.

Results

Study selection

Figure S1 summarises the study selection process. The literature search yielded 807 records and 24 studies were suitable for systematic review,[18 22,24 42] of which one trial was added after screening the reference lists of included studies.[41] Nineteen studies provided data for meta-analysis.[18 22,24 28,30,34 40,42]

Study characteristics

Table 1 summarises Table S1, which details the study characteristics of included studies. Controls where a vaginal examination was performed without administering an agent were counted as placebo for meta-analysis purposes. The authors of only one study sent data suitable for the meta-analysis of pain scores.[39]

No study examined whether routine mechanical dilatation of the cervix before outpatient hysteroscopy reduced pain associated with hysteroscopy. Twenty-one studies compared the use of a cervical preparation (misoprostol, mifepristone, carboprost, dinoprostone) against a control (placebo, nil, phloroglucinol, bladder distension, dinoprostone, buscopan),[18 22,24 29,31,32,34 36,38 42] three studies compared two different doses of the same cervical preparation (200 versus 400 μg misoprostol)[18,30,37] and one study compared two different timings of administration of the same cervical preparation (3 hours versus 12 hours pre-procedurally).[33]

Risk of bias

The risk of bias of all included trials is displayed in Figure S2, according to each methodological characteristic. Overall, 29% of studies showed a 'high risk of bias', 29% were of 'some concerns' and 42% of studies showed a 'low risk of bias'. Problems with randomisation included providing insufficient detail about the process itself,[8,31,41] using a predictable sequence,[19] showing statistically significant different baseline characteristics between groups[27] and failing to provide details regarding the distribution of diagnostic and therapeutic procedures between groups.[35] Studies where participants were excluded from final analysis without the potential for substantial impact on results,[20,21,40] or where there was insufficient detail on trial methodology,[27,41] led to concerns with regards to 'deviations from intended interventions'. Insufficient detail,[25,41] differences in the number of endometrial biopsies performed between groups,[26,29] potential differences in when pain scores may have been recorded,[37] confounding due to the administration of postoperative analgesia[22] and patient awareness of the intervention received,[27,31] all led to issues in 'measurement of the outcome'. Finally, concerns with 'selection of the reported result' were encountered where the spread of pain scores was not recorded,[25] the pain scores reported were likely to have been selected based on multiple eligible analyses[21,22,26,27] and where selected pain scores were not reported at all.[35]

Cervical preparation type

Impact on pain

Meta-analysis of 11 studies,[18,19,24,28,34 36,38 40,42] including 2653 women, showed that cervical preparation led to a statistically significant reduction in pain during outpatient hysteroscopy compared with placebo (SMD 0.67, 95% CI 1.05 to 0.29). Subgroup analysis according to study quality reduced, but failed to eliminate, the degree of inconsistency, lowering the I^2 value from 93 to 79% (Figure 1). Subgroup analysis according to the agent given showed that both misoprostol (eight studies,[18,19,28,34,35,38,39,42] 881 women) and dinoprostone (one study,[40] 100 women) significantly reduced mean pain scores during hysteroscopy with SMDs (95% CI) of 0.64 (0.97 to 0.31) and 2.24 (2.75 to 1.74), respectively (Figure 2). Although evidence was limited to one study each, mifepristone[24] (58 women) and carboprost[36] (1314 women) did not show a significant difference in intra-procedural pain when administered before hysteroscopy with SMDs (95% CI) of 0.13 (0.65 to 0.38) and 0.09 (0.02 to 0.20), respectively. Post-procedural pain (measured immediately[39], 30 minutes[34,40] or 1 hour[38] after), was not significantly reduced when cervical preparation was given (four studies,[34,38 40] 480 women; SMD 0.28, 95% CI 0.63 to 0.07) (Figure S3).

Table 1. Summary of included study characteristics

Study	Group 1	Group 2	Group 3	Menopausal status	Parity	Procedure type	Pain score data type	Details of timing of recorded pain	
								During	After
Abulnour 2018	Misoprostol 400µg PV 6 h prior	Dinoprostone 3 mg PV 6 h prior	N/A	Mixed	Nulliparous	Diagnostic	Mean ± SD	During	N/A
Bastu 2013	Misoprostol 200 µg PV 12–15 h prior	Misoprostol 400 µg PV 12–15 h prior	VE 12–15 h prior	Premenopausal	Nulliparous	Diagnostic	Mean ± SD	During	N/A
Ben-Chetrit 2004	Mifepristone 200 mg PO 30 h prior	Placebo PO 30 h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean ± SD	Uterine cavity inspection	N/A
Da Costa 2008	Misoprostol 200 µg PV 8 h prior	Placebo PV 8 h prior	N/A	Postmenopausal	Mixed	Diagnostic	Median	During	15 min
Duan 2018	Carboprost 0 5 mg PV 1 5 h prior	Placebo PV 1 5 h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean ± SD	During	N/A
El-Khayat 2015	Misoprostol 200 µg PV 3 h prior	Misoprostol 400 µg PV 3 h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean ± SD	During	N/A
El-Mazny 2011	Misoprostol 200 µg PV 3 h prior	VE 3 h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean ± SD	During	N/A
Esin 2013	Misoprostol 200 µg SL 2 h prior and placebo TOP 5 min prior	SL Placebo 2 h prior and lidocaine spray 60 mg TOP 5 min prior	N/A	Premenopausal	Mixed	Diagnostic & Therapeutic	Mean ± SD	Greatest pain during	10 min
Fouda 2016 (A)	Misoprostol 400 µg PV 12 h prior	Bladder distension (1 l water 2 h prior)	N/A	Postmenopausal	Parous	Diagnostic	Mean ± SD	During	30 min
Fouda 2016 (B)	Misoprostol 400 µg PV 12 h prior and placebo PV 3 h prior	Placebo PV 12 h prior and Misoprostol 400 µg PV 3 h prior	N/A	Premenopausal	Nulliparous	Diagnostic	Mean ± SD	During	30 min
Fouda 2018	Misoprostol 400 µg PV 12 h prior	Placebo PV 12 h prior	N/A	Premenopausal	Parous	Diagnostic	Mean ± SD	During	30 min
Hassa 2013	Misoprostol 200 µg PV 6 h prior and placebo PR 60 min prior	Placebo PV 6 h prior and Diclofenac 100 mg PR 60 min prior	Placebo PV 6 h prior and placebo PR 60 min prior	Premenopausal	Nulliparous*	Diagnostic	Median (IQR)	During	N/A
Hwang 2018	Misoprostol 200 µg PV 8 h prior	Misoprostol 400 µg PV 8 h prior	N/A	Mixed	Mixed	Therapeutic	Median (range)	N/A	<2 h
Issat 2014	Misoprostol 400 µg PV 4 h prior and 100 ml 5% IV glucose 30 min prior	Placebo PV 4 h prior and Ketoprofen 50 mg/ml in 100 ml 5% glucose 30 min prior	Placebo PV 4 h prior and 100 ml 5%	Mixed	Mixed	Diagnostic & Therapeutic	Median (IQR)	During	5 min

Table 1. (Continued)

Study	Group 1	Group 2	Group 3	Menopausal status	Parity	Procedure type	Pain score data type	Details of timing of recorded pain	
								During	After
Karasu 2020	Misoprostol 200 μg PR 2 h prior	Buscopan 20 mg PR 2 h prior	IV glucose 30 min prior Rectovaginal examination 2 h prior	Premenopausal	Mixed	Therapeutic	Median ± not specified	N/A	1 h
Nair 2020	Misoprostol 200 μg PV 4 h prior	Placebo PV 4 h prior	N/A	Premenopausal	Nulliparous	Diagnostic	Mean ± SD	Uterine cavity inspection	N/A
Nakano 2018	Misoprostol 200 μg PV 6 h prior	Placebo PV 6 h prior	N/A	Postmenopausal	Mixed	Diagnostic	Mean ± SD	During examination	1 h
Nandhini 2018	Misoprostol 200 μg PV 3 h prior	VE 3 h prior	N/A	Mixed	Mixed	Diagnostic	Mean ± SD emailed	Introduction of scope into cervical canal	Immediately after
Samy 2020	Dinoprostone 3 mg PV 12 h prior	Placebo PV 12 h prior	N/A	Postmenopausal	Mixed	Diagnostic	Mean ± SD	During	30 min
Singh 2009	Misoprostol 400 μg PV 4 –6 h prior	Nil	N/A	Mixed	Nulliparous*	Diagnostic	Median ± SD	During	N/A
Sordia-Hernandez 2011	Misoprostol 200 μg PO every 8 hours for 24 hours prior (600 μg total)	Misoprostol 200 μg PV every 12 hours for 24 hours prior (400 μg total)	Placebo PO every 8 hours for 24 hours prior	Premenopausal	Mixed	Diagnostic	Mean ± SD	During	N/A
Tasma 2018	Misoprostol 400 μg PO at 24 h and 12 h prior (800 μg total)	Placebo PO 24 h and 12 h prior	N/A	Mixed	Nulliparous	Diagnostic & Therapeutic	Mean ± SD	Introduction of scope into cervical canal	N/A
Valente 2008	Misoprostol 400 μg PV 6 h prior	Placebo PV 6 h prior	N/A	Premenopausal	Mixed	Diagnostic	Dichotomous	Most severe pain during	15 min
Xu 2015	Misoprostol 400 μg PO 2 h prior	Phloroglucinol 80 mg IM 30 min prior	N/A	Premenopausal	Mixed	Diagnostic	Mean ± SD	During	N/A

Abbreviations IQR, interquartile range; N/A, not applicable; NS, normal saline; PO, oral; PR, rectal; PV, vaginal; SD, standard deviation; SL, sublingual
*No previous vaginal deliveries; did not exclude caesarean sections.

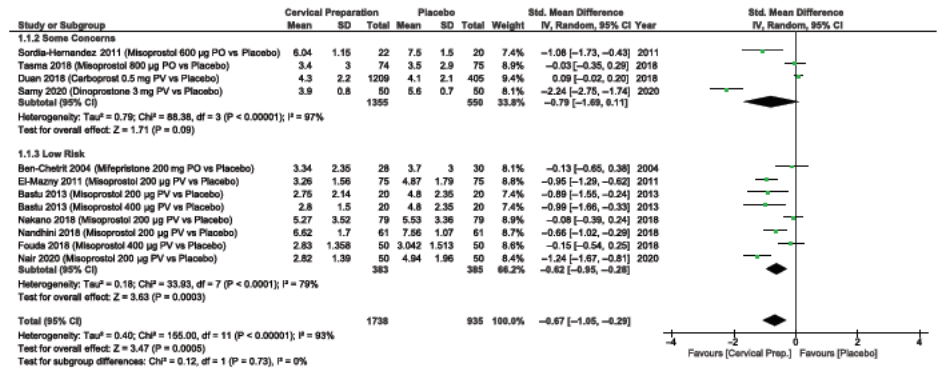

Figure 1. Effect of cervical preparation on intra-procedural pain according to study quality

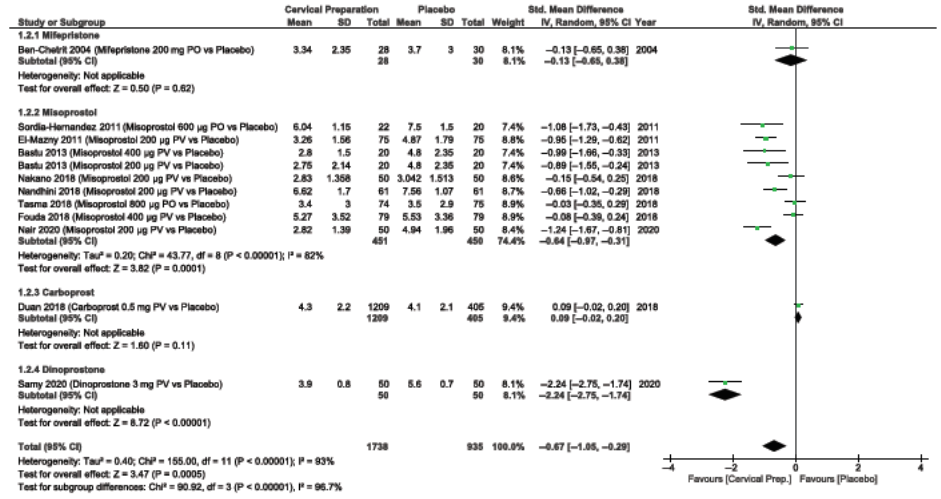

Figure 2. Effect of cervical preparation on intra-procedural pain according to the agent administered

Further subgroup analyses were performed to identify those women that may benefit most from misoprostol use. One study provided additional data based on menopausal status,[35] allowing for subgroup analysis to be performed based upon this; Figure S4 shows a significant reduction in pain when misoprostol was given to premenopausal women (six studies,[18,19,28,34,35,42] 490 women; SMD 0.86, 95% CI 1.18 to 0.54) but not to postmenopausal women (two studies,[35,38] 244 women; SMD 0.10, 95% CI 0.30 to 0.51). Subgroup analysis investigating the use of misoprostol based on parity produced a significantly reduced intra-procedural pain score in studies investigating nulliparous women (three studies,[18,35,42] 309 women; SMD 0.77, 95% CI 1.44 to 0.10), but not parous women (one study,[34] 100 women; SMD 0.15, 95% CI 1.44 to 0.10) (Figure S5). Subgroup analysis based on hysteroscopic approach following misoprostol administration showed significantly reduced pain scores when vaginoscopy was performed (five studies,[28,34,35,39,42] 621 women; SMD 0.60, 95% CI 1.04 to 0.15), but not when a vaginal speculum

was used (two studies,[18,38] 218 women; SMD 0.60, 95% CI 1.27 to 0.06) (Figure S6). Finally, subgroup analysis based on route of administration showed that vaginal misoprostol (six studies,[18,28,34,38,39,42] 690 women; SMD 0.68, 95% CI 1.04 to 0.32) significantly reduced pain compared with placebo whereas oral misoprostol did not (two studies,[19,35] 191 women; SMD 0.52, 95% CI 1.54 to 0.51) (Figure S7).

Feasibility

Meta-analysis of ease of hysteroscopic entry, scored by the hysteroscopist, on either a five-point Likert scale or a 10-cm visual analogue scale, showed that misoprostol (five studies,[18,28,34,39,42] 532 women; SMD 0.71, 95% CI 0.19 1.22) and dinoprostone (one study,[40] 100 women; SMD 1.91, 95% CI 1.44 2.39) were significantly associated with easier hysteroscopic entry when compared with placebo (six studies,[18,28,34,39,40,42] 632 women; pooled SMD 0.89, 95% CI 0.32 1.46) (Figure S8).

Meta-analysis of cervical dilatation achieved before hysteroscopy (three studies,[18,24,36] 1732 women) revealed significantly greater dilatation (gauged by the size of Hegar dilator the cervical canal could accommodate) when using a cervical preparation compared with placebo (SMD 0.81, 95% CI 0.08 1.53), where subgroup analysis showed that misoprostol (one study,[18] 60 women), in particular, conferred the greatest pre-procedural dilatation (SMD 1.53, 95% CI 0.85 2.22) (Figure S9). No significant benefit was reported in the proportion of women requiring additional cervical dilatation (four studies,[25,27,36,38] 550 women) when comparing a cervical preparation against placebo/nil (P 0.13) (Figure S10).

A significant reduction in procedural time was observed when a cervical preparation was given, compared with placebo (nine studies,[18,19,28,34 36,38,40,42] 2473 women; SMD 0.51, 95% CI 0.88 to 0.13). Subgroup analysis performed according to the specific prostaglandin given showed that only misoprostol significantly minimised procedural time (seven studies,[18,19,28,34,35,38,42] 759 women; SMD 0.67, 95% CI 1.21 to 0.12) (Figure S11).

The incidence of failed hysteroscopies among participants randomised to a cervical preparation or placebo/nil was too small for meta-analysis. Reasons for failure (total n 41/2001; 2.0%) among women randomised to a cervical preparation included cervical stenosis (n 29), genital tract bleeding (n 7), pain/non-cooperation (n 4) and a prolapsed fibroid (n 1); reasons for failure in women randomised to placebo/nil (total n 38/1183; 3.2%) included cervical stenosis (n 32), pain (n 5) and genital tract bleeding (n 1).

Adverse events

Meta-analysis of all adverse effects showed that significantly more occurred when a cervical preparation was administered compared with placebo/nil (16 studies,[18 22,25 28,34 36,38 40,42] 3111 women; OR 2.94, 95% CI 1.58 5.47), where subgroup analysis showed a significant increase in adverse effects only when misoprostol was administered (14 studies,[18 22,25 28,34,35,38,39,42] 1405 women; OR 3.56, 95% CI 1.60 7.93) (Figure 3). Table S2 outlines the distribution of specific adverse effects (e.g. genital tract bleeding, abdominal pain/cramping, nausea, vomiting, diarrhoea, pyrexia/fever, vasovagal episodes) according to the agent administered. In one study,[36] 383 adverse drug reactions were not attributed to specific adverse effects.

The incidence of complications among women randomised to a cervical preparation or placebo/nil was too small for meta-analysis. Complications (total n 18/711; 2.5%) among women randomised to misoprostol (from 14 studies[18 22,25 28,34,35,38,39,42]) included cervical trauma (n 7), false passage (n 4), severe pain (n 4), uterine perforation (n 1), infection (n 1) and genital tract bleeding requiring emergency department admission (n 1). Complications among women randomised to placebo/nil (total 13/694; 1.9%) included cervical trauma (n 4), false passage (n 5), uterine perforation (n 3) and severe pain (n 1). No complications were reported in the one study comparing dinoprostone to placebo,[40] and in the study investigating carboprost,[36] 1123 complications were reported without further details.

Satisfaction and acceptability

Only one study commented on clinician satisfaction,[36] and there was no significant difference when performing hysteroscopy in women randomised to either carboprost or placebo ($P > 0.05$). Likewise, four studies could not find a statistical difference in satisfaction between women randomised to a cervical preparation or placebo/nil ($P > 0.05$).[20,27,28,36] A significantly higher proportion of premenopausal nulliparous women, when randomised to misoprostol compared with placebo, would undergo the procedure again if required ($P \leq 0.02$),[35,42] would not prefer additional anaesthesia ($P < 0.01$)[35] and would recommend hysteroscopy to a friend/relative ($P \leq 0.02$).[35,42]

Dose

Impact on pain

Meta-analysis of the two studies (172 women),[18,30] that provided appropriate data comparing 200 µg against 400 µg vaginal misoprostol failed to show a significant benefit (P 0.32) of dose on pain (Figure S12).

Feasibility

No significant difference (P 0.20) in ease of hysteroscopic entry could be found between the two studies (172 women) providing mean (and standard deviation) Likert scale

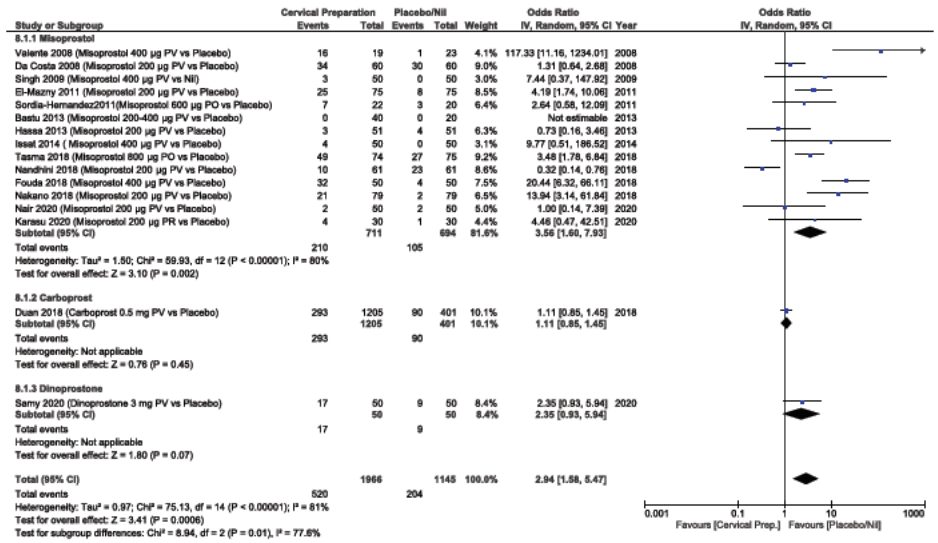

Figure 3. Effect of cervical preparation on the incidence of adverse effects according to the agent administered

scores investigating the use of 200 µg against 400 µg misoprostol (Figure S13).[18,30] There was, however, a significant reduction in procedural time when 400 µg misoprostol was given (SMD 1.03, 95% CI 0.01 2.05) (Figure S14). In the two studies investigating cervical dilatation achieved before hysteroscopy, there was no significant difference when comparing 200 µg against 400 µg misoprostol.[18,37] No failed procedures occurred across the three studies comparing the aforementioned doses.[18,30,37]

Adverse events

Two studies reported the incidence of adverse effects between women randomised to either 200 or 400 µg of misoprostol.[30,37] The first did not show a dose-related benefit with regards to adverse effects (nausea and abdominal pain) in women randomised to either 200 or 400 µg (P 1.0 and P 0.055, respectively);[30] however, the other showed a significant increase in the number of adverse events related to 400 µg only (P 0.015), such as fever, abdominal pain, diarrhoea, nausea, vomiting and vaginal spotting.[37] No complications were recorded in any of the three studies.[18,30,37]

Satisfaction and acceptability

No study commented on hysteroscopist satisfaction/acceptability. Women found hysteroscopy following 400 µg of misoprostol more acceptable than hysteroscopy following 200 µg ($P < 0.001$), as reported in one study consisting of 132 women.[30]

Timing of administration

Impact on pain

Pain was significantly reduced when 400 µg vaginal misoprostol was given 12 hours rather than 3 hours before hysteroscopy in one study comprising 120 women ($P < 0.001$).[33] There was no significant change in pain scores 30 minutes after hysteroscopy (P 0.28). No study compared multiple dosing schedules.

Feasibility

Hysteroscopic entry was easier (P 0.01), however, there was no difference in procedural time (P 0.43) when misoprostol was given 12 hours, rather than 3 hours before.[33] No failed procedures occurred.

Side-effects and complications

There was no significant difference in the incidence of abdominal cramps (P 0.64), nausea (P 0.79), diarrhoea (P> 0.99), genital tract bleeding (P 0.62) and fever (P> 0.99) between women receiving misoprostol 12 hours or 3 hours before hysteroscopy.[33]

Satisfaction and acceptability
No data with regards to hysteroscopist or patient satisfaction/acceptability were available.

Discussion

Main findings

Cervical preparation reduces pain during outpatient hysteroscopy. Cervical priming facilitated hysteroscopy by dilating the cervix, allowing for easier entry and reducing procedural time. Administration of a cervical preparation, however, increased the risk of adverse effects, namely genital tract bleeding, abdominal pain/cramping and gastrointestinal disturbance. No data were available regarding the impact of routine mechanical cervical dilatation before outpatient hysteroscopy.

There was considerable heterogeneity between included studies in all meta-analyses performed. Subgroup analysis according to study quality only slightly reduced the inconsistency between studies. Misoprostol proved to be the most efficacious cervical preparation in terms of pain and feasibility, however, this was also the only pharmacological agent to show a statistically significant increase in adverse effects. Premenopausal and nulliparous women appeared to benefit more than postmenopausal and parous women from misoprostol administration. Furthermore, misoprostol administration combined with the adoption of the vaginoscopic approach reduced pain during hysteroscopy, which was obviated if a vaginal speculum was used. Finally, misoprostol conferred less pain when given vaginally, rather than orally, and if administered 12 hours, rather than 3 hours before hysteroscopy.

Agents such as dinoprostone,[40] buscopan[22] and phloroglucinol[31] produced encouraging results, but trials were too small to provide robust conclusions. In addition, only one trial provided pain scores suitable for meta-analysis with regards to both operative and diagnostic hysteroscopy;[35] operative procedures invariably require larger-diameter hysteroscopes, where such patients may benefit the most from cervical priming.

Strengths and limitations

This is the first systematic review meta-analysing pain scores of women undergoing outpatient hysteroscopy investigating the use of a cervical preparation. Rigorous methodology was performed in-line with the Cochrane Handbook.[16] Selection bias was minimised by producing a clinically focused question and by searching a multitude of databases, using broad and comprehensive search terms. There were no restrictions and additional data were sought through scanning the reference lists of included papers and by contacting authors. Human error and misjudgement were minimised in having two reviewers independently selecting studies, extracting data and performing quality assessment.

Statistical heterogeneity, arising from the pooling of data from individual studies, was the major limitation of this review. Although we attempted to minimise confounding by only including randomised controlled trials, the variation in treatment effect is probably secondary to the methodological differences in how data were collected and assessed and the clinical differences between studies, including the populations investigated (e.g. body mass index), operative techniques (e.g. approach), use of analgesia/sedation/local anaesthesia, equipment (e.g. endoscope diameter) and operator experience.

Interpretation (in light of other evidence)

Five previous systematic reviews investigating the use of misoprostol before hysteroscopy, have found that it increases cervical width,[7 9] and so reduces the need for additional dilatation,[5 9] and the associated risk of cervical trauma,[7 9] but increases the risk of adverse effects.[5,6] Subgroup analysis according to menopausal status in three studies found that these outcomes were more pronounced in premenopausal women.[5,7,9] Although the use of misoprostol in these studies was not specific to outpatient hysteroscopy, our findings regarding the impact of misoprostol are in agreement with these former reviews.

The only previous systematic review investigating the use of cervical preparation for outpatient hysteroscopy, performed nearly a decade ago, failed to meta-analyse pain scores because of the limited number of studies available (n 6) and found no benefit in adverse effects, complications or failure when a cervical preparation was given.[10] This study removed two trials that did not report pain associated with hysteroscopy,[43,44] and added 20 further trials that have been published since.[18 22,28 42]

Conclusion

Cervical preparation, using prostaglandins, reduces pain experienced during outpatient hysteroscopy. The advantages of cervical priming with regards to pain and feasibility should be weighed against the risk of adverse effects, logistical efforts and costs required to facilitate administration, and this should be reflected in evidence-based guidance.[11] There is insufficient evidence to recommend routine mechanical cervical dilatation before outpatient hysteroscopy, especially in the context of modern miniature hysteroscopes, which avoid this unnecessary step. Uncertainties still remain regarding the ideal dose, timing and route of administration. Further research is therefore required to identify the optimal cervical preparation regimen with regards to not only the agent, but also the dose, route and timing of administration. In addition to pain,

data should be collected regarding patient acceptability and satisfaction, identifying the specific patients that would benefit the most from this (e.g. those who had a previously failed hysteroscopy), the particular circumstances when cervical preparation should be administered (e.g. operative hysteroscopy) and the role of cervical priming when local anaesthesia has been given. The views of clinicians regarding feasibility should also be collected.

Disclosure of interests
None declared. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship
TJC conceptualised the review. PDS performed the literature search, data collection and analysis, and drafted the manuscript. LW and AC contributed towards data collection. PS and TJC contributed to the production of the final manuscript.

Details of ethical approval
Ethical approval was not required for this study.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. PRISMA flow diagram depicting the study selection process.

Figure S2. Study quality of included studies, based on the Risk of Bias 2 (RoB 2) tool.

Figure S3. Effect of cervical preparation on post-procedural pain, according to the agent administered.

Figure S4. Effect of misoprostol on intra-procedural pain, according to menopausal status.

Figure S5. Effect of misoprostol on intra-procedural pain, according to parity.

Figure S6. Effect of misoprostol on intra-procedural pain, according to approach.

Figure S7. Effect of misoprostol on intra-procedural pain, according to route of administration.

Figure S8. Effect of cervical preparation on the ease of hysteroscopic entry, according to the agent administered.

Figure S9. Effect of cervical preparation on cervical dilatation achieved before hysteroscopy, according to the agent administered.

Figure S10. Effect of cervical preparation on the need for additional cervical dilatation before hysteroscopy, according to the agent administered.

Figure S11. Effect of cervical preparation on procedural time, according to the agent administered.

Figure S12. Effect of 200 μg versus 400 μg vaginal misoprostol, given as a cervical preparation, on intra-procedural pain.

Figure S13. Effect of 200 μg versus 400 μg vaginal misoprostol, given as a cervical preparation, on ease of hysteroscopic entry.

Figure S14. Effect of 200 μg versus 400 μg vaginal misoprostol, given as a cervical preparation, on procedural time.

Table S1. Detailed summary of included study characteristics.

Table S2. Distribution of specific adverseeffects according to the cervical preparation administered.

Appendix S1. Search strategy. ■

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Addendum to Chapter 7

The second sentence of page 2 of the manuscript should instead read: The only systematic review investigating the impact of any type of cervical preparation on pain during outpatient hysteroscopy accrued insufficient data for the meta-analysis of pain scores.[10]

CHAPTER 8: CONSCIOUS SEDATION

This work has been published in the European Journal of Obstetrics & Gynecology and Reproductive Biology; De Silva PM, Carnegy A, Graham C, Smith PP, Clark TJ. Conscious sedation for office hysteroscopy: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2021 Nov;266:89-98. doi: 10.1016/j.ejogrb.2021.09.001. Epub 2021 Sep 3. PMID: 34600190 (33).

My role in this publication is as follows: I carried out the literature search, collected the data, undertook the meta-analysis, and wrote the manuscript.

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Review article

Conscious sedation for office hysteroscopy: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the role of conscious sedation on pain control in office hysteroscopy.
Methods: MEDLINE, EMBASE, CINAHL and CENTRAL were searched from inception to the 30th October 2020 in order to perform a systematic review and meta-analysis of all randomized controlled trials investigating women undergoing office hysteroscopic procedures, allocated to either conscious sedation or a suitable comparator, where the outcome was pain. Data regarding adverse events, feasibility and satisfaction/acceptability were also collected. The Risk of Bias 2 tool was used to assess study quality. Standard mean differences (SMD) or Odds Ratios (OR), and their 95% confidence intervals (CIs) were calculated for continuous (e.g. mean pain) and dichotomous (e.g. side-effects) outcomes, respectively.
Results: The literature search returned 339 results, of which seven studies were included for systematic review, with five studies having data suitable for meta-analysis. Intravenous conscious sedation, when compared with local anesthesia, reduced pain during (SMD −0.26, 95% CI −0.51 to −0.01), but not after (SMD −0.18, 95% CI −0.43 to 0.07) office hysteroscopy. No significant difference in side-effects were noted (OR 15.58, 95% CI 0.08 to 2891.91). Intravenous conscious sedation, when compared to an oral analgesic and antispasmodic, was associated with increased pain, both during (SMD 1.03, 95% CI 0.56 to 1.49) and after (SMD 0.49, 95% CI 0.04 to 0.93) hysteroscopy and had significantly more side-effects (OR 134.33, 95% CI 16.14 to 1118.17). Inhalational conscious sedation (70% N_2O/30% O_2), when compared to oral analgesia and anxiolysis, showed the greatest reduction in pain during hysteroscopy (SMD −1.04, 95% CI −1.57 to −0.52), however side-effects were not reported. Whilst patients and hysteroscopists were more satisfied with deeper levels of sedation, resulting side-effects, such as delirium, increased the level of post-procedural attention required, leading to a significantly lower level of satisfaction amongst nursing staff.
Conclusion: The routine use of conscious sedation in contemporary hysteroscopic practice should be avoided in the absence of any clear reduction in pain and a higher risk of side-effects.

Contents

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Introduction

Office hysteroscopy is widely used in the investigation and treatment of abnormal uterine bleeding and uterine factor subfertility. This setting negates the need for a formal operating room and general anesthesia, reducing the time spent in hospital and thus increasing efficiency and reducing overall healthcare costs [1]. The greatest barrier to delivering this service is patient experience, which is significantly impacted by pain arising from genital tract instrumentation, uterine cavity distension and trauma to the endometrium (e.g. endometrial biopsy) [2,3].

Conscious sedation is widely employed during gastrointestinal endoscopy for pain relief and anxiolysis. However, it is less commonly used in office hysteroscopy, with no widely available evidence regarding its efficacy, feasibility and safety [4]. Sedation induces a depression in consciousness, resulting in a continuum of states ranging from minimal sedation and anxiolysis, through to moderate or 'conscious' sedation, deep sedation, and finally culminating in general anesthesia. Responsiveness is always suppressed, however, as the level of sedation increases, so does the potential ability of the patient to maintain control of their airway, ventilation and cardiovascular function [5]. The American Society of Anesthesiologists therefore defines conscious sedation as a "drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation" (i.e. not a painful stimulus) where "no interventions are required to maintain a patent airway when spontaneous ventilation is adequate" and "cardiovascular function is usually maintained" [6].

The risks and benefits of conscious sedation require rigorous evaluation before advocating its routine use for office hysteroscopy. We therefore performed a systematic review and meta-analysis investigating the impact of conscious sedation on pain experienced by patients undergoing office hysteroscopy, considering the risk of adverse events, procedural feasibility, and patient and operator acceptability/satisfaction.

Methods

Protocol and guidance

The study protocol was prospectively registered on PROSPERO (CRD42019138152) [7], and the study was performed with guidance from Cochrane [8].

Inclusion criteria

Randomized controlled trials (RCTs) investigating women undergoing office hysteroscopy randomized to either conscious sedation or a suitable comparator where the outcome was pain, were included for review. Suitable comparators included nil, placebo, or an alternative analgesic/local anesthetic/sedative regimen that allowed for investigation of different drug type(s), routes (e.g. inhalation, oral etc.) or timings of administration.

Exclusion criteria

Conference abstracts, case reports, case series and observational studies were excluded. Interventions classed as "minimal sedation" or anxiolysis by the American Society of Anesthesiologists (i.e. those which had "<50% nitrous oxide in oxygen with no other sedative or analgesic medications by any route" or "a single, oral sedative or analgesic medication administered in doses appropriate for the unsupervised treatment of anxiety or pain") were not considered forms of conscious sedation for the purposes of this review [6].

Outcomes

The primary outcome was pain. Secondary outcomes included adverse events (side-effects, complications), feasibility (failure rates, operative time and procedural difficulty) and the acceptability and/or satisfaction of patients and clinicians.

Search strategy

MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) was searched from inception to the 30th October 2020, using a combination of the keywords "hysteroscopy", "sedat*", "hypno*", "outpatient", "ambulatory", "office" and their associated medical subject headings (MeSH). Reference lists of included papers were scanned, and additional studies were included if deemed appropriate.

Study selection

Duplicate entries were removed from the citations received from MEDLINE, EMBASE, CINAHL and CENTRAL. Two reviewers (PDS and AC) independently selected relevant titles and abstracts from the remaining papers as per the inclusion and exclusion criteria. The selected full-texts were then scrutinized to determine the final eligible studies for systematic review. If there were any disagreements in study selection that could not be resolved through consensus, a third independent reviewer (PS) was asked to arbitrate.

Data collection

Data from included trials were extracted by two independent reviewers (PDS and AC) into a standardized data extraction form. Where available, intra-procedural and post-procedural pain scores, side-effects, complications, failure, operative time, procedural difficulty, and the acceptability and/or satisfaction of patients and hysteroscopists were recorded. Some studies scored intra-procedural pain according to separate phases of hysteroscopy; if diagnostic, the score given during uterine cavity inspection was recorded and if operative, the highest set of pain scores given during the operative phase was recorded, e.g. at first micro-insert coil placement in hysteroscopic sterilization. The post-procedural score was recorded for studies scoring pain felt after the end of hysteroscopy; where multiple pain scores were given at different timings post-procedure, the highest set of pain scores were recorded, which was invariably the pain score recorded closest to the end of hysteroscopy. Data were also extracted regarding the populations studied, type of hysteroscopy performed (e.g. diagnostic, therapeutic), use of analgesia, local anesthesia, cervical preparation, cervical dilatation, hysteroscopic approach, distension medium and hysteroscopes used.

Assessment of risk of bias

Two independent reviewers (PDS and AC) examined the risk of bias of included trials on an intention-to-treat basis using the Cochrane Collaboration Risk of Bias 2 tool [9]. Again, a third independent (PS) reviewer was involved where there were disagreements in bias assessment that could not be resolved by consensus.

Data synthesis

RevMan (version 5.3.5) was used to perform all statistical analyses on an intention-to-treat basis [10]. Intra-procedural and post-procedural mean pain scores and mean operative times (and their standard deviations) were evaluated using standardized mean differences (SMD) and their 95% confidence intervals (CI). Random-effects summary estimates were calculated from inverse-variance weighting. The incidence of side-effects were displayed using odds ratios (OR) and their 95% CI. A P-value<0.05 was considered significant. Heterogeneity of treatment effects were displayed graphically using forest plots and statistically analyzed using the chi-squared test.

Results

Study selection

Fig. 1 summarizes the study selection process. The literature search returned 339 records, of which seven were suitable for systematic review [11–17] and five were suitable for meta-analysis [11–15].

Study characteristics

Table 1 details the populations studied, procedures performed, and interventions compared across included studies.

Pain was recorded on either a 5-point [11] or 10 cm/10-point visual analogue scale (VAS) [12–16]. In one study, the range of the VAS was unclear [17]. Only one study gave pre-procedural analgesia to all women [14]. Similarly, only one study reported the use of a cervical preparation, in the form of vaginal misoprostol 400mcg given to all patients on the morning of hysteroscopy [17]. Three studies reported the use of cervical dilatation [12,14,15]; in one study this was performed routinely for all patients [15], however, in the other two, this was performed only when required, where the number of patients that underwent dilatation was balanced between intervention groups ($p > 0.05$) [12,14]. Of the five studies that reported hysteroscopic approach, all routinely used a vaginal speculum, and these same studies reported the distension medium instilled, with all using normal saline [11–15]. Three studies routinely administered intracervical and/or paracervical local anesthesia [13,14,17].

Study bias

The risk of bias for each study is depicted in Fig. 2. Two studies investigating conscious sedation against a suitable control were well-conducted placebo-controlled RCTs and so had the lowest risk of bias [13,14]. Three studies did not use a placebo and were classified as "some concerns" with regards to the "measurement of the outcome" because it was felt that the outcome assessors (i.e. patients) could, but were unlikely to, have been influenced by knowledge of the intervention received [11,12,15]. There were also concerns in the other two studies, which compared different conscious sedative agents [16,17]. In the first study, which compared the use of dexmedetomidine with propofol, there were "some concerns" in the "selection of the reported result", due to the fact that post-procedural pain scores were depicted graphically, rather than numerically [16]. The other study, which compared the use of pentazocine and promethazine with ketamine, was at "high risk" of bias in the "measurement of the outcome" because significantly more patients randomized to pentazocine and promethazine were given post-procedural intravenous fentanyl, which may have produced lower than anticipated pain scores and therefore a lack of statistical difference in mean pain scores between the two groups [17].

Impact on pain

Fig. 3 illustrates the effect of conscious sedation on pain during office hysteroscopy when compared to a control. Significantly reduced intra-procedural pain was seen with intravenous sedation when compared to local anesthesia (2 studies [11,12], 246 patients; SMD −0.26, 95% CI −0.51 to −0.01), and with inhaled sedation when compared to an oral analgesic and anxiolytic (1 study [14], 64 patients; SMD −1.04, 95% CI −1.57 to −0.52). In contrast, a significant increase in intra-procedural pain was seen when giving intravenous sedation when compared to the administration

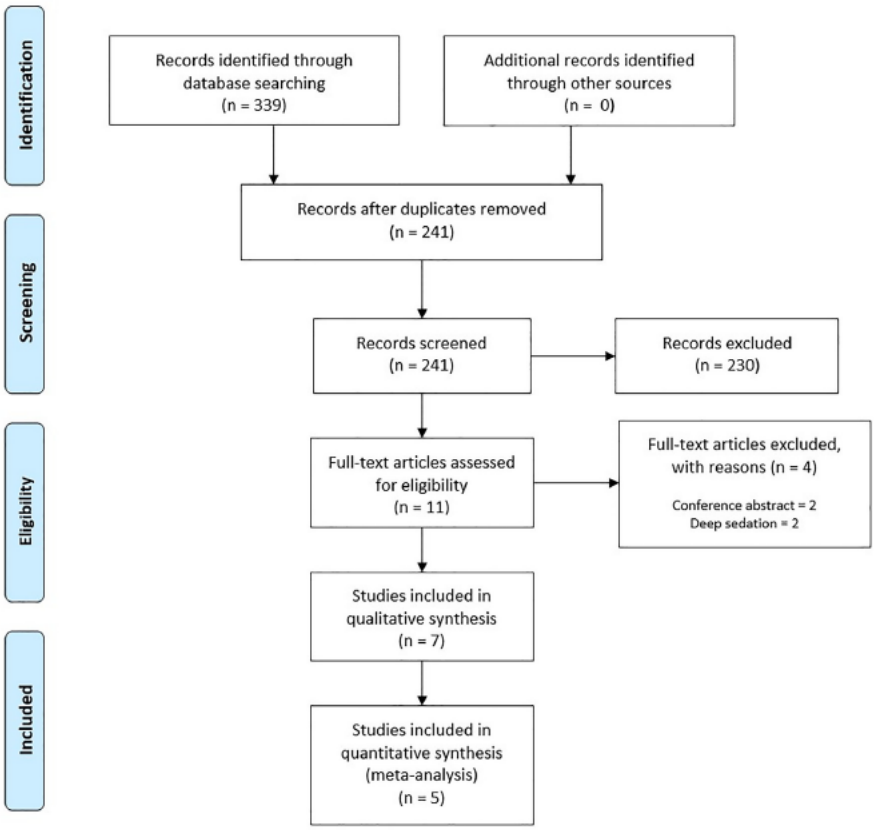

Fig. 1. PRISMA flow diagram of the study selection process.

of an oral analgesic and antispasmodic (1 study [12], 80 patients; SMD 1.03, 95% CI 0.56 to 1.49). There was no benefit in giving intravenous conscious sedation when compared to either oral analgesia (1 study [13], 84 patients; SMD −0.16, 95% CI −0.59 to 0.26) or a combination of rectal analgesia, oral anxiolysis and local anesthesia (1 study [15], 56 patients; SMD −0.49, 95% CI −1.03 to 0.04).

Fig. 4 depicts the effect of conscious sedation on pain after office hysteroscopy, when recorded at 15 min [11], 30 min [12], and 3 h [15] after the end of hysteroscopy. There was no significant difference in post-procedural pain with the administration of intravenous sedation when compared to local anesthesia (2 studies [11,12], 246 patients; SMD −0.18, 95% CI −0.43 to 0.07) or a combination of rectal analgesia, oral anxiolysis and local anesthesia (1 study [15], 56 patients; SMD −0.08, 95% CI −0.60 to 0.45). Similarly, to intra-procedural pain, a significant increase in post-procedural pain was found when giving intravenous sedation when compared to the administration of an oral analgesic and antispasmodic (1 study [12], 80 patients; SMD 0.49, 95% CI 0.04 to 0.93).

Women randomized to dexmedetomidine had significantly lower post-procedural pain scores than women randomized to propofol at 1, 15 and 30 mins after hysteroscopy [16]. Intra-procedural pain was not assessed and mean pain score data could not be extracted as this was only presented graphically. Women randomized to pentazocine and promethazine did not show a significant difference in pain compared to women randomized to ketamine, when recorded at 45, 60, 75, 90, 105 and 120 min from the start of hysteroscopy ($p > 0.05$), where women randomized to ketamine were unable to give pain scores recorded at 15 and 30 min because they were "deeply sedated and did not respond to verbal commands during the procedure time" [17].

Adverse events

Three studies reported on the incidence of side-effects when comparing conscious sedation against a control [11,12,15]. Abdominal cramps were not recorded as a side-effect for the purposes of this review, as this was considered an extension of post-procedural pain. The first showed a similar incidence of side-effects in women randomized to intravenous sedation (n = 9/84) or local anesthesia (n = 7/82), namely in the form of pallor/hypotension and nausea/vomiting [11]. The second study demonstrated a significantly higher proportion of side-effects in women randomized to intravenous sedation, in the form of dizziness (n = 20/40; where in 12 women, this persisted for over one hour after the end of

Table 1
Details of the populations studied, hysteroscopic procedures performed, and interventions patients were randomized to amongst all included studies.

Study	Population Studied	Procedural Details	Group 1	Group 2	Group 3
Guida 2003	166 premenopausal women with treatable lesions (fibroids, septa, intrauterine adhesions, endometrial polyps) associated with infertility or abnormal uterine bleeding.	**Therapeutic hysteroscopy** was performed with a 5.5 mm outer diameter Versapoint operative hysteroscope with a 5 F working channel, using bipolar electrodes and a grasper.	**Conscious IV sedation** performed immediately before hysteroscopy with IV atropine (0.5 mg) and fentanyl (0.25 mg), followed by a slow IV injection of midazolam (2 mg).	**Local anesthesia** was given by the form of a paracervical block with 10 ml 1% mepivacaine hydrochloride solution.	
Sharma 2009	120 women with abnormal uterine bleeding or infertility.	**Diagnostic hysteroscopy** was performed with a rigid 5 mm diameter 30° fore oblique hysteroscope, and **endometrial biopsy** with a 4 mm Karman's cannula.	**Conscious IV sedation** performed 10 min before hysteroscopy with IV diazepam (0.2 mg/kg body weight) and IV pentazocine (0.6 mg/kg body weight).	**Local anesthesia** was given 5 min before hysteroscopy by the form of a paracervical block with 10 ml 1% lignocaine solution.	An **oral analgesic and antispasmodic** given 1 h prior in the form of 250 mg mefenamic acid and 80 mg drotaverine.
Thiel 2011	85 women of reproductive age, seeking permanent contraception.	**Therapeutic hysteroscopic Essure Micro-Insert sterilization** was performed with a 5 mm single channel operative hysteroscope with a 12 degree 2.7 mm lens and a 5 F operating channel.	An **oral placebo** was given 1 h before hysteroscopy together with **conscious IV sedation** performed immediately before hysteroscopy with IV fentanyl (2 mg/kg) and IV midazolam (2 mg).	**Oral analgesia** was given 1 h before hysteroscopy by the form of 5 mg oral oxycodone, and 500 mg oral naproxen sodium together with 2 vials of saline as an **IV placebo** immediately prior to hysteroscopy.	
Asgari 2017	84 women with endometrial polyps and an American Society of Anesthesiologist (ASA) grades of I or II.	**Therapeutic hysteroscopic endometrial polypectomy** was performed with a Hamou 2.9 mm hysteroscope with a 30° fore oblique lens and a 4 mm sheath, where endometrial polyps were removed using grasper forceps, with or without scissors .	**Conscious IV sedation** performed 10 min before hysteroscopy with IV propofol 1% (2 3 mg/kg/h) and IV midazolam (0.02 mg/kg) and fentanyl (1 2 mcg/kg) with O_2 4 5 l/min via a face mask.	**Rectal analgesia** was given as a 100 mg diclofenac sodium suppository and **oral anxiolysis** was given by the form of 10 mg diazepam 1 h before hysteroscopy. **Local anesthesia** was given immediately before hysteroscopy by the form of a paracervical block with 10 ml 2% buffered lidocaine.	**General anesthesia**.[1]
Schneider 2017	72 women, aged 21 years or over, seeking permanent contraception.	**Therapeutic hysteroscopic sterilization** with a 5 mm operative hysteroscope.	An **oral placebo** (methylcellulose gel) was given $\geq$ 30 min before hysteroscopy. **Conscious inhaled sedation** was administered during hysteroscopy with N_2O/O_2 titrated to a maximum concentration of 70% N_2O and 30% O_2 based on the desired analgesic effects as per a predetermined sedation scale.[2]	**Oral analgesia** was given by the form of one 5/325 mg tablet of hydrocodone/ acetaminophen and **oral anxiolysis** was given by the form of a 1 mg tablet of lorazepam at least 30 min before hysteroscopy. **An inhaled placebo** (O_2) was administered during hysteroscopy.[2]	
Bingol Tanriverdi 2019	60 women, aged between 18 and 65 years, with American Society of Anaesthesiologist (ASA) grades I or II.	**Minor hysteroscopic surgery** of unknown type.	A midazolam (0.03 mg/kg) and fentanyl (1.5 mcg/kg) IV bolus were given immediately before hysteroscopy. Prophylactic O_2 (4 l/min) was provided by a suitable face mask during the hysteroscopy. **Conscious IV sedation** was performed with **dexmedetomidine** at a loading dose of 1 μg/kg over 10 min, followed by a 0.7 μg/ kg/h maintenance infusion which was adjusted as required.		A midazolam (0.03 mg/kg) and fentanyl (1.5 mcg/ kg) IV bolus were given as premedication immediately before hysteroscopy. Prophylactic O_2 (4 l/ min) was provided by a suitable face mask during the hysteroscopy. **Conscious IV sedation** was performed with a bolus of 1.5 mg/kg **propofol** followed by a 2.5 mg/kg/h maintenance infusion which was adjusted as required.

(*continued on next page*)

Table 1 (*continued*)

Study	Population Studied	Procedural Details	Group 1	Group 2	Group 3
Goswami 2020	72 nulliparous women, aged between 18 and 40 years, with American Society of Anaesthesiologist (ASA) grades I or II.	**Diagnostic hysteroscopy** using a 4 mm hysteroscope.	IV midazolam (50 mcg/kg) was administered 10 min before hysteroscopy. **Conscious IV sedation** was performed with an IV bolus of **pentazocine** (15 mg) and **promethazine** (12.5 mg) followed by an IV saline infusion.[3]	IV midazolam (50 mcg/kg) was administered 10 min before hysteroscopy as premedication. **Conscious IV sedation** was performed with an IV bolus of **ketamine** (0.75 mg/kg) followed by an IV ketamine infusion (10mcg/kg/min).[3]	

[1] Further details were not recorded, as the use of general anesthesia is not in the scope of this review.
[2] All participants received a minimum of 3 min of 100% O_2 at the end of the procedure.
[3] Any patient requiring additional analgesia during or within 2 h after the procedure (VAS > 3) was given IV fentanyl 0.5 mcg/kg, and the amount of rescue fentanyl was noted.

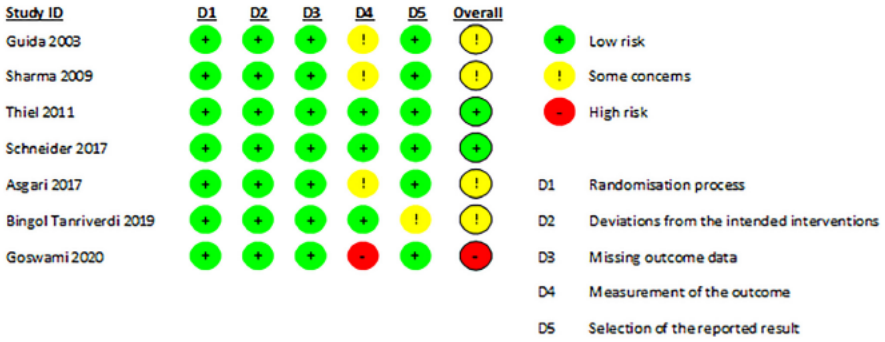

Fig. 2. Risk of bias assessment of included studies.

hysteroscopy), palpitations (n = 4/40) and nausea/vomiting (n = 7/40), when compared with women randomized to a local anesthetic (no side-effects reported) or to an oral analgesic and antispasmodic (gastritis (n = 1/40)) [12]. The final study, randomizing women to either intravenous sedation or a combination of rectal analgesia, oral anxiolysis and local anesthesia reported no side-effects [15]. Fig. 5 provides a meta-analysis of these data. This showed a non-significant increase in the incidence of side-effects when intravenous sedation was compared against local anesthesia (2 studies [11,12], 246 patients; OR 15.58, 95% CI 0.08 to 2891.91) and a significant increase in side-effects when intravenous sedation was compared against an oral analgesic and antispasmodic (1 study [12], 80 patients; OR 134.33, 95% CI 16.14 to 1118.17). No side-effects were reported in the study randomizing women to either dexmedetomidine or propofol [16]. 27/36 women were delirious ($p < 0.001$), and 3/36 women had nausea and vomiting ($p = 0.24$) following ketamine, whereas women receiving pentazocine and promethazine did not report any side-effects [17].

The only procedural complication recorded across all included studies was a uterine perforation during hysteroscope insertion [14]. No patients were reported to have required endotracheal intubation due to over-sedation in any of the included studies.

Feasibility

The incidence of failure was reported in all studies. Three studies reported no failures [11,12,16]. In one study, only unilateral placement of sterilization clips could be performed, however, the group to which this failure belonged to was not stated [13]. In another study, there were two failures in the group randomized to a combination of rectal analgesia, oral anxiolysis and local anesthesia due to unsuccessful insertion of the hysteroscope (n = 1/29) and patient intolerance (n = 1/29) [15]. Unsuccessful coil placement occurred in 2/36 women randomized to inhaled conscious sedation and 6/36 women randomized to oral anxiolysis and analgesia, however, this difference was not significant ($p = 0.15$) [14]. Two hysteroscopies (n = 2/36) were discontinued in women randomized to pentazocine and promethazine due to inadequate sedation scores [17].

Operative time was recorded in six of the seven included studies, where the average time taken for hysteroscopy ranged from 8.2 to 45.8 min [11,13–17]. Two of these studies showed a statistically significant difference in operative time between allocated groups; a shorter operative time was demonstrated in women randomized to promethazine and pentazocine when compared to ketamine (SMD −0.56, 95% CI −1.04 to −0.09) [17], and in women randomized to inhaled sedation when compared to oral analgesia and anxiolysis (SMD −0.52, 95% CI −1.02 to −0.02) [14]. The latter was the only study to investigate procedural difficulty and found no significant difference in hysteroscopic difficulty between women randomized to the aforementioned groups ($p = 0.61$) [14]. Only one study stated who administered conscious sedation, and this reported the presence of an anesthetist [17].

Satisfaction and acceptability

Three studies commented on patient satisfaction [11,14,17], and only one study reported the satisfaction of hysteroscopists and nursing staff [17]. There was no significant difference ($p > 0.05$) in the number of women satisfied with their procedure

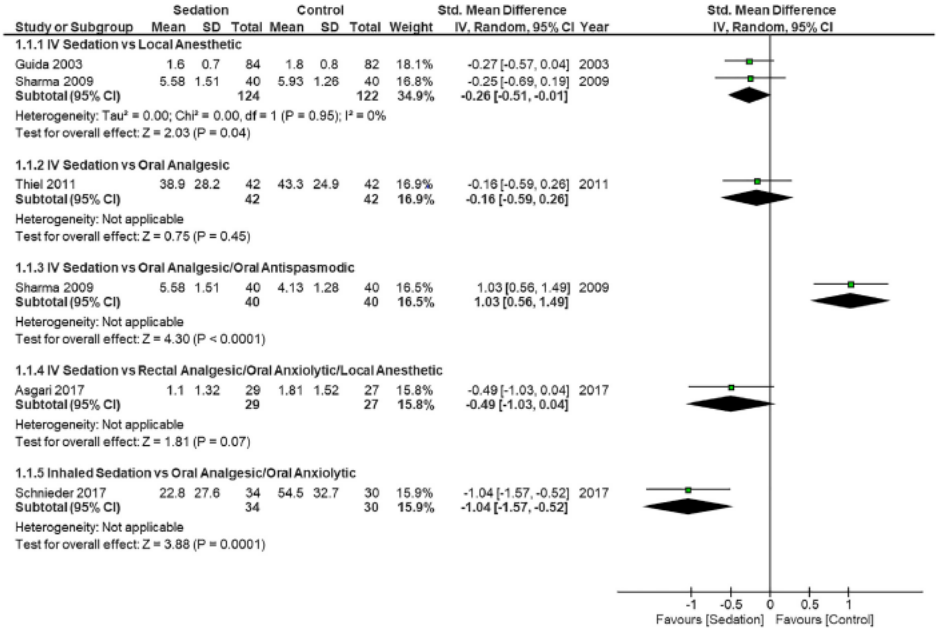

Fig. 3. Forest plots of intra procedural pain scores in studies randomizing women to either conscious sedation or a suitable control.

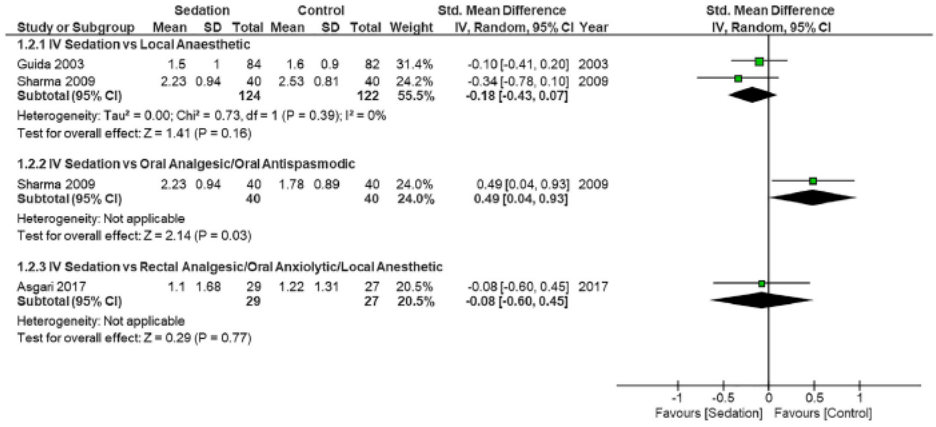

Fig. 4. Forest plots of post procedural pain scores in studies randomizing women to either conscious sedation or a suitable control.

between those randomized to intravenous sedation (96.4%) or local anesthesia (92.4%) [11]. Most women in the study randomizing women to either inhaled sedation or an oral analgesic and anxiolytic "were satisfied with their procedure pain management (81.3%) and would recommend this study to a friend (92.3%) regardless of study group" [14]. Patients and hysteroscopists were more satisfied with the effects of ketamine when compared to promethazine and pentazocine ($p < 0.001$), however, nursing staff showed significantly lower levels of satisfaction when ketamine was administered due to the greater level of nursing attention required because of a higher delirious state ($p < 0.001$) [17].

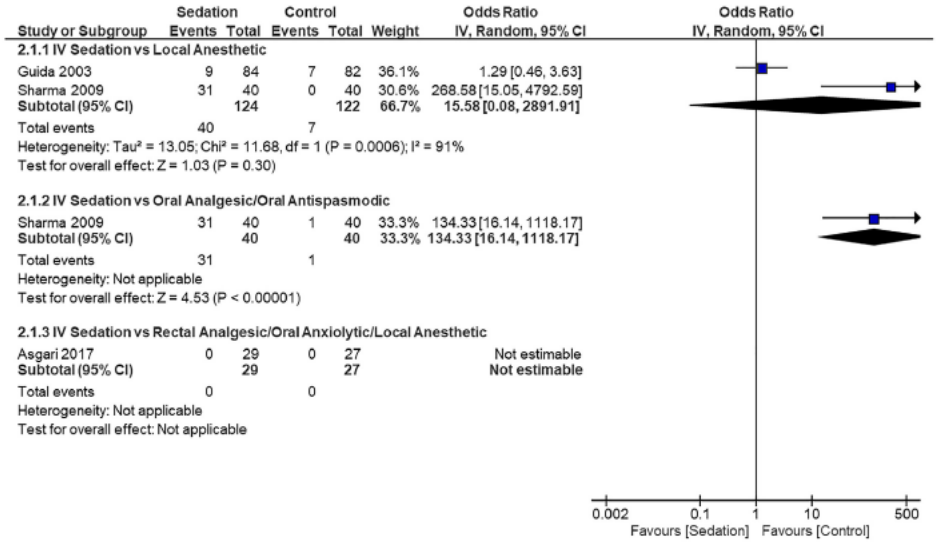

Fig. 5. Forest plots of the incidence of side effects randomizing women to either conscious sedation or a suitable control.

Discussion

Main findings

Intravenous conscious sedation did not show any benefit when compared to an oral analgesic and antispasmodic, and in fact, conferred increased pain, both during and after hysteroscopy [12]. Similarly, intravenous sedation did not confer any reduction in pain when compared to a composite local anesthetic, analgesic and anxiolytic regime [15]. Where intravenous conscious sedation was compared with local anesthesia, there was a marginal reduction in pain during, but not after, office hysteroscopy [11,12]. The two studies from which this data was pooled, however, does not reflect modern office hysteroscopic practice; the first evaluated a wide range of prolonged therapeutic procedures lasting over 20 min [11], a duration which is not typical for most operative office hysteroscopic procedures and in the second [12], all patients underwent diagnostic hysteroscopy using a 5 mm hysteroscope. This is a larger diameter than is used in contemporary practice, where the advent of miniaturized hysteroscopes facilitates the vaginoscopic approach which reduces pain and improves the acceptability of office hysteroscopy [18]. Intravenous conscious sedation was associated with more side-effects (e.g. dizziness and nausea & vomiting), when compared to their control groups [11,12]. Inhaled conscious sedation, in the form of 70% N_2O/30% O_2, showed promising results, demonstrating the greatest analgesic effect during office hysteroscopy when compared to an oral analgesic and anxiolytic [14]. These data were limited to one trial, and whilst generally well-accepted, the incidence of side-effects were not reported. Operative time across all studies was on average, 8.2 to 45.8 min [11,13–17], where inhaled sedation reduced the time taken for hysteroscopy, again when compared to an oral analgesic and anxiolytic [14]. In the one study where patients and clinicians reported satisfaction, patients preferred deeper levels of sedation, although the resulting delirium required more nursing attention [17].

Strengths and limitations

This systematic review was performed using a clinically-focused question. The search strategy was comprehensive, where multiple databases were searched, and the reference lists of included papers were scanned to ensure all potential studies were included. No restrictions were placed, and broad search terms were used to increase the sensitivity of the search. Two reviewers independently selected studies, extracted data and assessed bias to minimize human error. Finally, only RCTs were included to reduce selection bias.

The main limitation was that of heterogeneity arising from methodological weaknesses and differences in conduct between included RCTs. The robustness of comparisons and the ability to aggregate data was hindered by differences in the interventions administered for conscious sedation as well as for their control groups. Studies also had differences in the composition of their patient population, concomitant pain relief interventions (e.g. analgesia, local anesthesia etc.), technique (e.g. cervical dilatation), procedures performed (i.e. diagnostic or therapeutic), equipment used (e.g. hysteroscope diameter), procedural duration and experience of hysteroscopist.

Comparison with existing literature

There are no previous systematic reviews exploring the role of conscious sedation for office hysteroscopy, and previous evidence-based national guidance has highlighted this scarcity of data [4]. Recent guidance published in 2019 by the National Institute for Health and Care Excellence on the use of anesthesia or sedation for surgical abortion [19], identified two RCTs investigating the role of conscious sedation against placebo [20,21], where both failed to identify a significant difference in pain scores between groups, with a higher incidence of side-effects (e.g. drowsiness) in women randomized to conscious sedation, in keeping with the findings of this review.

Implications for clinical practice

The American Society of Anesthesiologists in the United States [6], and the Academy of Medical Royal Colleges, in the United Kingdom [22], have produced guidelines for the safe administration of conscious sedation. Both stress the importance of having separate practitioners (to the operating clinician) available who administer sedatives and are able to identify and rescue a patient who becomes over-sedated. This may require the administration of a reversal agent, maintenance of the patient's airway to establish satisfactory ventilation and oxygenation, and/or full cardiopulmonary resuscitation. Patients are therefore required to have vital observations monitored during and after the procedure (heart rate, blood pressure, respiratory rate, pulse oximetry, with electrocardiography and capnography performed where appropriate). Careful pre-procedural patient selection is key to reducing the risks associated with sedation, where elderly, obese and/or co-morbid patients may either not be suitable for conscious sedation or require different sedating agents and/or doses. In modern practice, the use of conscious sedation as a minimum will require an anesthetist or healthcare professional with anesthetic training. Furthermore, it will necessitate an environment in which conversion to general anesthesia is possible, where most outpatient clinics will not be able to accommodate this. Moreover, even where ambulatory units can induce general anesthesia safely, the safety and benefits of patients undergoing intravenous conscious sedation over a short general anesthetic in theatre should be weighed up.

Implications for future research

There is a need to find the specific patient populations (e.g. nulliparous women) and the type of office hysteroscopic procedures (e.g. endometrial ablation) where conscious sedation would be of most benefit. An ideal conscious sedation would be one with a quick onset of action, with analgesic, anxiolytic and sedative effects and a short duration of action, without any impact on vital observations (negating the requirement for a specific sedating practitioner), such that its effects wear away shortly after administration is stopped, allowing patients to return to their normal daily activities (e.g. driving, work, childcare) as soon as they leave the outpatient setting.

Conclusion

There are no clear, consistent data to inform strong clinical inferences about the role of conscious sedation on the pain experience associated with office hysteroscopy. This lack of clarity relates to the lack of uniformity in regimes used, or consistency in types of comparator. Available data suggests that intravenous conscious sedation administered to women undergoing office hysteroscopic procedures does not reduce pain and in fact, increases the risk of side-effects. There is, however, promise shown with the use of inhaled conscious sedation (in the form of 70% N_2O/30% O_2), with regards to pain and patient acceptability, however, data were limited to only one trial, where its side-effect profile was not evaluated. The routine use of conscious sedation cannot therefore be advocated for reducing the pain associated with office hysteroscopy outside of a research context.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CHAPTER 9: EQUIPMENT FOR OPERATIVE OUTPATIENT HYSTEROSCOPY

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My role in this publication is as follows: I carried out the literature search, collected the data, and wrote the manuscript.

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Review Article

Pain and Operative Technologies used in Office Hysteroscopy: A Systematic Review of Randomized Controlled Trials

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ABSTRACT **Objective:** To identify technologies associated with the least operative pain in women undergoing operative office hysteroscopic procedures.

Data Sources: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Central Register of Controlled Trials were searched until January 2021 using a combination of keywords "hysteroscop*," "endometrial ablation," "outpatient," "ambulatory," "office," and associated Medical Subject Headings.

Methods of Study Selection: Randomized controlled trials evaluating the effect of hysteroscopic devices on pain experienced by women undergoing operative office hysteroscopy were included. Data were also collected regarding efficacy, procedural time, adverse events, and patient/clinician acceptability and/or satisfaction.

Tabulation, Integration, and Results: The search returned 5347 records. Ten studies provided data for review. Two trials compared endometrial ablation using bipolar radiofrequency with thermal balloon energy, with no significant difference in pain observed ($p < .05$). Seven trials evaluated technologies for endometrial polypectomy, of which, 4 compared energy modalities: miniature bipolar electrode resection against resectoscopy (N = 1), morcellation (N = 2), and diode laser resection (N = 1). Two studies compared hysteroscope diameter, and one study compared methods of polyp retrieval. A significant reduction in pain was found using morcellators rather than miniature bipolar electrosurgical devices ($p < .001$), 22Fr rather than 26Fr resectoscopes ($p < .001$), and 3.5-mm fiber-optic hysteroscopes with 7Fr forceps rather than 5-mm lens-based hysteroscopes with 5Fr forceps ($p < .05$). One study investigating septoplasty showed significant reduction in pain when cold mini-scissors, rather than a miniature bipolar electrode, were used ($p = .013$). Average procedural times ranged from 5 minutes 28 seconds to 22 minutes. The incidence of adverse events was low, and data regarding efficacy and acceptability/satisfaction were limited.

Conclusion: Pain is reduced when mechanical technologies such as morcellators and scissors are used compared with electrical devices for removing structural lesions in the office. For hysteroscopic and ablative procedures, smaller and quicker devices are less painful. Large-scale RCTs investigating patient pain and experience with modern operative devices in the office setting are urgently needed. Journal of Minimally Invasive Gynecology (2021) 00, 1 13. © 2021 AAGL. All rights reserved.

Keywords: Ablation; Endoscopy; Outpatient; Polypectomy; Septum

Operative hysteroscopy, used to treat pathologies associated with abnormal uterine bleeding and uterine factor subfertility, is increasingly being performed in the "office," "outpatient," or "ambulatory" setting [1]. When compared with the formal theater setting under a general anesthetic, patients are in hospital for less time (and therefore have a higher turnover), fewer staff are required, less space and equipment are needed, and thus, this increases efficiency and reduces overall healthcare costs [2,3]. Many hysteroscopy clinics adopt a "see-and-treat" practice allowing both diagnosis and treatment of intrauterine pathology to occur in the same sitting, reducing the number of healthcare visits that the patients have to make [3]. The greatest barrier to delivering this procedure, however, is pain [4], which arises

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from genital tract instrumentation (use of a vaginal speculum ± cervical tenaculum ± cervical dilatation), uterine cavity distension, and trauma to the endometrium and myometrium [5].

A number of operative procedures, such as endometrial polypectomy [6] and endometrial ablation [7], have been shown to be feasible and well-tolerated in the office setting. It is clear that the smaller the hysteroscope diameter, the less the pain that is conferred with regard to diagnostic hysteroscopy [8]; however, no such evidence synthesis exists to make recommendations for the use of specific devices with regard to therapeutic hysteroscopic procedures. We, therefore, performed a systematic review to provide an overview of the randomized controlled trials investigating different therapeutic hysteroscopic technologies used in the office setting with regard to pain.

Methods

Protocol and Guidance

This study was performed using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [9] and Cochrane Handbook for Systematic Reviews of Interventions [10] and based on a protocol registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42019138676) [11]. The search set out to encompass studies comparing different therapeutic hysteroscopic devices in the office setting.

Inclusion Criteria

Randomized controlled trials (RCTs) investigating women undergoing office therapeutic hysteroscopy who were randomized to undergo hysteroscopy using a specific device that was compared against another distinct device with the aim of achieving the same therapeutic outcome (e.g., removal of an endometrial polyp, removal of a septum, ablation of the endometrium, etc.), where pain was assessed as an outcome.

Exclusion Criteria

Observational studies, conference abstracts (where no full-text manuscript was available), case reports, and case series were excluded.

Outcomes

The primary outcome for our review was pain. Secondary outcomes included efficacy (e.g., alleviation of symptoms e.g., heavy menstrual bleeding), procedural time, adverse events (side-effects, complications, failure), and the satisfaction/acceptability of both patients and hysteroscopists.

Search Strategy

MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to the January 4, 2021. A combination of the keywords "hysteroscop*," "endometrial ablation," "outpatient," "ambulatory," "office," and their associated medical subject headings were used to search MEDLINE, Embase, and CINAHL through the National Institute for Health and Care Excellence Healthcare Databases Advanced Search platform. The key words "hysteroscop*" and "endometrial ablation" were used to search CENTRAL. In order to capture as many studies as possible, restrictions were not placed on the search, the reference lists of all included papers were reviewed, and further studies were included if the inclusion criteria were met.

Study Selection

The Healthcare Databases Advanced Search platform was used to remove duplicates from MEDLINE, Embase, and CINAHL. Duplicates from the CENTRAL search were manually excluded. Two reviewers (P.D.S and H.S.) independently screened all titles and abstracts and reviewed selected full-text manuscripts to determine the studies suitable for qualitative synthesis. If disagreements were not resolved by consensus, a third independent reviewer (P.P.S.) determined study suitability.

Data Collection Process

Two reviewers (P.D.S and H.S.) independently used a standardized data extraction form to extract data from the included trials. In addition to outcome data already specified above, data were also collected regarding the population studied, procedural details, and agents used for pain relief (pre-, peri-, and postprocedurally).

Assessment of Risk of Bias

Two independent reviewers (P.D.S and H.S.) examined the quality of the included studies on an intention-to-treat basis, using the Cochrane Collaboration Risk of Bias 2 tool [12]. If consensus could not be reached, then the same third independent reviewer (P.P.S) determined study quality.

Data Synthesis

The interventions compared among included studies were too heterogeneous to allow for the meta-analysis of outcome data. Instead, a narrative review was performed.

Results

Study Selection

The literature search yielded 5347 records, where Fig. 1 details the process involved in selecting the 10 studies that were included for qualitative synthesis [13 22], one of which was selected after scanning through the reference lists of the already included full-text articles [13].

Study Characteristics

Table 1 outlines the study characteristics of the included trials, detailing the populations studied, procedures performed, instruments used, and pharmacological agents administered to minimize pain. As per manufacturer guidance [23], we considered the 1.8-mm diameter Alphascope (Gynecare, division of Ethicon, Somerville, NJ) as a hysteroscope which can be used alone or with a Versascope (Gynecare, division of Ethicon, Somerville, NJ) expandable sheath, which increases the total diameter to 3.5 mm. When using a 5Fr (1.7-mm diameter) or 7Fr (2.3-mm diameter) ancillary instrument, this increases the total diameter to 5.2 mm or 5.8 mm, respectively. Versapoint (Gynecare, division of Ethicon, Somerville, NJ) refers to the 5Fr bipolar electrode that is used for electrosurgical resection.

Two trials investigated technologies used for undertaking office endometrial ablation, comparing bipolar radiofrequency ablation against thermal balloon ablation [14,17]. While both used NovaSure devices for bipolar radiofrequency ablation, the first compared this against Thermachoice III (Gynecare, division of Ethicon, Somerville, NJ) [14], whereas the second study compared this against Thermablate (Idoman Teoranta, Toronto, Canada) [17]. Seven trials investigated technologies used for undertaking office endometrial polypectomy [13,15,16,18 21]. Four studies compared bipolar electrosurgical resection (using

Fig. 1

Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram depicting the study selection process.

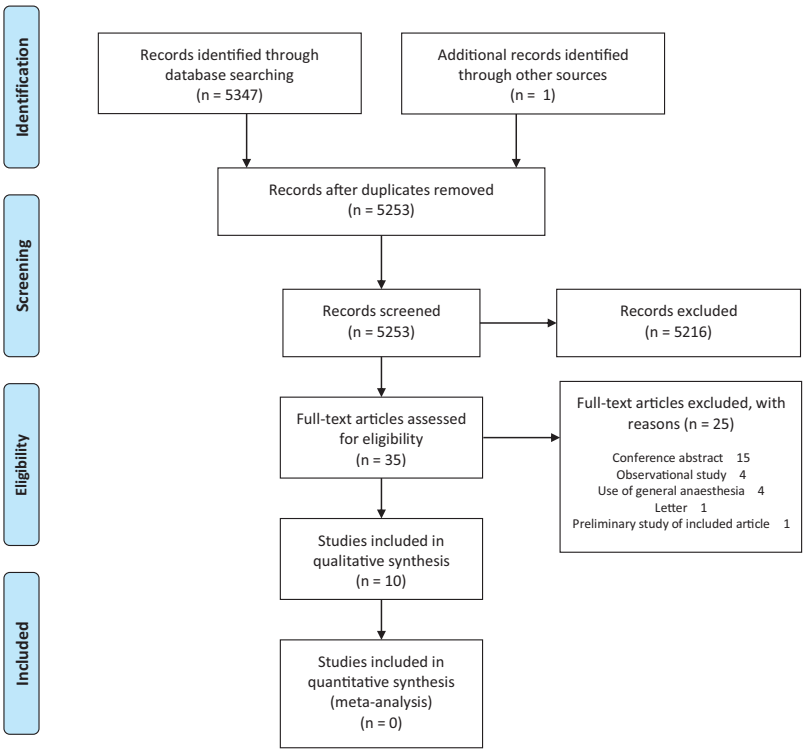

Table 1

Study characteristics

Procedure	Study	Population	Group 1	Group 2	Pain relief*
Endometrial Ablation	Clark et al [14] 2011	Women with HMB aged ≥25 yrs old with a FSH <40 iu/L and UCL ≤11 cm	NovaSure bipolar radiofrequency impedance-controlled endometrial ablation	Thermachoice III thermal balloon ablation	1 hr prior: 100 mg PR diclofenac (100 mg PO tramadol if allergic to NSAIDs), 20 mg/1 g PO codydramol, 50 mg PO cyclizine Immediately prior: 6.6 mL 2% mepivacaine ICB After: PRN 10 mg PO/IV morphine and/or 30−60 mg PO codeine
	Penninx et al [17] 2016	Women with HMB with an FSH <40 iu/L and UCL 6−12 cm with endometrial ablation performed at day 3 to 8 of the menstrual cycle	NovaSure bipolar radiofrequency impedance-controlled endometrial ablation.	Thermablate thermal balloon ablation	1 hr prior: 500 mg PO naproxen 3 mins prior: 12−20 mL articaïn with adrenaline PCB After: PRN 1 g QDS paracetamol and/or 500 mg PO naproxen or tramadol 100 mg
Endometrial	Polypectomy	Muzii et al [13] 2007	Women aged 18−75 years old with a BMI 18−30 kg/m^2 and a polyp on diagnostic hysteroscopy using a 3.5-mm Alphascope	5Fr Versapoint bipolar electrode passed through a 3.5-mm Versascope (total diameter 5.2 mm) for polyp resection. Polyp extraction with hysteroscopic forceps, or if failed, with polyp forceps after cervical dilatation, where necessary.	Cervical dilatation to 9 mm. Distension medium changed from normal saline to hypo-osmolar nonconductive medium. 8-mm resectoscope for polyp resection (total diameter 8 mm)
	IV sedation				
	Cicinelli et al [19] 2011	Women with a sonographically diagnosed endometrial polyp <2 cm in the follicular phase (day 5−11) of the menstrual cycle	5 Fr Versapoint bipolar electrode passed through a 3.5-mm Versascope (total diameter 5.2-mm) for polyp resection. 7Fr forceps used for polyp extraction (total diameter increased to 5.8 mm).	Rigid lens-based hysteroscope equipped with 5Fr forceps (total diameter 5 mm)	None recorded
	Smith et al [15] 2014	Women who had a hysteroscopically diagnosed endometrial polyp and in whom polypectomy was indicated	5 Fr Versapoint bipolar electrode passed through a 3.5-mm Versascope (total diameter 5.2 mm) or through a Bettocchi hysteroscope system (total diameter 5 mm) for polyp resection. 5Fr hysteroscopic instruments (e.g., grasping forceps, snares) or standard polyp forceps used for polyp extraction.	Truclear 5.0 hysteroscopy system with a 5-mm hysteroscope incorporating a 2.9-mm morcellator for polyp resection and extraction (total diameter 5 mm)	6.6 mL 3% mepivacaine ICB given if cervical dilatation anticipated (Use between groups not significant; p = .4)

Table 1

Continued

Procedure	Study	Population	Group 1	Group 2	Pain relief*
	Pampalona et al [16] 2015	Women with a sonographically diagnosed endometrial polyp >1 cm	5 Fr Versapoint bipolar electrode passed through a 5.5-mm 30° Olympus rigid hysteroscope system (3-mm hysteroscope and 5Fr working channel; total diameter 5.5 mm), with polyp resection performed at 50 W using a non-modulated current setting of VC3. Standard forceps with a polyp grip were used as the auxiliary instrument for polyp extraction.	Truclear 5.0 hysteroscopy system with a 5-mm hysteroscope incorporating a 2.9-mm morcellator for polyp resection and extraction (total diameter 5 mm)	Nil given
	Lara-Domínguez et al [18] 2016	Women with a polyp measuring between 10 and 40 mm on diagnostic hysteroscopy using a 30° Bettocchi hysteroscope	5 Fr Versapoint bipolar electrode passed through the 5Fr working channel of a rigid 5-mm hysteroscope for polyp resection (total diameter 5 mm).	Polyfiber connected to a 980-nm Biolitec Ceralas HPD laser device introduced through the 7Fr working channel of a rigid 6-mm hysteroscope for polyp resection (total diameter 6 mm)	Nil given
	Sudano et al [20] 2016	Women with a sonographically confirmed endometrial polyp	18° hysteroscope with a 5Fr working channel where polyp resection performed using either cold mechanical resection (micro-scissors or crocodile microforceps) or Versapoint (total diameter 5 mm). Polyp extraction using hysteroscopic "isterobasket."	18° hysteroscope with a 5Fr working channel where polyp resection performed using either cold mechanical resection (micro-scissors or crocodile microforceps) or Versapoint (total diameter 5 mm). Polyp extraction using classic surgical instruments e.g., 5Fr crocodile micro-forceps	Nil given
	Remondi et al [21] 2018	Women aged 18–80 yrs with an endometrial polyp <3 cm	Cervical dilatation to 7.5 mm using Hegar dilators. Polyp resection using unipolar resectoscope with a 30 cm × 4 mm, 12° optic rod lens hysteroscope and a 22Fr outer sheath (total diameter 7.3 mm).	Cervical dilatation to 9.5-mm using Hegar dilators. Polyp resection using unipolar resectoscope with a 30 cm × 4 mm, 12° optic rod lens hysteroscope and a 26Fr outer sheath (total diameter 8.7 mm)	Prior: 0.025 mg/kg IV midazolam and 5 mL 2% mepivacaine PCB During: 0.075 mcg/kg IV sufentanil if VAS >6 (Use between groups not significant; p = .754)
Uterine	Septoplasty	Kamel et al [22] 2014	Women aged 20–45 years, with a sonographically diagnosed short, narrow-based septum <2 cm in the early proliferative phase of the woman's menstrual cycle	3.5-mm Versascope allowing for insertion of 7Fr semirigid mini-scissors, for mechanical resection (total diameter 5.8 mm).	3.5-mm Versascope, allowing for insertion of 5 Fr Versapoint at vapor cut VC1 and 100W, for electrosurgical resection (total diameter 5.2 mm)
Nil given					

BMI = body mass index; FSH = follicle-stimulating hormone; ICB = intracervical block; IV = intravenous; NSAIDs = non-steroidal anti-inflammatory drugs; PCB = paracervical block; PO = oral; PR =rectal; PRN = as required; QDS = four times per day; UCL = uterocervical length; VAS = visual analogue scale; VC = visual analogue scale.

Fig. 2

RoB 2 assessment of included studies. D domain.

Versapoint) against resectoscopy [13], mechanical morcellation (using Truclear) [15,16], and diode laser resection [18]. One study compared Versascope expanded to 5.8 mm with 7Fr forceps against a 5-mm lens-based hysteroscope with integral working channel accommodating 5Fr forceps [19]. Another study compared different methods of polyp retrieval, comparing a specially manufactured "isterobasket" against traditional tissue-retrieval instruments (e.g., 5F forceps) [20]. The final study investigating devices for polypectomy compared a 22Fr (7.3-mm) mini-resectoscope against a 26Fr (8.7-mm) resectoscope [21]. Two studies did not comment on their method of polyp extraction once resection was completed [18,21]. One trial investigated electrosurgical (Versapoint) against mechanical (cold mini-scissors) resection for office uterine septoplasty (for sonographically diagnosed septa <2 cm) [22]. In this study, a single-dose intraoperative intravenous antibiotic was given according to hospital protocol to all patients. No trials investigated technologies used for office myomectomy. All but one study recorded pain on a 10-point visual analogue scale (VAS), which instead, recorded pain on a 100-point VAS [15].

Study Bias

The risk of bias for each study according to each methodological characteristic is displayed in Fig. 2.

Six studies displayed no concerns regarding study conduct [13,15,17,19,21,22]; however, 1 showed "some concerns [18]," and 3 were considered at "high risk" of bias [14,16,20]. In the one study that displayed "some concerns," this was because of a lack of detail regarding the randomization process. In the first study showing a "high risk" of bias [14], this was because of missing outcome data, where only 32/42 and 22/39 women randomized to bipolar radiofrequency and thermal balloon endometrial ablation, respectively, provided pain scores. In the second study that displayed a "high risk" of bias [16], the main issue arose from the fact that these results were "preliminary" with no reasons given for performing an interim analysis. In addition, little detail was given with regard to randomization, and pain scores were reported as means in one context and medians in another, without explanation, suggesting that these were presented in such a way due to the impact of their actual results. The authors of this study were contacted for clarification, but no response was received. The final study that was considered at "high risk" of bias [20], provided little detail on the randomization process, showed significant concerns in outcome measurement (which could have differed between groups as the designers of the "isterobasket" were the clinicians performing hysteroscopy) and reported result selection (as they used a 10-point VAS to record pain but presented results on a 4-point scale).

Table 2

Endometrial ablation outcome data

Study	Group 1	Pain	Group 2	Pain	p-value	Cervical dilatation	Average procedural time (min)	Adverse events
Clark et al [14] 2011	Bipolar radiofrequency impedance-controlled ablation (NovaSure) (n = 42)	During: 7.7 ± 2.0 (n = 32) 1 hr after: 5.1 ± 3.1 (n = 32) Discharge: 2.5 ± 2.1 (n = 31)	Thermal balloon ablation (Thermachoice III) (n = 39)	During: 6.5 ± 2.9 (n = 22) 1 hr after: 6.7 ± 3.1 (n = 22) Discharge: 3.7 ± 2.4 (n = 22)	p = .07 p = .07 p = .06	G1: 42/42 G2: 2/39	Ablation duration: 5.7 ± 2.1 (G1) 12.5 ± 2.3 (G2); (p <.001) Total procedural time: 12.4 ± 3.5 (G1); 18.6 ± 3.6 (G2); (p <.001)	G1: endometritis (2/42), admission 2° pain (1/42) G2: endometritis (5/39), admission 2° pain (1/39), vasovagal (1/39), failure 2° pain (2/39)
Penninx et al [17] 2016	Bipolar radiofrequency impedance-controlled ablation (NovaSure) (n = 49)	During: 7.1 ± 2.1 (n = 44) 1 hr after: 4.6 ± 3.1 (n = 44) 4 hr after: 5.7 ± 2.9 (n = 44) 12 hr after: 2.8 ± 2.0 (n = 44) 24 hr after: 1.5 ± 1.8 (n = 44)	Thermal Balloon Ablation (Thermablate) (n = 47)	During: 7.4 ± 2.1 (n = 44) 1 hr after: 4.5 ± 2.6 (n = 44) 4 hr after: 5.5 ± 2.4 (n = 44) 12 hr after: 2.5 ± 2.3 (n = 44) 24 hr after: 1.2 ± 1.8 (n = 44)	p >.05 at all time points	Yes for all patients	G1: 10.4* (6−30) G2: 12.1* (5−45); (p = .34)	G1: failure 2° pain (2/50), failure 2° cervical stenosis (1/50), failure 2° technical issues (1/50) G2: failure 2° technical issues (1/48)

G = group.
All data in mean ± standard deviation unless specified.
* median (x/y) number of patients (x − y) − range.

Table 3

Endometrial polypectomy outcome data

Study	Group 1	Pain	Group 2	Pain	p-value	Cervical dilatation	Average procedural time	Adverse events
Muzii et al [13] 2007	Bipolar electrosurgical resection [Versapoint] (n = 50)	During: not recorded 2 hr after: 0.4 ± 0.8 6 hr after: 0.3 ± 0.6 12 hr after: 0.4 ± 0.2 24 hr after: 0.3 ± 0.2	Resectoscope (n = 50)	During: not recorded 2 hr after: 0.6 ± 0.9 6 hr after: 0.3 ± 0.2 12 hr after: 0.3 ± 0.2 24 hr after: 0.3 ± 0.2	p >.05 at all time points	G1: only if polyp forceps required for polyp extraction G2: yes, to 9-mm	Total time: 12.2 ± 4.8 min (G1) 12.1 ± 2.8 min (G2) (p >.05) Operative time: 8.4 ± 4.3 min (G1) 6.5 ± 2.7 min (G2) (p <.01)	G1: instrument failure (6/50), false passage (1/50), conversion to other treatment (3/50) G2: instrument failure (3/50), vomiting (1/50) (p <.05)
Cicinelli et al [19] 2011	Versascope with 7Fr forceps (5.8-mm diameter) (n = 75)	During: 1.9 (1−9)	Lens-based hysteroscope with 5Fr forceps (5-mm diameter) (n = 75)	During: 3.6 (1−10)	p <.05	Not reported	Total time: 6.9 min (2−18) (G1) 5.1 min (1−17) (G2) (p <.05)	G1: failure 2° excessive endometrial mucosa thickness (2/75) G2: failure 2° pain (4/75), failure 2° polyp being too large (3/75) (p = .09)
Smith et al [15] 2014	Bipolar electrosurgical resection [Versapoint] (n = 59)	During: 52.0 ± 23.5 (n = 58) 15 min after: 31.0 ± 23.9 (n = 59)	Mechanical morcellation [Truclear 5.0] (n = 62)	During: 35.9 ± 23.5 (n = 60) 15 min after: 23.9 ± 21.2 (n = 60)	p <.001 p = .09	G1: 31/59 G2: 30/62 (p = .8)	Total time: 10 min 12 sec* (G1) 5 min 28 sec* (G2) (p <.001)	G1: vasovagal (6/59), failure 2° pain (3/59), failure 2° inadequate visualization (3/59), failure 2° inability to extract polyp (4/59) G2: vasovagal (1/62), failure 2° inadequate visualization (1/62), endometritis (1/62)
Pampalona et al [16] 2015	Bipolar electrosurgical resection [Versapoint] (n = 64)	Recorded but not reported	Mechanical morcellation [Truclear 5.0] (n = 63)	Recorded but not reported	P >.05 between groups	Not reported	Total time: 11 min 37 sec (G1) 6 min 49 sec (G2) (p <.01) Polypectomy time: 8 min 25 sec (G1) 3 min 7 sec (G2) (p <.01)	G1: failure 2° inability to access uterine cavity (1/64), failure 2° polyp being too large (4/64), failure 2° incomplete resection (6/64), failure 2° inability to extract polyp (4/64) G2: failure 2° inability to access uterine cavity (4/63), failure 2° incomplete resection (1/63)

Table 3

Continued

Study	Group 1	Pain	Group 2	Pain	p-value	Cervical dilatation	Average procedural time	Adverse events
Lara-Domínguez et al [18] 2016	Bipolar electrosurgical resection [Versapoint] (n = 52)	During: 4.4 ± −2.9	Diode laser resection (n = 50)	During: 4.4 ± 2.9	p = .91	Not reported	Polypectomy time: 329.56 ± 245.0 sec (G1) 245.96 ± 181.9 sec (G2) (p = .01)	G1: vasovagal (1/52), incomplete resection 2* poor distension (2/52) G2: vasovagal (2/50), PID (1/50), incomplete resection 2* poor distension/pain (4/50)
Sudano et al [20] 2016	Polyp extraction using "isterobasket" (n = 70)	During: 6−8/10: n = 3 4−5/10: n = 15 ≤3/10: n = 52	Polyp extraction using classical instruments (n = 70)	During: ≥9/10: n = 1 6−8/10: n = 10 4−5/10: n = 23 ≤3/10: n = 36	p = .01	Not reported	Polyp retrieval time: 29.5 sec (12-93) (G1) 54 sec (18-97) (G2) (p = .005)	Nil
Remondi et al [21] 2018	22Fr resectoscope (n = 35)	During: 1 (0−8) 1−3 hr after: 0 (0−5)	26Fr resectoscope (n = 35)	During: 2 (0−8) 1−3 hr after: 1 (0−5)	p = .003 p = .01	G1: to 7.5mm G2: to 9.5mm	Total time: 16 min (11−25) (G1) 22 min (12−55) (G2) (p = .001) Resection time: 4 min (1−13) (G1) 7 min (2−22) (G2) (p = .001)	Nil

G = group; PID = pelvic inflammatory disease.
All data in mean ± SD unless specified.
x (y − z) − median (range).
* median (x/y) − number of patients.

Table 4

Uterine septoplasty outcome data

Study	Group 1	Pain	Group 2	Pain	p-value	Cervical Dilatation	Average Procedural Time	Adverse Events
Kamel et al [22] 2014	Bipolar electrosurgical resection [Versapoint] (n = 20)	During: 6.98 ± 1.28	Cold mini-scissor resection (n = 20)	During: 4.01 ± 0.68	p = .013	No	Total time: 12.08 ± 2.62 min (G1) 12.68 ± 2.08 min (G2) (p = .25)	Nil reported

G = group.
All data in mean ± standard deviation unless specified.

Endometrial Ablation

Table 2 outlines the pain scores, procedural times, and adverse events (side-effects, complications, failures) associated with the different technologies compared for office endometrial ablation. There was no significant difference in pain scores between radiofrequency ablation (with NovaSure) and thermal balloon ablation (with either Thermachoice III or Thermablate) at all time points (p >.05) [14,17]. The first study showed a significant reduction in ablation and total procedural time (p <.001) with the use of NovaSure when compared with Thermachoice III [14] but not when compared with Thermablate (p = .34) [17]. Cervical dilatation was required for NovaSure and Thermablate but not routinely for Thermachoice III [14,17]. The incidence of adverse events was highest with Thermachoice III (23% [9/39]) [14], followed by NovaSure (8% [7/92]) and then Thermablate (2% [1/48]) [17].

The number of women reporting an acceptable procedure was higher in women receiving NovaSure (94%) when compared with Thermachoice III (77%); however, this difference was not statistically significant (p = .1) [14]. The procedural acceptability of Thermablate was not recorded [17]. When compared with thermal balloon ablation devices, NovaSure showed significantly higher amenorrhea rates [17] at 12 months after ablation in both studies (56% vs 23%; RR 2.4; 95% CI, 1.1 5.3) [14]; 56% vs 23%; RR 0.6; 95% CI, 0.4 0.8 [17]) [14]. At 12 months, significantly more patients were completely satisfied after NovaSure when compared with Thermablate (77% vs 56%; RR 0.5; 95% CI, 0.3 0.9) [17]. Satisfaction was not recorded in the study comparing NovaSure with Thermachoice III; however, both treatments resulted in an improvement in bleeding (100% vs 92% respectively; RR 1.1; 95% CI, 1.0 1.2) and dysmenorrhea (78% vs 57% respectively; RR 1.4; 95% CI, 0.9 2.1) at 12 months, with NovaSure showing a better treatment effect, although differences were nonsignificant [14].

Endometrial Polypectomy

Table 3 outlines the pain scores, procedural times, and adverse events (side-effects, complications, failures) associated with the different technologies compared for office endometrial polypectomy.

In the one study comparing miniature bipolar electrosurgical resection with resectoscopy, there was no significant difference in pain scores (p >.05) at all time points [13]. Whereas the total procedural time of around 12 minutes was similar between groups (p >.05), operative time was significantly shorter with resectoscopy by almost 2 minutes on average (p <.01). The incidence of adverse events was significantly higher with bipolar resection (p <.05); however, this was mainly due to instrument failure, and no serious adverse events were reported in either group. Although there was no significant difference in operative difficulty

between the 2 modalities (p >.05), resectoscopy left surgeons more satisfied (p <.001). Overall patient satisfaction remained high in both groups (> 9.6 on a 10-point VAS), with no significant difference in satisfaction rates in women randomized to either modality.

In the 2 studies comparing mechanical polyp morcellation with miniature bipolar electrosurgical resection [15,16], the earlier study showed a significant reduction in pain when using a morcellator (p <.001) [15], whereas the latter one did not (p >.05) [16]. The earlier study compared a 5-mm diameter hysteroscopic morcellator against either a 3.5-mm or 5-mm hysteroscope [15], whereas the latter one compared the same hysteroscopic morcellation system device against a slightly larger 5.5-mm hysteroscope [16]. Both trials demonstrated that morcellation was significantly quicker (p <.001) and associated with lower rates of failure [15,16]. Because more than 99% of women found office polypectomy acceptable, with only 1 (randomized to electrosurgical bipolar resection) out of 121 patients reporting the procedure as unacceptable, hysteroscopic morcellation was preferred (p = .009) [15].

There was no significant difference in pain experienced by women undergoing polypectomy with either miniature bipolar electrosurgery or diode laser (p >.05), with the rate of adverse events being balanced between the 2 modalities. Polyp resection, however, was quicker with the laser (p = .01) [18]. Polyp relapse was more common in women randomized to miniature bipolar electrosurgery when compared with diode laser resection at second-look hysteroscopy 3 months after the procedure (33% vs 2%; p = .001) [18]. Although there was no significant difference in satisfaction rates between these 2 methods of polypectomy (p = .21), more women stated that they would recommend diode laser resection (p = .02) [18].

Women found that the use of the Versascope system (3.5-mm diameter) with 7Fr forceps (increasing the total diameter to 5.8-mm) significantly less painful than a lens-based hysteroscope with 5Fr forceps (total diameter 5-mm) for polypectomy (p <.05), even though average procedural time was longer (6.9 minutes vs 5.1 minutes) [19]. The incidence of adverse events was small and balanced between groups (p = .09) [19]. Polyp extraction was significantly less painful (p = .01) and quicker (p = .005) using an "isterobasket" when compared with traditional ancillary hysteroscopic instruments [20]. When comparing resectoscope sizes, women randomized to a smaller 22Fr mini-resectoscope found this less painful (p <.001) and more satisfying (p = .025) when compared with a larger 26Fr resectoscope. The use of the smaller 22Fr mini-resectoscope resulted in a quicker procedure (p = .001) [21].

Uterine Septoplasty

Table 4 outlines the pain scores, procedural times, and adverse events (side-effects, complications, failures) associated with the different technologies compared for office uterine septoplasty. Cold mini-scissor resection was significantly less painful when compared with miniature bipolar electrosurgical resection (p = .013) [22]. Operative times were similar (p = .25), and no adverse events were noted with either technique [22]. All patients, regardless of the group they were randomized to, had complete resection of their uterine septum at hysterosalpingogram 3 months after septoplasty [22].

Discussion

Principal Findings

Bipolar radiofrequency endometrial ablation did not confer any advantage over thermal balloon ablation regarding pain but was advantageous in the symptomatic control of menorrhagia and patient satisfaction after 6 months; however, data were limited to 2 trials [14,17].

Polypectomy was less painful [15], quicker, and more successful [15,16] when using a hysteroscopic morcellator; however, data were limited to 2 studies. Diode laser polyp resection was only investigated in 1 study [18] and was found to be quicker and resulted in lower polyp recurrence (due to better soft tissue penetration and ablation/vaporization effect according to the authors), with patients left more satisfied when compared against women randomized to electrosurgical resection. An expandable sheath with a smaller-diameter hysteroscope conferred less pain than a rigid hysteroscope with working channel, despite the resulting total diameter being greater [19]. Polypectomy using smaller-diameter resectoscopes was less painful and quicker [21], as was polyp extraction using a specialized "isterobasket" compared with traditional ancillary hysteroscopic equipment [20].

Septoplasty using cold mini-scissors was less painful than miniature bipolar electrosurgery [22].

Comparison with Other Studies

There are no previous systematic reviews that provide an overview of all RCTs investigating the different devices used for operative office hysteroscopy.

Strengths and Weaknesses

This is the first systematic review to summarize randomized outcome data regarding technologies used for operative office hysteroscopy. Selection bias was minimized by formulating a clinically focused question, using broad search terms of multiple databases, not applying filters or restrictions, scanning the reference lists of included studies, and contacting authors where further clarification was required. Human error was minimized by having reviewers perform data collection independently.

The major limitation of this review relates to the relative dearth of high quality, large, randomized trials and the

restricted comparisons. For example, hysteroscopic morcellation was evaluated in 2 trials [15,16], and both evaluated Truclear, although systems from other manufacturers exist. Furthermore, some of the trials investigated devices that are no longer used (e.g., Thermachoice III) or have been adapted (e.g., NovaSure Advanced is 6-mm in diameter [2-mm smaller that NovaSure]) for contemporary practice, meaning that clinical inferences derived from these data must be interpreted with caution. Finally, many of the included studies were clinically and methodologically heterogenous, precluding reliable pooling of data.

Implications for Clinical Practice

Endometrial ablation is associated with moderate perioperative pain but high levels of acceptability and effectiveness. The utility of the office setting has been recognized by manufacturers, with a trend for smaller and more rapid ablative technologies (e.g., NovaSure Advanced, LiNA Librata, MiniTouch). These contemporary devices have replaced larger-diameter technologies such as NovaSure and Microsulis Microwave (MEA) or longer duration water-based thermal balloons such as Thermachoice III. However, these newer generation ablative devices have not been compared. Thus, in the absence of comparative data, the choice of device should be left to clinician discretion after considering additional sources of data pertaining to pain, patient experience, safety, feasibility, and efficacy.

Office polypectomy using a variety of mechanical and electrical devices is feasible, acceptable, and associated with low to moderate pain scores. To minimize pain, smaller-diameter hysteroscopes should be preferred, using mechanical over electrical approaches. Hysteroscopic tissue removal systems (HTRS), the preferred term for hysteroscopic morcellation devices, allow for the simultaneous resection and retrieval of intrauterine pathology under direct vision, without needing to reinsert the hysteroscope. Comparisons of HTRS with conventional mechanical forceps and scissors are lacking. Because HTRS requires bespoke hysteroscopes ranging from 5 to 7.25 mm in diameter, a smaller-diameter operative hysteroscope, such as the 3.5-mm Versascope (which can be expanded to 5.2-5.8 mm once in the uterine cavity) may facilitate vaginoscopy more readily and so be restricted to first-line use in women who do not tolerate the use of a vaginal speculum. Resectoscopy, which has a higher risk of resection into the myometrium and therefore higher resulting pain, requires larger-diameter systems (7.3 8.7-mm) and intravenous sedation, limiting its utility in the office setting.

Cold mini-scissors should be preferred over miniature bipolar electrodes for office-based septoplasty to minimize pain in the absence of clinical outcome data showing any differences in safety, feasibility, or efficacy.

Implications for Future Research

Operative hysteroscopy is increasingly performed in the office setting, and it is imperative that novel technologies are robustly assessed to inform clinicians and patients on the optimal devices from a patient experience perspective, in addition to evaluating efficacy, feasibility, and safety. Future large-scale RCTs should be performed in a standardized manner to allow wider, indirect comparisons with similar trials evaluating the same or alternative technologies.

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Addendum to Chapter 9

On page 3 of the manuscript, there is an error regarding the use of the Alphascope®. It cannot be used alone, as stated in the text, as it requires an inflow channel through which distension media can be instilled and therefore requires an outer sheath e.g. Versascope®.

CHAPTER 10: RCOG GREENTOP GUIDELINE NO. 59: BEST PRACTICE IN OUTPATIENT HYSTEROSCOPY (A NATIONAL EVIDENCE-BASED GUIDELINE FOR THE PROVISION AND PRACTICE OF OUTPATIENT HYSTEROSCOPY IN THE UNITED KINGDOM)

This work is currently under peer-review by the Royal College of Obstetricians & Gynaecologists (RCOG), for publication in the British Journal of Obstetrics & Gynaecology (BJOG).

My role in this publication is as follows: I carried out the literature searches, collected the data and wrote the manuscript. Where data was lacking, I created, disseminated and analysed the results for an online poll sent to members of the British Society for Gynaecological Endoscopy (BSGE) Ambulatory Care Network (ACN) meeting, held on Friday 18th June 2021. Further details regarding the methodology can be found in Part 2, Chapter 2.

Green-top Guideline No. 59
Second Draft – August 2022

Best Practice in Outpatient Hysteroscopy

This is the second edition of this guideline.

1. Purpose and Scope

The aim of this guideline is to provide clinicians with up to date, evidence-based information regarding outpatient hysteroscopy, with particular reference to minimising pain and optimising the patient experience. The scope has been widened since the first edition to cover operative outpatient hysteroscopy, prevention of infection, training, and documentation.

It is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2. Introduction and background epidemiology

Outpatient hysteroscopy is an established, diagnostic test[1–3] and is now in widely used across the UK.[4–6] The procedure involves the use of miniaturised endoscopic equipment (comprising an outer diameter ≤3.5mm) to directly visualise and examine the uterine cavity, without the need for formal theatre facilities, or general or regional anaesthesia.[7] Outpatient hysteroscopy is indicated primarily in the assessment of patients with abnormal uterine bleeding[1–3] but is also employed in the diagnostic work up of reproductive problems. Advances in endoscopic technology and ancillary instrumentation have facilitated the development of operative hysteroscopic procedures in an outpatient setting with or without the use of local anaesthesia. Common procedures include endometrial polypectomy,[6,8,9] removal of submucous fibroids,[10] endometrial ablation,[11–14] removal of chronic retained products of conception[15] and retrieval of lost intrauterine devices.[16]

Outpatient hysteroscopy, whether diagnostic[1,17] or operative[6,8–16] is successful, safe and well tolerated. However, as with any procedure requiring instrumentation of the uterus, outpatient hysteroscopy can be associated with significant pain,[18,19] anxiety and embarrassment.[20,21] This not only impacts upon the patient's satisfaction with their experience, but also limits the feasibility and possibly the safety, accuracy and effectiveness of the procedure. In order to minimise pain and discomfort, variations in hysteroscopic equipment, adaptations in technique and use of pharmacological agents have been advocated. This guideline assesses these components along with issues relating to optimal service provision.

3. Identification and assessment of evidence

Four databases (MEDLINE, EMBASE, CINAHL, Cochrane) were systematically searched from inception to February 2022. No restrictions were placed on the searches in an attempt to reduce selection bias. The databases were searched using relevant MeSH terms and keywords. The main keywords used were 'hysteroscopy', outpatient', 'office' and 'ambulatory' which were combined with the following words depending upon the area of hysteroscopy being examined; 'analgesia', 'analgesic', 'local anesthetic', 'local anesthesia', 'local anaesthetic', 'local anaesthesia', 'local infiltration', 'tetracaine', 'procaine', 'prilocaine', 'lidocaine', 'ethyl chloride', 'emla cream', 'cocaine', 'bupivacaine', 'benzocaine', 'sedation', 'sedative', 'hypnotic', 'tranquilizing agents', 'cervical ripening', 'prostaglandin', 'estrogen', 'oestrogen', 'progestin', 'laminaria', 'mifepristone', 'dilapan', 'progesterone', 'gestagen', 'cervical dilatation', 'cervical ripening', 'cervical preparation', 'cervix dilatation and effacement', 'no touch', 'vaginoscopy', 'vaginoscopic', 'sodium

chloride', 'carbon dioxide', 'glycine', 'mannitol', 'sorbitol', 'saline', 'dextrans', 'glucose', 'distension media', 'distension medium', 'hysteroscope', 'endometrial ablation', 'flexible', 'rigid', 'diameter', 'size', 'angle', 'infection', 'sepsis', 'endometritis', 'antibiotic', and 'pyometra'. The results of the searches were systematically reviewed to include randomised controlled trials or systematic reviews of randomised controlled trials only, in order to capture the highest level of evidence for the basis of this guideline. The definitions of the types of evidence used in this guideline originate from the US Agency for Healthcare Research and Quality.

Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'good practice points' (GPP), which were agreed upon by consensus at the British Society for Gynecological Endoscopy (BSGE) Ambulatory Care Network (ACN) Meeting, held virtually on Friday 18th June 2021.[22]

4. Service Provision

4.1 What are the requirements for running an effective outpatient hysteroscopy service?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All gynaecology departments should provide a dedicated outpatient hysteroscopy service to aid care of patients with abnormal uterine bleeding, reproductive problems, and insertion/retrieval of intrauterine devices.	**1+**	**A**	One RCT[23] showed that outpatient hysteroscopy provides quicker mobilisation and recovery, less time off work, less lost income and lower travel costs when compared to hysteroscopy performed under general anaesthesia, whilst maintaining equivalently high levels of patient satisfaction.
Outpatient hysteroscopy should be conducted outside of the formal operating theatre setting in an appropriately sized, equipped and staffed treatment room with adjoining, private changing facilities and toilet. This may be a dedicated hysteroscopy suite or a multipurpose facility.	**4**	**GPP**	An operating theatre environment is likely to provoke patient anxiety and negate the convenience and economic advantages associated with the outpatient setting.
There should be a minimum of two support staff consisting of at least one registered general nurse and one healthcare assistant.	**4**	**GPP**	Staff should provide reassurance, explanation, and support, one of whom should be dedicated to act as an advocate for the patient.[24]

An outpatient hysteroscopy service offers a safe, convenient and cost-effective means of diagnosing and treating abnormal uterine bleeding, as well as aiding the management of reproductive problems and insertion/retrieval of intrauterine devices.[25] A randomised controlled trial reported rapid mobilisation post-operatively (0 minutes [0–5] versus 105 minutes [80–120], $P<0.001$) and quicker recovery to pre-operative levels (2 days [range 1–2.7] versus 3 days, $P<0.05$) favouring diagnostic outpatient hysteroscopy compared with traditional day-case hysteroscopy under general anaesthesia.[23] The same study demonstrated high and equivalent levels of patient satisfaction with outpatient hysteroscopy when compared to hysteroscopy under general anaesthesia. Such patients also required significantly less time off work (0.8 days versus 3.3 days, $P<0.001$), lost less income and incurred lower travel costs.[26]

Outpatient hysteroscopy should be performed in an appropriately sized and fully equipped treatment room. This may be a dedicated hysteroscopy suite or a multipurpose facility. Outpatient hysteroscopy can be associated with substantial anxiety[20] and so the treatment room should be private and patient friendly, with a separate, and ideally adjoining, changing area with a toilet. Adequate resuscitation facilities should be available, as should a comfortable recovery area with refreshment making facilities. Access to on site or off-site decontamination facilities of an appropriate standard is necessary. Outpatient hysteroscopy should not be performed in a formal, operating theatre setting because this environment is likely to provoke patient anxiety and negate the economic advantages associated with the outpatient setting. Music[27,28] and the use of virtual reality headsets[29] have been shown to reduce the pain and/or anxiety associated with outpatient hysteroscopy, however, if these are to be used then units must ensure that communication with healthcare staff is not affected and that such adjuncts may not be suitable for all patients.

Appropriate staffing levels are required and these will vary according to local circumstances (patient populations, numbers seen per clinic) and the type of service offered (concomitant pelvic ultrasound, pure diagnostic service or diagnostic and therapeutic service). In general, there will be a complement of ideally three, but a minimum of two, support staff, consisting of at least one registered general nurse and one healthcare assistant. When possible, one of the staff members should act as an advocate for the patient during the procedure to provide reassurance, explanation and support. Communication with the patient in this way may help alleviate anxiety and divert their attention, thereby minimising pain and embarrassment. If the patient wishes a partner or friend to be present during their appointment, then this wish should be accommodated unless infection control precautions prevent this.[24]

4.2 What information should be provided prior to outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Written information should be provided to the patient prior to their appointment. This should include details about the procedure, the benefits and risks, advice regarding pre-operative analgesia as well as alternative management options and contact details for the hysteroscopy unit.	**4**	**GPP**	Pre -procedural information is essential to allow patients to make informed decisions regarding their care, which can be clarified and discussed further at the time of their appointment.[24]

Adequate, clear and simple, written information should be provided to the patient with the appointment letter, in the preferred language for the patient where possible. This information should include the recommendation to take a simple oral NSAID such as ibuprofen, unless contraindicated, 60 minutes before their scheduled appointment. It should also provide details about what the procedure entails, benefits and risks (including pain), and alternative options for care (e.g. alternatives to undergoing an outpatient hysteroscopic procedure) and pain-relief (e.g. inhaled analgesia, local anaesthesia etc.). Where simultaneous treatments are offered ('see and treat' services), it is important that this fact is reflected in the patient information to facilitate informed choice. In addition, the provided information should make patients aware that there are alternative types of pain management (e.g. intravenous sedation, regional and general anaesthesia) that they can choose if they have concerns about undergoing hysteroscopy in the outpatient setting or if the procedure needs to be abandoned at the patient's request. Patients should be aware that these alternative options can be discussed at their clinic appointment and that their hysteroscopy can be rescheduled to accommodate the preferred model of care and pain management as necessary.[7] Finally, patients should also be provided with up to date local contact details, should they have any questions or concerns before their procedure.

Units are advised to access the joint Royal College of Obstetricians and Gynaecologists (RCOG) and British Society for Gynaecological Endoscopy (BSGE) standards for further guidance,[24] however, the information may vary according to local circumstances and the type of service offered. Patients should be directed to,

or provided with, the joint Royal College of Obstetricians and Gynaecologists (RCOG) and British Society for Gynaecological Endoscopy (BSGE) patient information leaflet on outpatient hysteroscopy, in the absence of adequate, contemporary local patient information or to supplement the local information.[30]

4.3 How should consent be obtained prior to outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Verbal and written informed consent should be given by the patient during their appointment, prior to hysteroscopy being performed.	4	GPP	This is considered good clinical practice.[24]
The patient should be advised that if they find the procedure too painful or distressing at any point, they must alert the clinical team who will stop the procedure immediately.	4	GPP	This is considered good clinical practice.[24]

The clinical team should be mindful of the fact that arrival of the patient at the clinic does not imply consent has been given for the procedure. The hysteroscopist is the responsible clinician and must be certain that the patient has had sufficient information and enough time for consideration to give informed verbal and written informed consent on the day of their procedure. Their appointment should be rescheduled if the patient feels that they need more time to consider their decision, especially if they have not received or read the pre-procedural patient information prior to attending.[24]

The hysteroscopist must inform the patient that they are likely to experience period-like cramping and lower abdominal pain during and/or after the procedure. The patient should be advised that if they find the procedure too painful or distressing at any point, then they must alert the clinical team who will stop the procedure immediately.[24]

The Royal College of Obstetricians and Gynaecologists (RCOG) and British Society for Gynaecological Endoscopy (BSGE), in conjunction with NHS England and NHS Improvement "Getting it Right First Time (GIRFT)" programme, have recently developed relevant standardised consent documents for outpatient hysteroscopy, operative hysteroscopy and endometrial ablation.[31–33] This should include the indication for the procedure, what it involves, any additional procedures that may be necessary, possible adverse effects, and the benefits and risks when compared to other alternative options for management, which should encompass other settings and modes of anaesthesia for hysteroscopy.

4.4 Should a pre-procedural safety checklist be performed prior to outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Completion of a safety checklist should be considered prior to outpatient hysteroscopy.	4	GPP	This can help ensure that essential information such as patient identity checks and allergy status is not missed.[24]
Pregnancy should be excluded in all patients who are premenopausal and sexually active.	4	GPP	A urinary pregnancy test should either be undertaken routinely in patients who are premenopausal and sexually active, or based upon the timing of their last menstrual period

			and history of unprotected sexual intercourse.[24]

Units should consider using a checklist (e.g. a specifically adapted World Health Organisation [WHO] surgical safety checklist[34] or a locally developed outpatient procedure safety standard checklist) to make sure essential elements such as patient identity checks, allergy status and exclusion of pregnancy are recorded where appropriate.[24] While involving patients in a checklist can be empowering, for others, it may make the outpatient setting feel more like an operating theatre and induce anxiety. Units should therefore consider how and when they complete the safety checklist prior to the outpatient hysteroscopy. In self-contained, enclosed clinical areas with adjoining procedure rooms and changing areas, safety checks can be completed with the patient during the pre-procedural consultation. If safety checks are undertaken in the procedure room, patients should not be unnecessarily exposed during the process.

A urinary pregnancy test should either be undertaken routinely in patients who are premenopausal and sexually active, or based upon the timing of their last menstrual period and history of unprotected sexual intercourse.[24] If unable to exclude a pregnancy, based upon the fact that it may be too early for a urinary pregnancy test to provide a reliable result, then the appointment should be deferred.

A checklist which captures the following information is suitable for use in outpatient hysteroscopy:

- Date
- Confirmation of identification (3 identifiers; e.g. name, date of birth, address)
- Discussion of alternative pain management and settings in which these will be offered (e.g. intravenous sedation, regional/general anaesthesia in a day-case theatre setting)
- Consent performed (verbal and written)
- Allergy status
- Exclusion of pregnancy (with urinary pregnancy test if applicable)
- Details of whether and what pre-procedural pain relief has been taken (including timing and dose)

4.5 How should care after outpatient hysteroscopy be provided?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Clinical findings, further care and likely timescales of results, where appropriate, should be discussed with the patient once they are changed and comfortable. A written summary of this information should be provided to the patient and their general practitioner (GP).	**4**	**GPP**	This is considered good clinical practice.[24]
Patients should be provided with both verbal and written information as to when and how to contact their local unit.	**4**	**GPP**	This allows for the patient to be reviewed in the case of severe pain, heavy bleeding and/or signs and symptoms of genital tract sepsis.[24]
Units should have a dedicated recovery area with comfortable chairs/recliners and curtained off areas with bed(s)/trolley(s). Access should be available to extended recovery when pain cannot be easily controlled, or complications have arisen during the procedure.	**4**	**GPP**	This allows for the patient's condition, comfort and pain control to be assessed and monitored, and analgesia be provided when necessary.[24]

Following the procedure, the patient should be given time to change back into their clothes for a post-procedure consultation, which should ideally take place away from the procedure area. The hysteroscopist should explain the clinical findings and explain when and how histological/cytological/microbiological results will be communicated, if appropriate. If further care is required, it should be discussed in light of the clinical findings, and the patient should be informed when and how this will take place. This information should be summarised and written copies given to both the patient and their general practitioner (GP).[24]

The patient should be given post-procedural information, ideally both verbally and written.[24] This should include contact numbers (e.g. a direct line to the clinic and an out of hours contact number) should the patient have any problems or concerns over the next two weeks. In particular, patients should be told to make contact if they experience abdominal pain not controlled with simple analgesia, bleeding heavier than a period, or symptoms/signs of sepsis (fever, rigors and/or malodourous vaginal discharge).

Patients may prefer to leave after their post-procedure consultation without staying for a period of observation. However, recuperation and refreshments should be offered to all patients in a dedicated recovery area with comfortable chairs/recliners and privacy (e.g. curtained off areas with bed(s)/trolley(s)). The patient's condition, comfort and pain control should be assessed, monitored and analgesia be provided when necessary. Access should be available to a longer duration recovery area when pain cannot be easily managed or complications have arisen during the procedure.[24]

4.6 How should training and standards in outpatient hysteroscopy be provided and assessed?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
A hysteroscopic training programme should include knowledge and understanding of both basic and advanced skills relevant to hysteroscopic procedures alongside aspects of clinical governance in hysteroscopy.	**4**	**GPP**	Hysteroscopists should be proficient in outpatient procedures and also have a thorough understanding of pre-operative planning, case selection and service development.
Simulation should be considered an important adjunct to hysteroscopy training.	**2++**	**B**	This allows hysteroscopists in-training to learn basic manoeuvres without impacting adversely on the patient experience.
A minimum annual caseload of 50 hysteroscopies is recommended	**4**	**GPP**	This is considered best practice in order to maintain competencies, based on a survey by the BSGE ACN.

The RCOG offers Advanced Skills Training Modules in "Benign Abdominal Surgery – Open and Laparoscopic (BASOL)" and "Benign Gynaecological Surgery – Hysteroscopy (BGSH)", both of which require competence in hysteroscopy, with the latter having a greater emphasis on performance in the outpatient setting.[35] The European Society for Gynaecological Endoscopy (ESGE) has developed a diploma programme for laparoscopic and hysteroscopic skills training, known as the Gynaecological Endoscopic Surgical Education and Assessment Minimal Access Surgery (GESEA MIGS) Diploma, of which there are two hysteroscopy modules of different levels of difficulty (Hysteroscopic Skills Training and Testing method [HYSTT® 1 and 2]).[36] These curricula not only cover hysteroscopic procedures but also pre-operative planning, case selection and service development.

Achievement of competency in outpatient hysteroscopy requires having the opportunity to undertake training in the clinical setting on patients whilst they are awake. It is important to consider, however, that this may lead to a prolonged procedure time and in turn impact upon the patient experience. Training packages have tried to address this by using various models and simulators in order to improve

psychomotor skills and performance As illustrated by a systematic review on training and assessment of hysteroscopic skills, vegetables (e.g. potatoes, pears, butternut squash etc.), animal organs (e.g. porcine hearts, pig bladders, cattle uteri, etc.) and synthetic models (e.g. HYSTT box trainer [European Academy of Gynecological Surgery, Leuven, Belgium]) have been used to simulate intrauterine pathology, allowing for the development of a variety of different hysteroscopic skills (e.g. fibroid resection, septoplasty, etc.).[37] Virtual reality simulators (e.g. HystSim™ [VirtaMed AG, Zurich, Switzerland]) have a variety of pathologies and cases that the user can access, allowing for a standardised environment where data can be collected to allow an objective assessment of the trainee's performance.

For clinicians who have outpatient hysteroscopy in their job plan, then a minimum annual caseload of 50 hysteroscopies is recommended to maintain competencies. For clinicians who have a job plan comprising mainly of outpatient hysteroscopy (e.g. nurse hysteroscopists, clinical leads for outpatient hysteroscopy), they should aim to perform a minimum of 100 hysteroscopies per year, in line with guidance from the BSGE.[38]

5. Analgesia

5.1 What analgesia should be recommended prior to outpatient hysteroscopy and how should it be given in order to reduce the pain felt by patients during and after their procedure?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Patients should be advised to take standard doses of oral non-steroidal anti-inflammatory agents (NSAIDs) one hour before their scheduled appointment.	**1++**	**A**	Meta-analysis[39] showed that NSAIDs are the only medication that have been shown to reduce pain both during and after hysteroscopy without an increase in side-effects.
Where NSAIDs are contraindicated or declined, the use of transcutaneous electrical nerve stimulation (TENS), could be considered. Oral opioid or antispasmodic agents can be used for patients with contraindications to NSAIDs, provided they are made aware of the increased risk of adverse effects.	**1++**	**A**	Meta-analysis[39] showed that TENS reduced pain without an increase in side-effects. As these devices are not widely available, opioids and antispasmodics can be used instead, so long as patients are made aware of the increased risk of drowsiness with opioids and vasovagal episodes with antispasmodics.
Patients should be offered inhaled nitrous oxide (at an equimolar gas mixture of 50% nitrous oxide and 50% oxygen) for the reduction of pain associated with outpatient hysteroscopy, especially if directed endometrial biopsies or operative procedures are planned.	**1+**	**B**	One RCT[40] demonstrated a reduction in intra-procedural pain with the use of inhaled nitrous oxide, although some patients felt dizziness.

A systematic review and meta-analysis[39] identified twenty-two randomised controlled trials (RCTs)[41–62] examining the use of analgesics against a control prior to outpatient hysteroscopy for the reduction of pain.

Meta-analysis showed a statistically significant reduction in intra-procedural (SMD −0.72; 95% CI −1.27 to −0.16)[50,52,55,57–59,62] and post-procedural (SMD −0.55; 95% CI −0.97 to −0.13)[50,52,55,57,59,62] pain when giving an NSAID compared to a control. Subgroup analysis showed that the oral route[52,55,57,59,62] was associated with the greatest reduction in pain both during (SMD −0.87; 95% CI −1.59 to −0.15) and after (SMD −0.56; 95% CI

−1.02 to −0.10) hysteroscopy. The NSAID was given one hour prior to the procedure[55,57,59,62] in all but one[52] study. There was no significant difference in side-effects (namely in the form of vasovagal reactions [e.g. nausea, vomiting, sweating, dizziness, vertigo, bradycardia, hypotension]) in patients randomised to NSAIDs or their controls (Peto OR 1.01; 95% CI 0.52–1.98)[46,47,49,52,57,59,62].

There was a statistically significant reduction in intra-procedural (SMD −0.99; 95% CI −1.67 to −0.31)[54,61] and post-procedural (SMD −0.54; 95% CI −0.95 to −0.12)[61] pain when comparing TENS to a control. Reported side-effects were vasovagal episodes, but there was no significant difference between patients receiving TENS or a suitable control (Peto OR 0.86; 95% CI 0.46–1.61). A statistically significant reduction in intra-procedural (SMD −0.50; 95% CI −0.97 to −0.03)[43,51,53,59] and post-procedural (SMD −0.73; 95% CI −1.07 to −0.39)[43,59] pain was demonstrated when giving an opioid (given 40–60 minutes prior to commencing hysteroscopy) compared to a control. Patients randomised to opioids were also significantly more likely to suffer from side-effects when compared to their controls(Peto OR 7.30; 95% CI 3.96–13.47)[43,45,53,59], with drowsiness being commonly cited. Meta-analysis showed a statistically significant reduction in intra-procedural (SMD −1.48; 95% CI −1.82 to −1.13) and post-procedural (SMD −1.02; 95% CI −1.34 to −0.69) pain[55,62] when giving an antispasmodic one hour prior to hysteroscopy, when compared to a control. The risk of side-effects, however, primarily in the form of vasovagal episodes, was significantly greater (Peto OR 11.34; 95% CI 3.96-13.47)[62].

Three trials[40,63,64] have been published since the aforementioned systematic review[39] was performed. The first trial[64] randomised postmenopausal patients undergoing diagnostic hysteroscopy to tramadol or placebo, and was in keeping with the conclusions of the aforementioned systematic review. The second trial[63] randomised patients undergoing diagnostic hysteroscopy and directed biopsy or operative hysteroscopy to either oral diclofenac, oral diclofenac and hyoscine, or, placebo. Their findings contrasted slightly with the systematic review because a significant reduction in intra-procedural pain with oral diclofenac was restricted to patients with a prior history of chronic pelvic pain (*P*=0.04). The third trial[40] evaluated the use of inhaled nitrous oxide (at an equimolar gas mixture of 50% nitrous oxide and 50% oxygen, also known as Entonox®) compared to inhaled air and to a paracervical block using 1% lidocaine. Approximately one third of the 314 participants had a diagnostic hysteroscopy and directed biopsy with the remainder undergoing operative hysteroscopy. A significant reduction in pain recorded 5–10 minutes after the procedure was demonstrated in patients randomised to nitrous oxide compared to inhaled air alone (p=0.001). No significant difference in adverse events (*P*=0.26) was found between these groups (attributed to pain, anxiety and vasovagal symptoms), although it was noted that 5% of patients reported dizziness with nitrous oxide.

6. Cervical Preparation

6.1 Should cervical preparation be used in order to facilitate outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Cervical preparation should not be used routinely.	**1++**	**A**	Meta-analysis[65] showed that vaginal prostaglandins reduced pain, although they are associated with genital tract bleeding, abdominal pain and gastrointestinal side-effects. The risk of failure and complications such as cervical trauma and uterine perforation was not reduced.
If vaginal prostaglandins are to be administered, they should be given 12 hours before hysteroscopy. However,	**1++**	**A**	Two RCTs[66,67] showed that giving vaginal prostaglandins 12 hours before hysteroscopy provided better

clinicians should consider the feasibility of administration, side-effect profile and alternative management options (including the use of local anaesthesia and cervical dilatation).			pain relief than when given 3 hours before.
Cervical preparation with vaginal prostaglandins can be considered in selected cases (e.g. where cervical stenosis is anticipated or there is need to dilate the cervix beyond 6mm to accommodate uterine instrumentation).	**4**	**GPP**	There is no robust evidence to identify specific patient groups who may benefit most from cervical preparation.

Uterine trauma (lacerations to the cervix or uterine perforation) is recognised with blind and endoscopic instrumentation of the uterus,[1,68–71] with an estimated incidence of perforation of 0.002–1.7%. The incidence of uterine trauma is low for diagnostic outpatient hysteroscopy performed with small diameter endoscopes (≤3.5mm outer sheath diameter) under direct vision, however, cervical preparation has been historically used to dilate the cervix to facilitate easier hysteroscopic entry and reduce the risk of uterine trauma.[1] Factors associated with uterine trauma include the need for blind dilatation beyond 6mm for intrauterine instrumentation (e.g. for the use of larger-diameter operative hysteroscopes), cervical stenosis (e.g. atrophy, cervical surgery, previous caesarean section, nulliparity), a tortuous cervical canal (e.g. in association with fibroids) and a deviated uterine cavity (e.g. acute flexion, pelvic adhesions, fibroids).[17,25]

A systematic review and meta-analysis[65] investigating the impact of cervical preparation on pain during hysteroscopy, identified twenty-four[46,49,66,72–92] randomised controlled trials. Administration of a cervical preparation (between 3–24 hours prior), when compared against a placebo, significantly reduced intra-procedural pain (SMD –0.67, 95% CI –1.05 to –0.29).[73,74,76,78,81,84–87,89,90] Subgroup analysis according to the agent given found that misoprostol (SMD –0.64; 95% CI –0.97 to –0.31),[73,78,81,84–86,89,90] and dinoprostone (SMD –2.24; 95% CI –2.75 to –1.74)[87] significantly reduced intra-procedural pain, however, mifepristone (SMD –0.13; 95% CI –0.65 to 0.38),[74] and carboprost (SMD 0.09; 95% CI–0.02 to 0.20)[76] did not. Subgroup analysis based on route of administration of misoprostol showed pain was only reduced during hysteroscopy when given vaginally (SMD –0.68, 95% CI –1.04 to –0.32),[73,78,81,84,86] rather than orally (SMD –0.52, 95% CI –1.54 to 0.51).[89,90] Subgroup analysis based on menopausal status found that misoprostol reduced intra-procedural pain in premenopausal patients (SMD –0.86, 95% CI –1.18 to –0.54),[73,78,81,84,89,90] but not postmenopausal patients (SMD 0.10, 95% CI –0.30 to 0.51).[85,90] Only two studies[73,77] randomised patients to different doses of cervical prostaglandins, where 400µg of vaginal misoprostol did not show any significant reduction in pain when compared to 200µg (*P*=0.32). Only one study[66] randomised patients to receive a cervical preparation at different times and found that pain was only significantly reduced when 400 micrograms vaginal misoprostol was given 12 hours, rather than 3 hours before hysteroscopy (*P*<0.001). Since this systematic review[65] was published, a further randomised controlled trial has supported these findings, with 3mg vaginal dinoprostone only showing a significant reduction in intra-procedural pain when given 12 hours (*P*<0.001), rather than 3 hours (*P*=0.1) before outpatient hysteroscopy.[67]

Prostaglandins are associated with gastrointestinal side-effects and are contraindicated in severe uncontrolled asthma, chronic adrenal failure, acute porphyria and renal or hepatic impairment.[93] In the systematic review[65] described above, meta-analysis of adverse events in patients randomised to either a cervical preparation or placebo prior to outpatient hysteroscopy found a significant increase in their incidence when a cervical preparation was given (OR 2.94, 95% CI 1.58–5.47).[46,49,73,75,76,78,81,83–91] These included genital tract bleeding, abdominal pain/cramping, nausea, vomiting, diarrhoea, pyrexia/fever and vasovagal episodes. The incidence of complications were too small and balanced between groups for meta-analysis, and were only reported in studies randomising patients to either misoprostol or placebo/nil.[46,49,73,75,78,81,83–86,88–91] These included cervical trauma (n = 7), false passage (n = 4), severe pain (n = 4), uterine perforation (n = 1), infection (n = 1) and genital tract bleeding requiring emergency

department admission (n = 1) in patients randomised to misoprostol (n=18/711; 2.5%) and cervical trauma (n = 4), false passage (n = 5), uterine perforation (n = 3) and severe pain (n = 1) in patients randomised to placebo/nil (total 13/694; 1.9%).

One of the main reasons for failure to successfully perform an outpatient hysteroscopy is the inability to access the uterine cavity due to cervical stenosis, and this is most commonly encountered in a postmenopausal population.[25] The previously mentioned systematic review,[65] showed that administration of cervical preparation was associated with significantly greater cervical dilatation prior to hysteroscopy (gauged by the size of Hegar dilator the cervical canal could accommodate), when compared with placebo (SMD 0.81, 95% CI 0.08–1.53).[73,74,76] In addition, meta-analysis of ease of hysterosopic entry, as scored by the operator on either a 5-point Likert scale or 10cm Visual Analogue Scale (VAS), showed that giving a cervical preparation was associated with significantly easier hysteroscopic entry when compared to placebo (SMD 0.89, 95% CI 0.32–1.46).[73,78,81,84,86,87] The incidence of failed hysteroscopies due to cervical stenosis, however, was too small for meta-analysis, with 29/2001 (1.4%) patients randomised to a cervical preparation and 32/1183 (2.7%) patients randomised to placebo/nil.

No comparative studies were identified for other methods of cervical dilatation prior to outpatient hysteroscopy (e.g. local / systemic administration of oestrogens or osmotic agents).

7. Type of hysteroscope

7.1 What size and angle of hysteroscope should be used in the outpatient setting?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Hysteroscopes of 3.5 mm or less in outer diameter should be used for diagnostic outpatient hysteroscopy.	1+	A	Meta-analysis[94] showed that miniature hysteroscopes confer less pain to patients during hysteroscopy.
When performing operative hysteroscopy, the smallest diameter hysteroscope should be used, with consideration given to the use of hysteroscopes with expandable outer working channels because they are associated with less pain.	1+	B	One RCT[95] showed that a hysteroscope with a smaller initial diameter but larger resultant diameter confers less pain than a rigid hysteroscope.
When performing operative hysteroscopy using mechanical hysteroscopic tissue removal systems, the smallest diameter system available that is appropriate for the procedure should be used.	4	GPP	This is considered best practice.
Choice of hysteroscope lens angle should be left to the discretion of the clinician.	4	GPP	There is insufficient evidence to recommend 0° or fore-oblique optical lenses for routine outpatient hysteroscopy.

A systematic review and meta-analysis[94] identified seven randomised controlled trials[96–102] examining how the diameter of the hysteroscope with its outer sheath affected pain during outpatient hysteroscopy. Patients randomised to mini-hysteroscopes (outer diameter 3–3.5mm) experienced significantly less pain during hysteroscopy when compared to patients randomised to conventional hysteroscopes (outer

diameter 5mm) (SMD −3.64; 95% CI −5.16 to −2.12). Data pertaining to image quality, failure rate, procedural timing and adverse events were not meta-analysed. Image quality was either not reported,[97,98] showed no significant difference between scope sizes,[96,99,100] or found significantly better visualisation with the use of a smaller-diameter hysteroscope.[101] In one study,[102] hysteroscopy was significantly less conclusive with the use of a miniature hysteroscope but this was due to the leakage of carbon dioxide distension media, rather than due to the device used. Two studies[101,102] reported a significant increase in success when using a smaller-diameter hysteroscope, whereas the other three studies[96–98] reporting failure showed no significant difference between groups. In the three studies commenting on procedural duration, a significantly shorter time was required with the use of a miniaturised hysteroscope in two,[96,98] with no significant difference found between scope sizes in the other.[97] The incidence of vasovagal reactions was significantly lower when using a smaller-diameter hysteroscope in one study,[96] with the rest[97–101] showing no significant difference between the two groups.

A systematic review[103] identifying the operative devices used in outpatient hysteroscopy to determine which technologies confer the least pain, found one randomised controlled trial[95] comparing hysteroscope diameters for operative hysteroscopy in the outpatient setting. Patients randomised to the use of a semi-rigid hysteroscopic system (Alphascope™ [Gynecare, division of Ethicon, NJ, USA]) with a collapsible sheath (3.5mm diameter) and 7Fr forceps (total diameter 5.8mm) found polypectomy significantly less painful than when randomised to a lens based hysteroscope with 5Fr forceps (total diameter 5mm) (P<0.05), despite the resulting hysteroscopic diameter being greater, with the incidence of adverse events minimal and balanced between groups (P=0.09).

There were no studies comparing the outer diameters of mechanical hysteroscopic tissue removal (mHTR) systems for the reduction of pain in operative hysteroscopy, however, these are generally between 5 and 6.25mm which are suitable for use in the outpatient setting.[104]

No studies were identified that compared 0° hysteroscopes with off-set distal lenses (e.g. 12°, 30°). Off-set lenses offer a wider field of view and this property can be advantageous in visualising the corneal recesses and tubal ostia within the uterine cavity with minimal external movement of the hysteroscope. Fore-oblique lenses facilitate visualisation of ancillary instrumentation and so are advantageous for operative hysteroscopy. However, 0° hysteroscopes are more intuitive, facilitating entry into the uterine cavity through the cervical canal which may reduce the need for cervical dilatation, as well as minimising discomfort and uterine trauma.

7.2 Should rigid or flexible hysteroscopes be used routinely in the outpatient setting?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Choice of whether a rigid or flexible hysteroscope is used should be left to the discretion of the hysteroscopist.	1+	B	Two RCTs[105,106] have shown that flexible hysteroscopes are associated with less pain during diagnostic outpatient hysteroscopy. However, rigid hysteroscopes may provide better images, fewer failed procedures, quicker examination time and reduced cost.

Two, small randomised controlled trials compared the pain experienced during out-patient hysteroscopy with the use of a flexible hysteroscope versus a rigid hysteroscope.[105,106] Both found that the use of the flexible hysteroscope significantly reduced pain during the procedure (P = 0.0001 and P < 0.001, respectively). One of these studies reported no difference between the flexible and rigid groups in terms of procedure time and image view, with no failed hysteroscopies in either group.[106] The other study found that rigid scopes gave significantly better image quality (P < 0.001), significantly shortened the time taken to perform the procedure (P = 0.003), were cheaper to purchase and easier to sterilise and maintain.[105] In

addition, whilst there were no failed hysteroscopies when rigid scopes were used, seven patients randomised to flexible scopes had a failed procedure due to the inability to negotiate the cervical canal (n = 5) and an inadequate view (n = 2).[105]

7.3 What devices should be used for operative procedures in the outpatient setting?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Mechanical hysteroscopic tissue removal systems should be preferred over miniature bipolar electrodes to remove endometrial polyps.	1+	A	One RCT[107] showed that mechanical hysteroscopic tissue removal systems are less painful, quicker, more successful and more acceptable to patients for the removal of endometrial polyps when compared to using a miniature bipolar electrode.
The choice of device for outpatient endometrial ablation should be left to clinician discretion and familiarity.	4	GPP	There is an absence of comparative data examining newer generation (quicker and smaller-diameter) ablative devices.
Mechanical scissors should be preferred over miniature bipolar electrodes to remove uterine septa.	1+	B	One RCT[108] showed that mechanical cold scissors is associated with less pain than the use of a miniature bipolar electrode.

A systematic review[103] identifying the operative devices used in outpatient hysteroscopy to determine which technologies confer the least pain, found seven randomised controlled trials[95,107,109–113] investigating technologies for endometrial polypectomy, two trials[114,115] investigating endometrial ablation devices, and one trial[108] for uterine septoplasty.

Two trials[107,110] compared the use of bipolar electrosurgery (using a 5Fr Versapoint™ [Gynecare, division of Ethicon, NJ, USA] mini-electrode) for polypectomy, against a mechanical hysteroscopic tissue retrieval (mHTR) system (Truclear™ 5mm system [Medtronic, MN, USA]) that allows for simultaneous cutting and aspiration of polyp tissue. Whilst the earlier study, which was larger and of higher quality, found a significant reduction in pain during polypectomy when using a mHTR system ($P < 0.001$),[107] the later one did not ($P > 0.05$).[110] This difference in findings may be explained by the fact that the earlier study[107] compared a 5mm diameter mHTR system (Truclear™ 5mm system [Medtronic, MN, USA]) with an expandable 3.5mm (Alphascope® [Gynecare, division of Ethicon, NJ, USA]) or rigid 5mm operative hysteroscope (Bettocchi® [Karl Storz, Tuttlingen, Germany]), whereas the later study[110] compared the same 5mm diameter mHTR system with a larger 5.5mm diameter hysteroscope (Olympus GmbH, Hamburg, Germany). Both studies showed that morcellation was significantly faster ($P < 0.001$) and associated with a higher success rate. Whilst the incidence of adverse events was higher in patients randomised to bipolar electrosurgery in both studies, the majority of these related to procedural failure, with no serious complication (e.g. uterine perforation), reported in either group. When patient satisfaction was reported, there was a statistically significant preference for the use of the mHTR system ($P = 0.009$).[107] Another trial[111] found no significant difference in pain experienced by patients undergoing polypectomy using a diode laser (980nm Ceralas® HPD laser [Biolitec AG, Vienna, Austria]) when compared to bipolar electrosurgery (5Fr Versapoint™ [Gynecare, division of Ethicon, NJ, USA] mini-electrode) ($P > 0.05$), however, it should be noted that laser fibres like these are not in widespread use and comparisons with modern mechanical hysteroscopic tissue removal (mHTR) systems are lacking.

In the two trials[114,115] comparing endometrial ablation devices, patients were randomised to either bipolar radiofrequency impedance-controlled ablation (Novasure® [Hologic, MA, USA]) or thermal balloon ablation (Thermachoice III® [Gynecare, division of Ethicon, NJ, USA] or Thermablate® [Idoman Teoranta, Toronto, Canada]). Pain scores were not significantly different with the use of either device type, however, these older devices have been replaced by smaller-diameter and more rapid ablative technologies (e.g. Novasure® ADVANCED [Hologic, MA, USA], LiNA Librata™ [LiNA Medical, Glostrup, Denmark], Minitouch™ [MicroCube, Fremont, CA, USA] etc.).

One small randomised controlled trial[108] compared the use of cold 7Fr mini-scissors against bipolar electrosurgical resection (using a 5Fr Versapoint™ [Gynecare, division of Ethicon, NJ, USA] mini-electrode) through an expandable 3.5mm (Alphascope® [Gynecare, division of Ethicon, NJ, USA]) operative hysteroscope for sonographically diagnosed uterine septa <2cm, and found that mechanical resection was significantly less painful (P = 0.013), with similar operative times (P = 0.25) and no adverse events recorded with either technique. All patients, regardless of which technique was used, had complete resection of their septum noted at hysterosalpingogram 3 months post-procedure.

8. Distension Medium

8.1 Which uterine distension medium should be used during outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Saline is recommended as the distension medium for outpatient hysteroscopy.	**1++**	**A**	Meta-analysis[116] showed that saline is associated with less post-procedural pain, better image quality, fewer side-effects, shorter procedural time, greater patient satisfaction and allows for operative hysteroscopy.

A systematic review and meta-analysis[116] investigating the optimal distension media for outpatient hysteroscopy identified 18 randomised controlled trials.[49,99,117–132] The only distension media types that were compared in this systematic review were saline and carbon dioxide.

Meta-analysis showed no significant difference in intra-procedural pain[99,117–123] (SMD −0.12; 95% CI −0.36 to 0.13) or post-procedural pain (immediately after,[119] 1 minute after[124] and 15 minutes[99] after hysteroscopy) (SMD 5.54; 95% CI −2.34 to 13.43) between saline and carbon dioxide, however, after excluding the lower quality study,[124] a statistically significant reduction in post-procedural pain was demonstrated with the use of saline[99,119] (SMD −0.65; 95% CI −1.14 to −0.16). There was a statistically significant reduction in hysteroscopies with an unsatisfactory view with saline (Peto OR, 0.38; 95% CI, 0.22–0.66).[99,117,119,121,123] Patients randomised to saline had significantly fewer side-effects compared to patients randomised to carbon dioxide (Peto OR, 0.29; 95% CI 0.20–0.40).[99,117–124] Vasovagal symptoms (e.g. nausea, vomiting, dizziness, and fainting) (n = 38/50, 76%) were the main side-effects attributed to saline, however, shoulder pain (n = 8/50, 16%) and bleeding (n = 4, 8%) were also cited. Similarly, vasovagal symptoms (n = 71/134, 53%) were the predominant side-effects noted with carbon dioxide, however, shoulder pain was much more prevalent (n = 49/134, 44%) and bleeding (n = 4/134, 3%) was also reported. Complications either did not occur or were not recorded. A statistically significant reduction in procedural time was found when carbon dioxide was used (SMD 5.46; 95% CI 0.96–9.96),[117–119,122,124] however, when subgroup analysis was performed according to risk of bias, the highest quality studies[119,122] showed a significant reduction in time taken when saline was used (SMD −0.40; 95% CI −0.74 to −0.05). Finally, a significant increase in patient satisfaction was noted when using saline compared to carbon dioxide (SMD, 1.39; 95% CI 0.51–2.28).[118,119]

Saline allows for the efficient practice of "see and treat" services, where diagnosis is immediately followed by treatment, in the same outpatient hysteroscopy appointment. Furthermore, it is isotonic, which

minimises risks associated with fluid overload and conducts electricity to allow for the operation of miniature bipolar electrosurgical electrodes.[133] Finally, saline is the distension medium of choice when using hysteroscopic tissue retrieval systems, as the use of carbon dioxide with these devices has not been evaluated.

8.2 How should uterine distension media be delivered during outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Saline should be instilled at the lowest possible pressure to achieve a satisfactory view.	**1++**	**A**	Meta-analysis[116] showed that higher uterine distension pressures cause more pain.
Warming saline to approximate body temperature for outpatient hysteroscopy can be considered.	**1-**	**B**	Meta-analysis[116] did not show a reduction in pain with warmed saline, however, one RCT[130] showed improved patient satisfaction.

Fluid instillation methods and the effect on pain, acceptability and feasibility have not been compared for outpatient hysteroscopy, however, current approaches include:[24,104]

- Use of automated fluid management systems, e.g. setting initial intrauterine pressures at 40–50 mmHg and increasing to the minimum needed to obtain a satisfactory view.
- Manually distilling fluid via a syringe and titrating distention.
- Titrating inflow using the tap on the inflow channel (and/or outflow channel if a continuous flow hysteroscope).
- Using continuous flow via a gravity feed or external compression, although care needs to be taken to ensure initial pressure is kept low and that it is maintained to ensure the view is adequate.

A systematic review and meta-analysis[116] identified four randomised control trials[125–128] randomising patients to receive saline distension media at different filling pressures, of which, three studies[125–127] compared more than one pressure threshold. Patients randomised to undergo hysteroscopy at pressures of ≤40 mmHg had intra-procedural pain scores that were significantly reduced when compared to patients undergoing hysteroscopy at pressures above this threshold (SMD, −0.67; 95% CI −1.09 to −0.26). When comparing patients receiving filling pressures of ≤50mmHg versus >50mmHg, ≤60mmHg versus >60mmHg, ≤70mmHg versus >70mmHg and ≤80mmHg versus >80mmHg, no significant difference in pain scores could be found. With regards to post-procedural pain, any reduction in distension media pressure resulted in a statistically significant reduction in pain. Despite lower filling pressures being associated with less pain, it also resulted in lower likelihood of a satisfactory view. At pressures of 30–40mmHg, the proportion of satisfactory hysteroscopies was between 81.25–88.75%, whereas at pressures of 50–100mmHg, the proportion increased to a range between 94.87–98.75%.[125–127] There was insufficient data available to comment upon the impact of filling pressure on procedural time and side-effects. No serious complications were reported in the studies investigating distension media filling pressure. Data relating to the impact of distension media filling pressure on pain associated with outpatient hysteroscopy should be interpreted cautiously because unless using modern fluid management systems (which themselves are not completely reliable due to dynamic fluid losses through the fallopian tubes, cervix, intravascularly etc.), then intrauterine pressures are not being accurately measured. Finally, one must consider that the flow rate of distension media through the hysteroscope and subsequent uterine pressure will depend on the hysteroscope diameter, fluid reservoir height and dynamic losses.

Four randomised controlled trials[129–132] allowed for the meta-analysis of pain scores of patients randomised to either saline at room temperature or warmed saline in the previously mentioned systematic review,[116] of which three[129–131] reported intra-procedural pain and all four reported post-procedural pain (recorded immediately after,[132] and at 1,[129] 5[131] and 15[130] minutes following the end of hysteroscopy). No significant difference in pain was observed either during (SMD 0.59; 95% CI −0.14 to 1.33) or after (SMD 0.22; 95% CI

–0.35 to 0.79) hysteroscopy. Additionally, no significant difference was found regarding procedural time (SMD –0.17; 95% CI –0.47 to 0.13). Adverse events or failure either did not occur or were not reported. Three of the trials, however, did comment on patient satisfaction,[129–131] with only one study[130] finding a significant difference, where patients randomised to warmed saline reported higher satisfaction rates (P = 0.05). Since the publication of the aforementioned systematic review,[116] a quasi-randomised control trial investigating the impact of warmed saline against room temperature found that warming was associated with a significant reduction in intra-procedural (P = 0.02) and post-procedural (P = 0.003) pain at diagnostic hysteroscopy, although the clinical significance of the observed reduction in pain is unclear.[134] Again, no adverse events were recorded in either group.

9. Local anaesthesia and cervical dilatation

9.1 Should routine dilatation of the cervical canal be performed prior to insertion of the hysteroscope in the outpatient setting?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Routine cervical dilatation should be avoided prior to outpatient hysteroscopy	**2+**	**C**	This practice is associated with pain, vasovagal reactions and uterine trauma, and is unnecessary where miniature hysteroscopes (with an outer diameter ≤3.5mm) are used.

Blind dilatation of the cervix in order to instrument the uterine cavity is commonly performed under general anaesthesia and is associated with cervical and uterine trauma.[1,68–71] However, in the outpatient setting, dilatation of the cervix causes pain and discomfort and generally requires the use of local anaesthesia.[25] No randomised controlled trials examining the routine or selective use of blind cervical dilatation prior to outpatient hysteroscopy were identified.[65]

9.2 Should local anaesthesia be administered prior to outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Local anaesthesia should not be routinely administered prior to outpatient hysteroscopy. It should be considered where cervical dilatation is anticipated, due to either cervical stenosis and/or the utilisation of larger-diameter hysteroscopes (≥5mm outer diameter).	**1++**	**A**	Whilst meta-analysis[135] showed that local anaesthesia reduces pain during and after outpatient hysteroscopy, the clinical benefit regarding its analgesic benefit is uncertain when compared to the use of vaginoscopy. The same meta-analysis does not show that local anaesthesia reduces the risk of vasovagal episodes nor the chances of a failed procedure.

A systematic review and meta-analysis[135] identified 37 randomised controlled trials[42,47,51,55,58,79,102,121,136–164] examining pain in patients undergoing outpatient hysteroscopy randomised to receive either a local anaesthetic or a control. Meta-analysis showed that administering local anaesthesia significantly reduced pain during outpatient hysteroscopy (SMD –0.57, 95% CI –0.79 to –0.34) when compared against placebo or nil.[51,102,121,136–138,140–142,144,146,149,153–157,160–162] Local anaesthesia also reduced pain after outpatient hysteroscopy (SMD –0.30, 95% CI –0.54 to –0.06), when aggregated from pain scores recorded at 5,[140] 10,[136] 15,[141,142,149] 30[138,146,153,154,156,157] and 60[155] minutes following hysteroscopy. Local anaesthesia did not, however, reduce the incidence of vasovagal episodes (OR 0.73, 95% CI 0.50–1.09),[47,102,136,137,141,142,145,149,150,153,155–157,159,160,162,164] nor reduce the rate of failure (OR 0.72, 95 % CI 0.47–

1.11),[102,137,138,140–146,149,150,153,155–157,159–162] when compared against placebo or nil. The incidence of complications was too small to determine an association to either local anaesthesia or its control.

The clinical significance for the demonstrated reduction in average pain scores remains unclear, especially when considering that few studies commented on the impact of the reduction in pain on satisfaction and acceptability of administration of local anaesthesia when compared to their control. In studies where a placebo was administered, instead of a local anaesthetic, a lower than expected difference in mean pain was likely observed because instillation of placebo into the cervix/uterus still causes pain. A systematic review[165] investigating the impact of the vaginoscopic approach on pain in outpatient hysteroscopy identified one randomised control trial randomising patients to either hysteroscopy with intracervical mepivacaine or to hysteroscopy using the vaginoscopic approach.[166] This found a significant reduction in pain both during (3.8±2.7 versus 5.34±3.23) and after (3.02±2.50 vs 4.57±3.30) diagnostic hysteroscopy when the vaginoscopic approach was used, despite using a hysteroscope with a 3.7mm diameter. The adoption of vaginoscopy has been facilitated by the development of miniature hysteroscopes (≤3.5mm outer diameter), and so as this has been found to confer less pain and side-effects, this supports the use of local anaesthesia only when cervical dilation is anticipated.[165]

9.3 Which local anaesthesia should be administered and how should it be given prior to outpatient hysteroscopy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
The choice of local anaesthetic agent for outpatient hysteroscopy should be left to the discretion of the hysteroscopist.	**1++**	**A**	Whilst meta-analysis[135] showed that mepivacaine and bupivacaine were the only agents associated with both a reduction in pain during and after outpatient hysteroscopy and mepivacaine was the only agent to reduce vasovagal episodes, there are no direct head-to-head comparisons between anaesthetic agents to make robust conclusions as the existing comparisons are against either nil or placebo.
The choice of route(s) of administration of local anaesthesia for outpatient hysteroscopy should be left to the discretion of the hysteroscopist, however, intrauterine fundal anaesthesia should be considered for the reduction of pain during outpatient endometrial ablation.	**1++**	**A**	Meta-analysis[135] showed that all routes of administration of local anaesthesia prior to outpatient hysteroscopy reduce pain during the procedure. One RCT demonstrated a significant reduction in pain during endometrial ablation when intrauterine fundal anaesthesia was given.
Short-acting local anaesthetics (e.g. mepivacaine, lidocaine and prilocaine) require at least 2 minutes and longer acting agents (e.g. bupivacaine) require at least 5 minutes to allow for onset of effect.	**1++**	**A**	Meta-analysis[135] showed that the interval between administration of local anaesthesia and commencement of the procedure will depend upon the pharmacokinetics of the local anaesthetic and how it is administered.

In the previously mentioned systematic review and meta-analysis,[135] subgroup analyses were performed in order to identify the specific local anaesthetic agents that were effective in reducing pain during and after outpatient hysteroscopy, when compared to nil or placebo. Bupivacaine, a long-acting local anaesthetic, produced the greatest reduction in intraprocedural pain (SMD –4.27, 95% CI –5.06 to –3.49).[136] There was a significant reduction in pain during hysteroscopy with the use of short acting local anaesthetics (lidocaine [SMD –0.34, 95% CI –0.52 to –0.16][121,138,140,144,146,149,153,156,157,160,162]; mepivacaine [SMD –0.60, 95% CI –1.03 to –0.17][51,102,141,142,161] and prilocaine [SMD –0.40, 95% CI –0.68 to –0.12][154]). Mepivacaine (SMD –0.66; 95% CI –1.19 to –0.14)[141,142] and bupivacaine (SMD –1.55; 95% CI –2.05 to –1.06)[136] were the only local anaesthetics to significantly reduce pain after hysteroscopy. Whilst meta-analysis of vasovagal episodes did not show any benefit when local anaesthesia was given, subgroup analysis according to the type of local anaesthetic given found a significant reduction in vasovagal episodes, only when mepivacaine was given (OR 0.33, 95% CI 0.19–0.60).[102,141,142,159,164]

The same systematic review and meta-analysis[135] also performed subgroup analyses to identify which specific routes of local anaesthesia administration led to a reduction in pain during and after outpatient hysteroscopy. Topical (application of local anaesthesia directly onto the ectocervix), transcervical (instillation of local anaesthesia through the cervix via either a cannula or within the distension medium), intracervical (injection of local anaesthesia directly into the ectocervix) and paracervical (injection of local anaesthesia into the cervicovaginal junction) routes were investigated when given in an outpatient setting. All routes of administration were associated with a significant reduction in pain during outpatient hysteroscopy when compared against placebo or nil; this encompassed the topical (SMD –0.36, 95% CI –0.66 to –0.06),[137,153,160,162] transcervical (SMD –0.33, 95% CI –0.64 to –0.02),[121,141,144,149,153,157] intracervical (SMD –0.38, 95% CI –0.57 to –0.19)[51,138,146,154] and paracervical (SMD –1.09, 95% CI –0.90 to –0.31)[102,136,140,142,156,161] routes. In contrast, no specific route of administration of local anaesthesia led to a significant reduction in pain following hysteroscopy. When subgroup analysis was performed to determine the optimal route of administration for the reduction of vasovagal episodes, a significant reduction was observed only when given through the transcervical route (OR 0.39, 95 % CI 0.18–0.83).[47,141,153,157,164] A randomised controlled trial found that giving intrauterine fundal anaesthesia, using a combination of mepivacaine and bupivacaine, during outpatient hysteroscopy three minutes prior to outpatient endometrial ablation, showed a statistically significant reduction in intra-procedural (SMD –0.49, 95 % CI –0.90 to –0.07) but not post-procedural (SMD 0.00, 95% CI –0.40 to 0.41) pain, when compared against placebo.[155] The incidence of vasovagal episodes was balanced between groups (OR 2.44, 95% CI 0.53–11.32).

Unless given within the distension media,[121] local anaesthesia in the aforementioned systematic review and meta-analysis[135] was given two minutes (lidocaine[144,149]), five minutes (lidocaine,[138,140,153,156,157,160,161] mepivacaine,[51,102,141,161] bupivacaine[136]) or ten minutes (EMLA,[137] mepivacaine[142]) before outpatient hysteroscopy. No randomised controlled trials randomised patients to receive the same local anaesthetic route or agent at different times prior to outpatient hysteroscopy. In the absence of data to support a specific local anaesthetic regime, standard local protocols regarding the type, maximum dosage and route of administration of local anaesthesia should be implemented to ensure adequacy of anaesthesia and help both recognise and prevent rare, but potentially serious side-effects resulting from systemic vascular absorption.[167]

10. Conscious sedation

10.1 Should conscious sedation be used to reduce pain associated with outpatient hysteroscopic procedures?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Conscious sedation should not be routinely used in outpatient hysteroscopic procedures.	**1-**	**B**	Meta-analysis[168] showed no benefit of intravenous conscious sedation and led to more side-effects. There were

			no data regarding adverse events available to make recommendations for the use of inhaled conscious sedation.
If conscious sedation is to be employed, patients must be appropriately selected beforehand and hysteroscopy must be performed in a suitable environment, where there is a separate staff member who has the skills and equipment necessary to monitor vital observations and recognise and manage patients who are over-sedated.	**4**	**GPP**	Life threatening complications can result from the use of conscious sedation and so it is imperative that guidance produced by the Academy of Medical Royal Colleges in the safe use of conscious sedation is followed.[169]

Conscious sedation is used widely in outpatient endoscopic procedures of the gastrointestinal system. It is less commonly employed in outpatient hysteroscopy. Sedation induces a depression in consciousness, which ranges from minimal sedation and anxiolysis, through to moderate or 'conscious' sedation, deep sedation, and finally ending with general anaesthesia. While responsiveness is always suppressed, as the level of sedation becomes deeper, so does the potential ability of the patient to maintain their airway, ventilation and cardiovascular function.[170] Conscious sedation is therefore defined as a "drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation" (i.e. not a painful stimulus) where "no interventions are required to maintain a patent airway when spontaneous ventilation is adequate" and "cardiovascular function is usually maintained".[171]

A systematic review and meta-analysis[168] investigating the role of conscious sedation against suitable controls for the control of pain for outpatient hysteroscopy, included seven randomised controlled trials.[44,55,56,60,148,172,173] Intravenous conscious sedation, when compared with local anaesthesia, reduced pain during (SMD –0.26, 95% CI –0.51 to –0.01), but not after (SMD –0.18, 95% CI –0.43 to 0.07) outpatient hysteroscopy.[55,148] No significant difference in side-effects were noted when the studies were pooled (OR 15.58, 95% CI 0.08–2891.91).[55,148] Intravenous conscious sedation, when compared to an oral analgesic and antispasmodic, was associated with increased pain, both during (SMD 1.03, 95% CI 0.56–1.49) and after (SMD 0.49, 95% CI 0.04–0.93) hysteroscopy and was associated with significantly more side-effects (OR 134.33, 95% CI 16.14–1118.17).[55] Side-effects in patients randomised to conscious sedation were either vasovagal symptoms occurring at the time of or shortly after hysteroscopy, or dizziness that persisted longer than one hour following the end of hysteroscopy. Intravenous sedation, when compared with an oral analgesic alone, did not show any significant difference in intra-procedural pain (SMD –0.16, 95% CI –0.59 to 0.26).[56] Inhaled conscious sedation (in the form of 70% N_2O/30% O^2), when compared to oral analgesia and anxiolysis, showed the greatest reduction in pain during hysteroscopy (SMD –1.04, 95% CI –1.57 to –0.52), however side-effects were not recorded, and so its use cannot be supported outside of a research context.[60]

Because sedative drugs depress the central nervous system and have the potential to impair respiration, circulation or both, close monitoring of the patient must be undertaken by a designated staff member, separate to the hysteroscopist, to ensure maintenance of vital observations (heart rate, blood pressure, respiratory rate, pulse oximetry, with electrocardiography and capnography performed where appropriate) peri- and post-procedurally, in accordance with guidance produced by the Academy of Medical Royal Colleges.[169] This individual must be able to identify and rescue a patient who becomes over-sedated, requiring the administration of a reversal agent, airway maintenance, and, rarely, full cardiopulmonary resuscitation. Patient selection is of paramount importance, in order to minimise the risks associated with conscious sedation, where obese, elderly and/or comorbid patients may either, not be suitable, or, require different sedating regimes. Many centres do not have the equipment, clinic space and staff necessary to deliver conscious sedation safely in the outpatient setting, which require facilities to convert to a general

anaesthetic in the event of cardio-respiratory compromise. In those that do, it is performed in an endoscopy suite, and does not confer the benefits of being in an "office setting"; patients still need to arrive at the start of the session to be seen by an anaesthetist, be fasted prior to their procedure, and cannot be discharged until the effects of the conscious sedative wear away, often necessitating a hospital bed. In keeping with this, the European Society for Gynaecological Endoscopy (ESGE), the American Association of Gynecologic Laparoscopy (AAGL) and the Global Congress of Hysteroscopy (GCH) recently produced a standardised nomenclature to enable consistency in reporting of hysteroscopic procedures, where the facility to administer parenteral medications with a sedative effect, or regional/general anaesthesia is considered an operating room, as opposed to an outpatient setting.[7]

11. Vaginoscopy

11.1 Does a vaginoscopic approach to outpatient hysteroscopy reduce pain and increase the feasibility of the procedure?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Vaginoscopy should be the standard technique for outpatient hysteroscopy unless the use of a vaginal speculum is required (e.g. when dilating the cervix or obtaining a blind endometrial biopsy).	**1++**	**A**	Meta-analysis[165] showed that vaginoscopy is significantly less painful, quicker and associated with fewer vasovagal episodes when compared to the use of a vaginal speculum.
Vaginoscopy should still be considered after using a vaginal speculum to administer local anaesthesia to the cervix and/or cervical dilatation in order to reduce the pain associated with genital tract instrumentation and increase manoeuvrability of the hysteroscope.	**4**	**GPP**	This is in order to reduce the pain associated with genital tract instrumentation and increase manoeuvrability of the hysteroscope.

Vaginoscopy or the 'no touch' approach to hysteroscopy refers to a technique where the hysteroscope is introduced into the vagina, through the cervical canal and into the uterine cavity without the need for a vaginal speculum or cervical instrumentation. By performing hysteroscopy without a vaginal speculum, which causes lower genital tract pain, manoeuvrability of the hysteroscope within the uterine cavity is improved because there is no vaginal speculum restricting movement. This is particularly advantageous in patients who cannot lie supine due to medical comorbidities (e.g. heart failure, respiratory disease etc.), are obese, who have acutely flexed uteri and in those who have restricted hip movement. Patients who are nulliparous, suffer from vaginismus, are virgo intact and/or suffer from genital tract atrophy may also benefit from vaginoscopy, where distension of the vagina is minimised. A systematic review and meta-analysis[165] identified six randomised controlled trials comparing vaginoscopic versus traditional outpatient hysteroscopy, which employed the use of a vaginal speculum as a minimum.[166,174–179] The vaginoscopic approach was significantly less painful during (SMD -0.27, 95% CI -0.48 to -0.06)[166,174,177,179] and 15 minutes after hysteroscopy (SMD -0.55, 95 % CI -0.91 to -0.18)[166]. Vaginoscopy was also significantly quicker (SMD -0.25, 95 % CI -0.43 to -0.08)[166,174–177,179] and associated with significantly fewer vasovagal episodes (OR 0.35, 95 % CI 0.15 to 0.82).[166,174,179] Complications were only found in one of the six trials;[179] this reported no significant difference in the incidence of post-operative infection between the two methods; infection was reported in 27/798 patients (3.4%) who had vaginoscopy, compared with 31/799 patients (3.9%) who underwent the traditional approach (p = 0.60). All other complications that were reported occurred in patients randomised to the use of a vaginal speculum and included cervical trauma (n = 2), admission for

analgesia (n = 2) and postprocedural haemorrhage (n = 1). Neither the vaginoscopic technique nor the traditional approach reduced failure rates (OR 0.98, 95 % CI 0.69–1.38).[166,174–179]

In patients who require a vaginal speculum for administration of local anaesthesia, many clinicians remove the speculum before performing hysteroscopy to invoke the aforementioned benefits of the vaginoscopic approach.[47,79,137,154]

12. Prevention of Infection

12.1 Should routine antibiotic prophylaxis be employed in outpatient hysteroscopic procedures to reduce the incidence of procedural-related infection?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Routine antibiotic prophylaxis is not recommended for outpatient hysteroscopic procedures.	**1++**	**A**	One RCT[180] found no benefit in administering antimicrobial prophylaxis for the reduction of post-procedural infection. Clinicians should also bear in mind that there is no evidence to support the use of prophylactic antibiotics when performing an endometrial ablation.
Outpatient hysteroscopy should be delayed and genital tract swabs taken and / or antibiotics administered if pelvic infection is suspected and confirmed microbiological infection should be treated with antibiotics. If a pyometra is diagnosed at the time of outpatient hysteroscopy, antibiotics should be administered immediately to minimise the risk of systemic infection.	**3**	**D**	This recommendation was made based on a survey of practice.[181]

Only one randomised controlled trial examined the incidence of post-procedural infection in patients undergoing outpatient hysteroscopy randomised to receive either antibiotic prophylaxis (in the form of 1g cefazolin intramuscularly) or placebo (10ml saline intramuscularly).[180] No trials have investigated the role of prophylactic antibiotics for the reduction of post-operative infection following endometrial ablation. All procedures were therapeutic; including hysteroscopic polypectomy, septoplasty, myomectomy and intrauterine adhesiolysis. Post-procedural infection was diagnosed if two or more of the following criteria were met in the 5 days post-hysteroscopy: "(i) fever (body temperature greater than 38ºC or 100.4 F at repeated measurements over a period of at least 48 hours); (ii) low abdominal pain; (iii) uterine, adnexal, or cervical motion tenderness; (iv) purulent leucorrhoea; (v) vaginal discharge or itchiness; and (vi) dysuria". In the 1046 patients who underwent hysteroscopy, only 12 (1.15%) were found to meet the criteria of post-procedural infection, where 5/523 patients (1.0%) were initially allocated cefazolin and 7/523 patients (1.3%) were allocated placebo (p>0.05). Antibiotics were prescribed in all cases, leading to complete resolution of infection in all cases, with no patients developing upper genital tract/pelvic infection, as confirmed by clinical and sonographic examination. No trials have investigated the role of prophylactic antibiotics for the reduction of post-operative infection following endometrial ablation.

Despite the low incidence of pelvic infection following hysteroscopy[182] and the absence of evidence for reduction of post-operative infection with the routine use of antibiotics, patients with symptoms and signs of genital tract infection, including a pyometra, should have their procedure deferred, genital tract swabs

taken and/or empirical antibiotics administered. In elderly patients, a non-sterile pyometra should be suspected when intrauterine fluid is seen on pelvic scanning and/or there is a mucoid vaginal discharge. If a pyometra is diagnosed during an outpatient hysteroscopy there is a risk of rapid dissemination of pelvic and systemic infection and so antibiotics should be administered as soon as possible, with the initial dose ideally administered intravenously to optimise the onset of action followed by a full oral course.[181]

13. Documentation

13.1 How should procedural technique and findings at hysteroscopy be recorded?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
A standardised proforma is recommended for the documentation of hysteroscopic technique and findings.	**4**	**GPP**	This is considered best practice.[24]

The majority of units use either a written or digital/computerised standardised proforma to record procedural technique and findings.

Items that should be recorded pertaining to technique include:

- Operator / surgeon
- Hysteroscope/operative device used, including instrument diameter as a minimum
- Approach (vaginoscopy or speculum)
- Distension medium used
- Local anaesthesia (agent, volume, route)
- Cervical instrumentation (tenaculum, cervical dilatation)
- Biopsy performed (and if so, method used e.g. directed/blind and device used i.e. pipelle or other device)
- Operative procedure performed, if applicable (e.g. polypectomy, myomectomy, septoplasty, coil removal, removal of chronic RPOC etc.)
- Use of oral or inhalational medications with an analgesic or sedative effect (e.g. Entonox®)
- Procedural success (yes/no) and reasons for abandonment (e.g. intolerable pain, poor visualisation etc.), if applicable
- Complications (e.g. vasovagal reaction, uterine perforation, heavy bleeding etc.)

Items that should be recorded regarding findings include:

- Impression and description of vulva, vagina, cervix and endometrium (functional or pathological)
- Visualisation of both ostia
- Details of any congenital (hypoplastic 'T' or 'Y' shaped uterus, septum, other structural anomalies) or acquired uterine pathology (adhesions, cervical niches, fibroids FIGO Type 0-3), polyps, retained products of conception)
- The uterocervical length should be recorded when a global biopsy is taken or an intrauterine device fitted.

Pictures and/or diagrams may also be helpful in recording findings at hysteroscopy. Where possible, digital images of the uterine cavity and/or cervix (e.g. panoramic view of the cavity, magnified views of the tubal ostia/cornual regions, fundus, uterine walls, cervical canal etc.) should be captured, especially where there is any intrauterine pathology (e.g. global endometrial appearances such as vascularity, thickening, irregularity, necrosis; focal endometrial lesions, vascular polyps, fibroids, adhesions, congenital uterine anomalies, embedded coils etc.).[24]

14. Recommendations for research

- Effect of cervical preparation with prostaglandins on pain relief and feasibility of outpatient hysteroscopy.
- Safety, acceptability and feasibility of hysteroscopy according to angle of distal optical lens.
- Effectiveness of the vaginoscopic approach to outpatient hysteroscopy in relieving pain compared with traditional approaches with local anaesthesia.
- Relative effectiveness of different types, routes, doses and timings of local anaesthesia on pain and incidence of vasovagal reactions.
- Effectiveness of warming fluid distension media on pain relief and satisfaction.
- Effectiveness of inhalational agents on pain relief and satisfaction.
- Assessment of specific operative hysteroscopic technologies including endometrial ablative devices, regarding pain, acceptability, feasibility and effectiveness.
- Evaluation of technical, analgesic, anaesthetic and sedative interventions for specific operative outpatient hysteroscopic procedures.
- Qualitative research exploring patient experience and preferences.

15. Auditable topics

The lower estimate of the confidence intervals have been used to define the minimum audit standard or where data are lacking or considered inappropriate, expert opinion has been relied upon (BSGE Ambulatory Care Network).[22] However, the data sources have been provided to allow units / practitioners to set and aim for higher standards as appropriate.

Criteria	Procedure(s)	Standard	Source(s)
PATIENT-CENTRED			
Provision of pre-appointment written information		≥ 95%	88.7% (95% CI 87.8% - 89.5%)[21] however expert opinion[22] felt that the standard should be higher
Mean intra-procedural pain score	Diagnostic hysteroscopy +/- global endometrial biopsy	≤ 5.2	≤5.2 (95% CI 5.12-5.29)[21]
	Insertion/retrieval of IUCD	≤ 5.2	≤5.16 (95% CI 4.91-5.41)[21]
	Hysteroscopic polypectomy	≤ 5.1	≤5.1 (95% CI 4.91-5.29)[21]
	Hysteroscopic myomectomy	≤ 6.4	≤6.37 (95% CI 5.37-7.36)[21]
	Endometrial ablation	≤ 6.5	≤6.48 (95% CI 5.8-7.16)[21]
Acceptability	Diagnostic hysteroscopy	≥ 97%	≥97.8% (95% CI 97.0-98.5%)[179]
	Hysteroscopic polypectomy	≥ 95%	97.8% (95% CI 94.9%-99.3%)[183]; 99.2% (95% CI 95.4%-99.9%)[107]
	Endometrial ablation	≥ 77%	93.6% (95% CI 78.6-99.2%)[114]; 77%-94%[184]
Mean overall level of care	All hysteroscopies & endometrial ablation	9.7/10	≥9.73 (95% CI 9.70-9.75)[21]
SURGICAL			
Success	Diagnostic hysteroscopy	≥ 92%	≥93.8% (95% CI 92.5-94.9%)[179]

	Hysteroscopic polypectomy	≥ 86%	91.1% (95% CI 86.4%-94.%)[183]; 90.9% (95% CI 84.3%-95.4%)[107]
	Endometrial ablation	> 97%	97.9% (95% CI 97.1%-98.4%)[184]
Vasovagal reaction	Diagnostic hysteroscopy	≤ 2%	1.1% (95% CI 0.7% – 1.9%)[179]
	Hysteroscopic polypectomy & endometrial ablation*	< 12%	5.8% (95% CI 2.4%-11.6%)[107]
Uterine / cervical trauma	All hysteroscopies & endometrial ablation*	≤ 0.5%	≤0.1% (95% CI 0.02-0.50%)[179]; 0%[183]
Infection	All hysteroscopies#	≤ 5%	≤3.6% (95% CI 2.80-4.70%)[179]
	Endometrial ablation	≤ 16%	4.8% (95% CI 0.6% - 16.1%)[114]
Hospital admission	All hysteroscopies & endometrial ablation+	< 5%	≤2.0% (90% CI 0.3% -4.8%)[185]
Hospital readmission	All hysteroscopies & endometrial ablation+	≤3 .5%	≤1.5%; (90% CI 0.1%-3.5%)[185]
PROCEDURAL			
Compliance with safety checklists	All hysteroscopies & endometrial ablation	≥ 99%	Expert opinion[22]
Documentation completion rates°	All hysteroscopies & endometrial ablation	≥ 99%	Expert opinion[22]

Nb. There are no reliable data for operative outpatient myomectomy or removal of retained products of conception

* No data for outpatient endometrial ablation
# No data for outpatient hysteroscopic polypectomy or outpatient endometrial ablation
+ No data for outpatient hysteroscopic polypectomy or outpatient endometrial ablation
° documentation should cover the points listed in section 13.1 of the GTG

The following British Society for Gynaecological Endoscopy (BSGE) quality assurance tools for outpatient hysteroscopy are recommended:

- BSGE outpatient hysteroscopy patient satisfaction survey, allowing for local data to compared with national standards.[21] A template of the survey be accessed from: https://www.bsge.org.uk/wp-content/uploads/2019/09/Outpatient-hysteroscopy-patient-survey-FINAL-010919.pdf
- BSGE Surgical Information Collection System (BSGE SICS) to collect data on demographic, technologies, feasibility and complications of outpatient hysteroscopic procedures (diagnostic outpatient hysteroscopy, polypectomy, myomectomy, septoplasty, removal retained products of conception, tubal cannulation / sterilisation, endometrial ablation). This can be accessed from: https://www.bsgesics.com/

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Appendix 1 : Explanation of grades and evidence levels

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation	
A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
Good Practice Points	
✓	Recommended best practice based on the clinical experience of the guideline development group.*

*on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by ✓. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg59.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

Addendum to Chapter 10

1. The following changes have been made to this updated version of the green-top guideline since the previous one, published in 2011 (11):

Table 2 – Specific changes to the updated version of the green-top guideline since it was published in 2011:

Guideline topics	Changes made
1. Service provision	a) Updated guidance was made regarding the number and type of ancillary staff required based on expert opinion from the BSGE ACN (12) b) More detailed information has been specified regarding the information that patients should be provided before, during and after their hysteroscopy, post-procedural care, the consent process and the use of a safety checklist based on the publication of the RCOG Good Practice Paper in Outpatient Hysteroscopy (35) c) A new section on training and standards was added based on based upon current advanced training modules in hysteroscopy(36), standards set by the BSGE (37) and consensus from the BSGE ACN (12)
2. Analgesia	a) Guidance regarding analgesia has been updated in light of the findings from Chapter 3 of this thesis. The guidance was previously based upon an unpublished systematic review containing six RCTs whereas chapter 3 is a systematic review and meta-analysis including 22 RCTs. As a result new recommendations regarding the use of TENS machines and

	antispasmodic agents has been provided which were not present in the former guideline b) Based on an additional RCT (38) found since the publication of Chapter 3, further guidance has been provided based on the use of inhaled nitrous oxide
3. Cervical preparation	a) Guidance regarding cervical preparation has been updated in light of the findings from Chapter 7 of this thesis. The guidance was previously based upon an unpublished systematic review including five RCTs whereas chapter 7 is a systematic review and meta-analysis including 24 RCTs. As a result, rather than stating that there is no benefit at all of cervical preparation, we have found that whilst there is a reduction in pain but an increase in side-effects and logistical challenges regarding their administration and so clinicians should take this into consideration
4. Type of hysteroscope	a) No changes have been made to the guidance regarding the use of diagnostic hysteroscopes in the updated version of the green-top guideline b) Guidance regarding devices that should be used regarding operative hysteroscopy, which was not present in the previous guideline, has been provided based on the findings of Chapter 9
5. Distension medium	a) Guidance regarding distension has been updated in light of the findings from Chapter 6 of this thesis. The guidance was previously based upon a systematic review (39) including seven RCTs whereas chapter 6 is a

	systematic review and meta-analysis including 24 RCTs. b) Clear benefits in the use of saline rather than carbon dioxide in terms of pain, operative view, side-effects, procedural time and satisfaction were found in Chapter 6, and so guidance has changed to recommend the use of saline rather than to leave it to clinician preference c) There was previously insufficient evidence to make recommendations regarding the temperature and intrauterine distension pressure with regards to the administration of saline as a distension medium, however, in light of the evidence provided by Chapter 6, we have been able to make new recommendations regarding this
6. Local anaesthesia and cervical dilatation	a) Guidance regarding the use of local anaesthesia in the former green-top guideline was based on a systematic review and meta-analysis (40) that included 20 RCTs. This only found a significant reduction in pain with the use of intracervical and paracervical local anaesthesia, with the latter producing a greater effect. Updated guidance in this area, provided by data from chapter 4 of this thesis, a systematic review and meta-analysis including 37 RCTs, found that all methods of administration led to a significant reduction in pain b) Chapter 4 also provided data regarding pain scores after hysteroscopy, which were not collected in the systematic review (40) cited by the previous guideline c) The findings from chapter 4 also allowed for recommendations to be made regarding the type of local anaesthesia and the timing of

	administration, which were not present in the previous guideline
7. Conscious sedation	a) Guidance regarding conscious sedation was updated in light of the findings from Chapter 8 of this thesis. The guidance was previously based upon one RCT (41) whereas chapter 8 is a systematic review and meta-analysis including seven RCTs. The updated evidence did not show any need to change the recommendation that conscious sedation should not be routinely performed for outpatient hysteroscopy, and updated this recommendation in line with guidance from the Academy of Medical Royal Colleges standards on safe sedation practice (42).
8. Vaginoscopy	a) Guidance regarding vaginoscopy was updated in light of the findings from Chapter 5 of this thesis. The guidance was previously based a systematic review and meta-analysis that included six RCTs (43) whereas chapter 5 is a systematic review and meta-analysis also including seven RCTs; the RCTs included are different, as it was felt that there were . The updated evidence did not show any need to change the recommendation that vaginoscopy should remain the primary approach for hysteroscopy.
9. Prevention of infection	a) This is a new section in the guideline based on one RCT (23) and one survey of practice (44)
10. Documentation	a) This is a new section in the guideline based on expert opinion from the BSGE ACN (12)

2. The guidance provided under section 4.4 on page 4 of 34 should read "Pregnancy should be excluded in all premenopausal and sexually active patients who are not using a long-acting reversible (e.g. coil, implant, depot etc.) or irreversible form of contraception (e.g. sterilisation)" instead of "Pregnancy should be excluded in all patients who are premenopausal and sexually active".
3. The final recommendation of page 16 of 34 under "9.3 Which local anaesthesia should be administered and how should it be given prior to outpatient hysteroscopy?" should read "Clinicians should wait at least 2 minutes after administering short-acting local anaesthetics (e.g. mepivacaine, lidocaine and prilocaine) and at least 5 minutes after administering longer acting agents (e.g. bupivacaine) require at least 5 minutes before commencing hysteroscopy to allow for onset of effect."
4. There is an error on page 19 of 34 of the guideline with regards to vaginoscopy; seven, rather than six RCTs were included in the systematic review referred to based on Chapter 5 of this thesis.
5. The first research recommendation on page 22 of 34 of the guideline should be changed from "Effect of cervical preparation with prostaglandins on pain relief and feasibility of outpatient hysteroscopy" to "Identify the specific patient groups that would benefit from cervical preparation and determine the effect of this benefit to them with regards to side-effects and feasibility."
6. Another research recommendation on page 22 of 34 that should be added to the current set should be: "Evaluation of the patient characteristics that influence pain, side-effects and success in diagnostic and therapeutic hysteroscopy".

PART 3: A NOVEL APPLICATION OF OUTPATIENT HYSTEROSCOPY IN THE MANAGEMENT OF MISCARRIAGE - THE HYSTEROSCOPIC MISCARRIAGE MANAGEMENT (HYMMN) PILOT RANDOMISED-CONTROLLED TRIAL

CHAPTER 1: AUTHOR ROLES

I was responsible for designing the trial and the protocol, gaining funding and ethical approval, day-to day clinical management of the trial, arranging and performing follow-up, performing hysteroscopies in randomised women and in eligible women after their 12-month follow-up, data analysis and manuscript preparation.

Sister Oonagh Pickering was responsible for performing the transvaginal ultrasound scans and contributed towards arranging and performing follow-up at 14 weeks, 6 months and 12 months.

Sister Siobhan O'Connor and Z.S. assisted in performing the hysteroscopies in participants that were eligible at 12 months.

Miss Natalie Woodhead was responsible for managing the women randomised to standard treatment.

Mr. Paul Smith contributed towards day-to-day clinical management of the trial, performing hysteroscopies in randomised women and in eligible women after their 12-month follow-up, as well as data analysis and manuscript preparation.

Professor Arri Coomarasamy contributed towards gaining funding and manuscript preparation.

Professor T. Justin Clark conceived the trial and assisted with the design of the trial, the protocol, gaining ethical approval, day-to-day clinical management of the trial, assisted in performing the hysteroscopies in participants that were eligible at 12 months and was responsible for manuscript preparation.

CHAPTER 2: INTRODUCTION

Background

A first-trimester miscarriage is defined as the loss of a pregnancy less than 14 weeks' gestation, affecting as many as 1 in 4 pregnancies (45). As well as causing women symptoms such as bleeding and abdominal cramping, such a diagnosis carries a significant psychological burden to affected women and their partners. Management comprises expectant, medical or surgical options.

Expectant management, which is the first-line recommended management from the National Institute for Health and Care Excellence (NICE) comprises a "watch and wait" approach for 7-14 days (46), however, has a success rate of 58% (47). Medical management, invariably using vaginal prostaglandins, speeds this process up, increasing the chances of success to 81% (47), but risks significant uterine cramping and increased blood loss. Surgical treatment involves dilatation of the cervical canal followed by blind curettage or vacuum aspiration of pregnancy tissue within the uterine cavity. The blind nature of this procedure risks incomplete removal of pregnancy tissue, as well as serious complications such as uterine perforation (48), however, has the highest success rate of all treatment options at 96% (47). The results of a pilot randomised-controlled trial aiming to reduce these risks through the comparison of standard suction evacuation against ultrasound guided evacuation are awaited (49).

Pregnancy tissue, sometimes referred to as 'placental remnants' that remains inside the womb despite initial treatment is known as retained products of conception (RPOC). It can occur after a first or second trimester miscarriage or

after the delivery of a baby. For the purpose of this thesis, the focus will be on RPOC that occur following a first trimester miscarriage.

Complications

The presence of RPOC may be asymptomatic but can often lead to prolonged uterine bleeding, pain and infection requiring additional interventions including ultrasound scans, antibiotics and repeated medical and/or surgical treatment options, for which there is no evidence-based guidance. These additional hospital visits, which may necessitate inpatient admission, impose an additional burden on women, their partners and an already overburdened healthcare service. Furthermore, there is evidence that if left untreated, chronic RPOC can cause intrauterine adhesions and endometritis, both of which can delay, or permanently adversely affect fertility (7). It is therefore no wonder why the diagnosis of RPOC causes great psychological distress to patients and their partners in the context of miscarriage (50,51).

Diagnosis

In the UK, women are only offered a transvaginal ultrasound scan (TVUS) to detect RPOC if they present with symptoms following a miscarriage (e.g. abnormal vaginal bleeding, pain, vaginal discharge), however in some centres in Europe (e.g. Ghent, Belgium; Amsterdam, Netherlands, etc.) women are offered this investigation routinely in order to capture those that are asymptomatic due to the reproductive morbidity these women may suffer if chronic RPOC are not treated promptly. There remain questions over what ultrasound parameters should be used to diagnose RPOC (52) and how particularly vascular remnants

should be defined and managed (53,54). The endometrial echo complex (EEC), refers to the highest sonographic dimension of the endometrium (including that of both layers) in the sagittal plane. Whilst the literature describes using a minimum cut-off of between 8-13mm, a sensitivity of over 80% is reported when 10mm is used as the cut-off (54).

The timing of diagnosis and subsequent treatment is also another area that has not been clearly defined. Clinicians should be wary of offering an ultrasound scan too soon after a miscarriage as the presence of blood may give a falsely large EEC. Additionally, the number of women with RPOC who may pass these with their first menstrual period following their miscarriage is unknown, and so again, early sonography should be avoided to prevent overdiagnosis and overtreatment. Available literature cites the importance of delaying diagnosis and treatment by 2-3 months following a miscarriage to allow for any pregnancy tissue that would have passed naturally to pass, to avoid operating on a soft, gravid uterus (where the risk of uterine perforation is greater) and to allow for de-vascularisation of the RPOC (in order to improve intraoperative views and reduce periprocedural blood loss, both of which reduce the risk of a failed procedure) (55–57).

Current Treatment Options

There is a lack of consensus regarding how best to manage RPOC after miscarriage because evidence-based guidance is absent. Expectant management risks delayed return of fertility and the presence of chronic RPOC may induce local inflammatory responses making the endometrium vulnerable to adhesion formation which may compromise subsequent fertility. Medical

management, in similarity, risks incomplete treatment and the need for further medical and/or surgical treatment options, and so is not a definitive option. One could argue that the risks of uterine perforation and adhesion formation (due to injury to the vulnerable pregnant endometrium) are greater with surgical evacuation for RPOC when compared to when performed for miscarriage, as the performing clinician will make more of an effort to curette all walls of the uterus so that pregnancy tissue is not left behind, especially if local inflammatory processes have rendered the tissue adherent.

There is clearly great uncertainty regarding the optimal treatment method for RPOC with regards to future fertility. A systematic review (58) found that women treated with curettage had a pooled prevalence of intrauterine adhesions of 29.6% (56/189) at second-look hysteroscopy, however, what is unknown is the impact of these on subsequent reproductive outcome. Additionally, unfortunately no data exists regarding reproductive outcomes following medical or expectant treatment of RPOC (58).

Hysteroscopic Management

The use of hysteroscopy for the treatment of RPOC was first described by Goldenberg in 1997 (59), using an inactivated ‘cold’ cutting loop of a resectoscope to remove pregnancy tissue under direct vision to avoid inadvertent curettage of the endometrium. Whilst electrical energy should generally be avoided in order to prevent thermal damage to the endometrium and possibly the myometrium, electrocautery has been described in situations where there has been adherent tissue and/or excessive bleeding in order to allow for complete

uterine evacuation and/or haemostasis (9). Resectoscopes require the use of a larger-diameter hysteroscope, typically 8-9mm, and so invariably, this requires the use of general anaesthesia to facilitate their use. Tissue retrieval can often be challenging as the operator has to trap the RPOC between the loop and the hysteroscope and gently remove the device so that tissue is not lost as it is removed from the uterus. Therefore multiple insertions and withdrawals of the hysteroscope are required which not only prolongs operating times but increases the risk of uterine perforation, air emboli and/or cervical trauma (60).

The use of a hysteroscope with a working channel through which ancillary instruments, such as miniature hysteroscopic forceps, graspers and scissors, has been described although the literature available is much more limited when compared to other hysteroscopic techniques (61–63). Although similar challenges regarding tissue retrieval exist when compared to the use of resectoscopy, these hysteroscopes classically employ a smaller outer diameter (≥3.5mm), and so can be used in the outpatient setting, avoiding the additional staff and infrastructure required for inpatient surgery under general anaesthesia.

Mechanical hysteroscopic tissue removal systems (mHTRS) represent the latest advance in uterine surgery (60). These systems allow for intrauterine pathology, such as endometrial polyps and submucous fibroids in addition to RPOC, to be directly visualised and simultaneously removed with greater precision and less trauma to the endometrium with promising results (64). They are the only technology that allow for the continuous removal and aspiration of tissue through the use of a small cutting window situated at 90º to the end of an ancillary

instrument that is pushed down the existing hysteroscope. As a result there is no need to continuously remove and reinsert the hysteroscope to retrieve excised tissue, reducing the risk of uterine perforation and/or cervical trauma. In addition, because these devices employ a smaller diameter telescope (typically 5-8mm) than the outer diameters of most resectoscopes. Furthermore, because they do not require the use of electrosurgery that can cause pain, mHTRS are successfully used in the outpatient setting (65).

When evaluating a new surgical technique it is important to determine its treatment efficacy and risk of complications. A recent systematic review and meta-analysis found a pooled complete resection rate of 91% (95% CI 83-96%) with the use of hysteroscopy for the treatment of RPOC (66). All sixteen studies, apart from one (56) which is discussed later, were retrospective cohort studies spanning close to two decades, with great heterogeneity in study populations (both in terms of number and characteristics), study settings (and therefore levels of analgesia/anaesthesia), hysteroscopic devices and techniques, and study quality. What is clear, however, is that the use of mHTRS showed much higher complete resection rates than the use of resectoscopy and ancillary instruments regardless of the setting, with a minimum pooled resection rate of 93%. Another systematic review and meta-analysis, which had the inherent limitations of the first, depicted a complication rate of 1.9% (95% CI 0.1%-5.5%) that was limited to uterine perforations, cervical trauma, excessive bleeding and fluid overload (67). When an outlying study with a high complication rate attributed to the fact that the antecedent pregnancy was a birth rather than miscarriage or termination, was removed the pooled complication rate was 0.6% (95% CI 0.0-1.5%).

The latter systematic review also meta-analysed pregnancy rates following the hysteroscopic management of RPOC and where available compared these rates against cohort data evaluating uterine curettage (67). Setting aside inherent issues when meta-analysing cohort studies with follow-up ranging from 6 to 60 months, the meta-analysis of 8 retrospective cohort studies involving the use of hysteroscopy against three studies that published comparative cohorts, showed an increase in pooled conception rates when hysteroscopy was used (81.1% (95% CI 75.3-86.8%) vs 65.4% (95%CI 54.1-76.6%)), although this difference was not significant. What was interesting, however, was that in the three studies that had comparative cohorts (68–70), all showed a significantly shorter time to conception with the use of hysteroscopy compared to conventional blind curettage. Unfortunately, their results could not be meta-analysed due to the use of medians and means to describe the average. This finding could perhaps be explained by the significantly lower intrauterine adhesion rate following the use of hysteroscopy (29.6%) when compared to curettage (12.8%) ($p<0.01$) as exhibited by another systematic review that also found a tendency to earlier conception with the use of hysteroscopy (58).

The best quality data that exists for the use of hysteroscopy for the management of RPOC, is a randomised-controlled trial that randomised 84 women with RPOC to either the use of the resectoscope or mHTRS, published in 2016 (56). The use of a mHTRS was associated with a significantly shorter operating time (6.2 vs 10.0 minutes; $p=0.023$). Incomplete resection rates were low occurring in one patient in the mHTRS group and two in the resectoscope group. Conception

rates following hysteroscopy were not investigated, however, the risk of intrauterine adhesions at second-look hysteroscopy were also low as they were present in one patient in each group.

Summary

Current evidence suggests that hysteroscopic resection of RPOC is associated with the formation of less intrauterine adhesions, low rates of incomplete evacuation, and a shorter time to subsequent conception when compared to current surgical treatment. However, these observations are based upon limited numbers of small, non-randomised and underpowered studies with poor reporting of confounding factors. Since women are most strongly influenced in their choice of management by the likelihood of complete evacuation of the uterine cavity without impairment of future fertility (10), it is clear that we need better evidence to inform patients and clinicians of the potential efficacy of hysteroscopic management of RPOC. We therefore designed a pilot RCT to compare outpatient hysteroscopic management against standard (expectant, medical, or surgical) management of RPOC following first-trimester miscarriage in order to determine the feasibility of a future well-powered large multi-centre RCT.

CHAPTER 3: MATERIALS AND METHODS

Study design and oversight

A parallel-group, unblinded, single centre pilot RCT comparing outpatient hysteroscopy against standard treatment (comprising expectant, medical, or surgical management) for the management of RPOC diagnosed by routine transvaginal ultrasound scan following first-trimester miscarriage was designed. Trial process data and clinical outcomes were collected to inform the feasibility and design of a future, substantive, full-scale trial. The National Research Ethics Service, UK, granted ethical approval (identifier: 20/WM/0287) on the 18th December 2020. The trial was registered on clinicaltrials.gov (identifier: NCT04751500). The original protocol can be found in Appendix 7.1.

Participants

Women above the age of 18 years, opting for non-surgical management of their miscarriage at ≤14 weeks gestation who were wanting to conceive as soon as possible were eligible for recruitment. Women who did not understand written and spoken English or had findings suspicious of gestational trophoblastic disease or septic miscarriage were excluded.

Plan of Investigation

All women eligible for recruitment were approached for inclusion into the trial and a patient information leaflet (Appendix 7.2) was discussed and given. Written informed consent (Appendix 7.3) and baseline assessments (Appendix 7.4) were performed on women that agreed to participate. Participants were invited for a transvaginal ultrasound scan approximately 8 weeks following their miscarriage to determine the presence of RPOC. This was performed using the GE Voluson

E8 ultrasound system by a single operator. Images were archived electronically for later reference and a written report was generated detailing the endometrial thickness, the presence of any mass measured in three dimensions and the presence of vascular RPOC when colour doppler was applied with pulse repetition frequency (PRF) set at 0.6-0.9kHz. The presence of an endometrial mass or endometrial-echo complex (EEC) ≥10mm was considered to indicate a positive diagnosis of RPOC. Written assessments were completed by the sonographer and participant at the time of the scan to ascertain feasibility and acceptability (Appendices 7.5 and 7.6). Women diagnosed with RPOC were randomised in a 1:1 ratio to either outpatient hysteroscopic morcellation or standard treatment using a computer-generated online random allocation sequence (71). Blinding was not possible due to the nature of the trial.

Outpatient hysteroscopic morcellation was performed using the TruClear™ 5.0 (Medtronic, Minneapolis, USA) 5mm hysteroscopy system, vaginoscopically, without the outer sheath. Patients were advised to take standard doses of paracetamol (e.g. 1g) and/or non-steroidal anti-inflammatory medication (e.g. ibuprofen 400mg) 30-60 minutes prior to their procedure. Intracervical local anaesthesia using mepivacaine was administered beforehand in nulliparous patients, or patients deemed to have cervical stenosis at initial vaginoscopy. Entonox® (50% nitrous oxide and 50% oxygen) was offered to all women. Written assessments were performed to evaluate the feasibility and acceptability of outpatient hysteroscopy to the patient and clinician immediately after the procedure (Appendices 7.7 and 7.8). Standard treatment comprised an initial assessment (telephone or face-to-face) by the lead clinician for early pregnancy

at Birmingham Women's Hospital, which enquired about non-menstrual bleeding, menstrual history and post-miscarriage pregnancy test result before reviewing the ultrasound images from the 8-week post-miscarriage scan and recommending either a further scan, or expectant, medical or surgical management of their RPOC, at the discretion of the clinician. Randomised women were followed-up at 14 weeks post-randomisation to complete a written questionnaire regarding their symptoms, satisfaction of treatment pathway, quality of life and healthcare resource use (Appendix 7.9).

All participants were followed-up by telephone at 6 and 12 months post-ultrasound scan to ascertain clinical pregnancy rates and pregnancy outcomes to allow for calculation of time to conception. Participants who were not pregnant or who had not had a live birth at 12 months and were still trying to conceive were eligible for an outpatient hysteroscopy to determine the presence of and allow for the treatment of intrauterine pathology (e.g. intrauterine adhesions, chronic RPOC, etc.).

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Birmingham. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (72,73).

Outcomes

Process and clinical outcomes were collected. Process outcomes, relating to the feasibility of the trial, included the number of eligible women that were screened

and met the inclusion criteria, the proportion of eligible women that agreed to participate, and the attrition rate of the trial interventions and follow-up processes. Data were collected to determine why patients declined participation or withdrew after agreeing to participate. Further data were collected to determine whether the additional trial interventions such as a routine ultrasound scan and, where applicable, outpatient hysteroscopy, which are outside of standard practice, were acceptable to patients.

Primary clinical outcomes revolved around pregnancy; data regarding clinical pregnancy rates and pregnancy outcome (miscarriage, ectopic, live birth etc.) were collected from all patients, regardless of whether they were randomised or not, to determine any difference in fertility between women with RPOC and women without, and also to allow for time to conception to be calculated. Secondary clinical outcomes, collected from randomised patients, included symptoms associated with RPOC, satisfaction of treatment pathway, quality of life assessment, and healthcare resource use at 14 weeks post-randomisation. Specific additional data collected at ultrasound scan included the sonographic characteristics of RPOC (EEC/mass dimensions and vascularity) and presence of a positive urinary pregnancy tests 3 weeks after miscarriage which is considered standard practice (46). Specific additional data that were collected included findings at hysteroscopy (in those randomised to the intervention and where applicable, at 12 months post-ultrasound scan), ease of hysteroscopic morcellation (on a 100mm VAS), operative time, and intra-procedural patient pain (collected post-procedurally on a 100mm VAS). Where possible, suspected RPOC were sent for histological examination (e.g. at hysteroscopy or following

surgical management) which were subsequently confirmed if chorionic villi, trophoblast, fetal somatic tissue or a combination of these were present.

Data analysis

No formal sample size calculation was made. We aimed to recruit 40 women over a 6-month period as we felt this was an adequate time frame and number to understand trial processes and test data collection tools. Summary statistics including percentages and means for baseline characteristics and outcome measures at each time point are presented. Although this is a feasibility study the participants have been presented in the group to which they were randomised. The size of the study prevented us from doing reliable analysis to test the effect of the intervention on outcomes, so hypothesis testing was avoided. Analysis was initially by intention to treat (ITT), however, after it was found that randomised patients achieved the primary clinical outcome (pregnancy) before receiving their allocated intervention (e.g. hysteroscopy), we also performed per-protocol (PP) analysis. Women were excluded from analysis of the primary clinical outcome if they were uncontactable or stopped trying to conceive before falling pregnant during their 12 month follow-up.

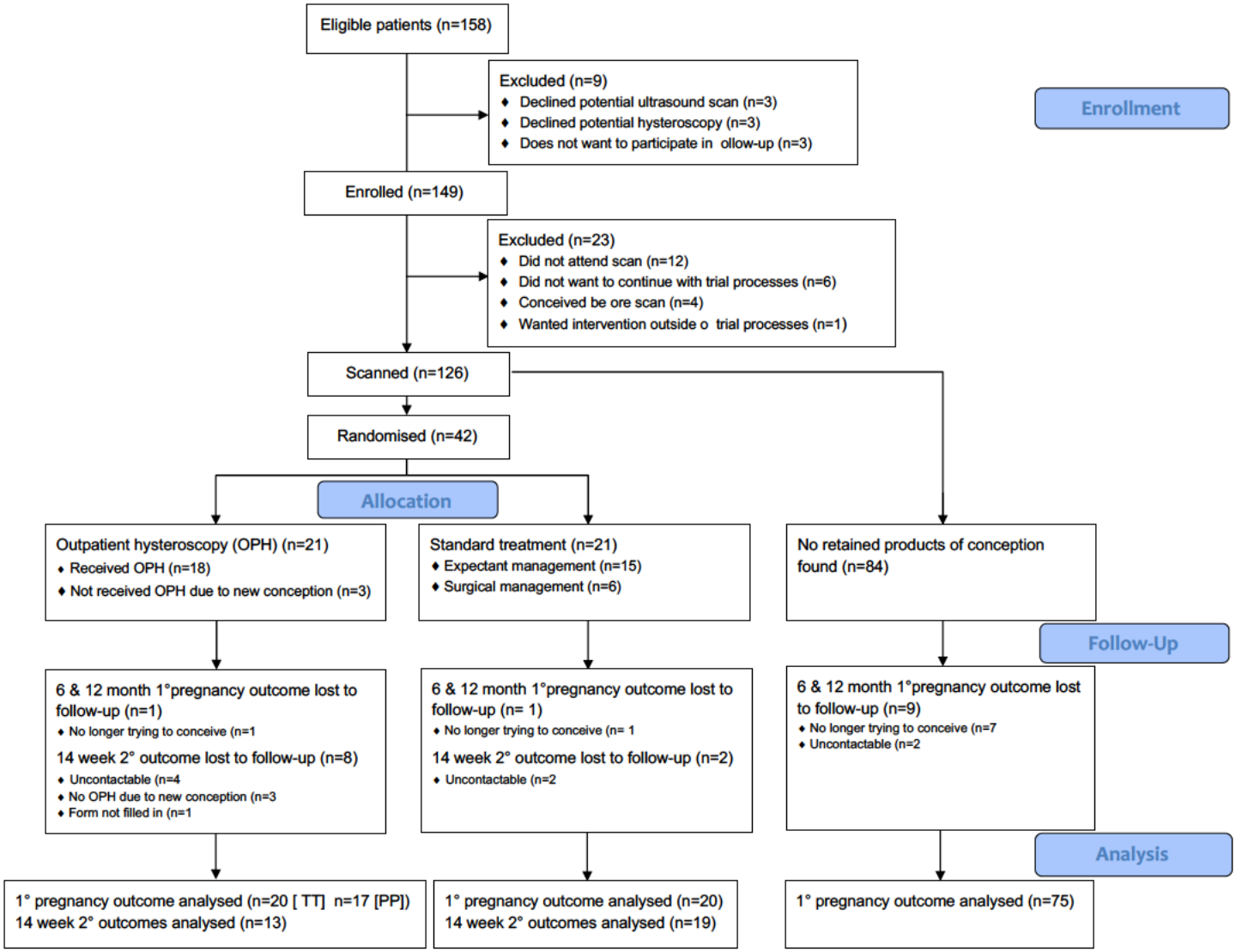
CHAPTER 4: RESULTS

Trial process outcomes

Participants

Eligible participants were recruited from the Early Pregnancy Unit and the gynaecology ward at Birmingham Women's Hospital between 31st January 2021 and 31st July 2021, with follow-up interventions continuing until 2nd November 2022. A flow diagram outlining the course of patients through the study and reasons for declining participation, study withdrawal and loss-to-follow-up can be found in Figure 1.

Figure 1: CONSORT flowchart



A total of 158 women were approached for inclusion into the trial, of which 149 (94.3%) agreed. Of the 126 women that underwent transvaginal ultrasound, RPOC were diagnosed in 42 women, giving a sonographic detection rate of 33.3%. Table 1 outlines the baseline characteristics of all participants at ultrasound scan, based on presence of RPOC and randomisation outcome.

Table 1: Baseline characteristics of included participants

		RPOC		No RPOC
		OPH (n=21)	ST (n=21)	(n=84)
Age [mean+/-SD]		33.4+/-6.0	34.0+/-4.2	33.2+/-5.8
BMI [mean+/-SD]		26.7+/-4.4	26.4+/-3.4	27.4+/-7.2
Race (n (%))	White	13 (61.9%)	13 (61.9%)	45 (53.6%)
	Asian	3 (14.3%)	5 (23.8%)	19 (22.6%)
	Black	3 (14.3%)	1 (4.8%)	13 (15.5%)
	Mixed	2 (9.5%)	2 (9.5%)	3 (3.6%)
	Other	0 (0%)	0 (0%)	4 (4.8%)
Mean gestational age at miscarriage in weeks (+/-SD)		8.3+/-2.1	7.4+/-1.8	8.1+/-2.1
Conception (n (%))	Natural	21 (100%)	20 (95.2%)	81 (96.4%)
	IVF	0 (0%)	1 (4.8%)	3 (3.6%)
Type of miscarriage (n (%))	Missed	11 (52.4%)	18 (85.7%)	44 (52.4%)
	Incomplete	7 (33.3%)	2 (9.5%)	25 (29.8%)
	Complete[1]	3 (14.3%)	1 (4.8%)	15 (17.9%)
Initial management (n (%))	Expectant	11 (52.4%)	7 (33.3%)	49 (58.3%)
	Medical[2]	10 (47.6%)	14 (66.7%)	35 (41.7%)
Parous (n (%))		11 (52.4%)	14 (66.7%)	39 (46.4%)
Previous miscarriage (2nd miscarriage) (n (%))		3 (14.3%)	6 (28.6%)	22 (26.2%)
Recurrent miscarriage (≥3rd miscarriage) (n (%))		5 (23.8%)	6 (28.6%)	20 (23.8%)
Previous uterine surgery (n (%))	SMM	1 (4.8%)	4 (19.0%)	8 (9.5%)
	STOP	0 (0%)	2 (9.5%)	8 (9.5%)
	Intrauterine	1 (4.8%)*	2 (9.5%)^	1 (1.2%)†
	Abdominal	3 (14.3%)‡	3 (14.3%)‡	13 (15.5%)‡
Mean number of days from miscarriage to scan (+/-SD)		53.6+/-3.3	55.8+/-4.3	56.5+/-6.4
Method of diagnosis (n)	EEC	7 (33.3%)	1 (4.8%)	
	EM	14 (66.7%)	20 (95.2%)	
Mean EEC in mm (+/-SD)		19.4+/-10.7	14 [SD N/A]	
Mean largest EM dimension in mm (+/-SD)		27.6+/-7.0	28.2+/-10.1	
Vascularity present (n)		8 (38.1%)	12 (57.1%)	

*D&C, ^D&C (n=1), uterine septoplasty (n=1), †intrauterine adhesiolysis, ‡all were Caesarean deliveries
[1]defined as women with an empty uterus on ultrasound or women in whom the whole miscarriage had thought to have been passed and bleeding had resolved therefore fulfilling the criteria for discharge
[2]using 800mcg vaginal misoprostol alone

Legend
RPOC: retained products of conception, OPH: outpatient hysteroscopy, ST: standard treatment, SD: standard deviation, IVF: in-vitro fertilisation, SMM: surgical management of miscarriage, STOP: surgical termination of pregnancy, EEC: endometrial echo complex, EM: endometrial mass, mm: millimetres, D&C: dilatation & curettage outside of pregnancy, N/A: not applicable

The characteristics of randomised patients were generally balanced between the two groups but there were some baseline differences. A higher proportion of women randomised to standard treatment were diagnosed with missed miscarriages (86% vs 52%), were prescribed medical management (67% vs 48%), had a history of one previous miscarriage (29 vs 14%), intrauterine curettage in pregnancy (29% vs 5%) and a lower proportion of women with an incomplete miscarriage (10% vs 33%) were randomised to hysteroscopy. More women randomised to hysteroscopy had RPOC diagnosed after finding a thickened EEC (33% vs 5%) and more women randomised to standard treatment had RPOC diagnosed by finding a mass in the uterine cavity (95% vs 67%). Vascular RPOC were more common in women randomised to standard treatment (57% vs 38%).

Routine transvaginal ultrasound scan 8 weeks post-miscarriage

A routine transvaginal ultrasound scan, performed 8 weeks after a miscarriage was considered very acceptable by 124 patients (98%), somewhat acceptable by 1 patient (1%) and very unacceptable by 1 patient (1%). All women (n=126) recommended this investigation to other women.

Outpatient hysteroscopy for treatment of RPOC

21 women were randomised to outpatient hysteroscopy, however, 3 women became pregnant following their ultrasound scan, so 18 women underwent hysteroscopy. The mean time from miscarriage to hysteroscopy was 70.9+/-8.0 days. 13/18 women (72%) who had a hysteroscopy underwent morcellation of suspected RPOC, however, this was confirmed histologically in only 6 women

(33%), one of whom was also diagnosed with endometritis and treated with oral antibiotics. Five of these women were diagnosed as having RPOC at ultrasound scan based on an endometrial mass and the other had an EEC of 12mm. The mean ease of morcellation of suspected RPOC on a 100mm VAS (where the higher the number, the easier the morcellation) was 96.4+/-6.3. The mean operating time (and standard deviation) for all cases was 3.8 minutes +/- 245 seconds, which increased to a mean of 4.8 minutes +/- 268 seconds in cases where suspected RPOC were morcellated. Hysteroscopy was successful in all cases apart from one patient in whom the procedure was stopped after 427 seconds as she was too uncomfortable to continue. This was successfully treated at her next hysteroscopy two weeks later which took 254 seconds. Her ultrasound scan showed an endometrial mass, where the largest dimension was 34mm and was noted as being “particularly cystic and vascular”.

Data regarding pain and acceptability were recorded in 17/18 patients, as one patient left without completing the questionnaire. Mean intraprocedural pain recorded on a 100mm VAS, was 46.59+/-25.56. 13 patients (76%) found the procedure very acceptable and 4 (24%) found it somewhat acceptable. 15 patients (88%) stated that they would have the same treatment again and four patients (24%) would request that the procedure be performed under general anaesthesia if needed again. One patient had a vasovagal episode following hysteroscopy requiring hospital ward admission but was discharged after two hours; no other complications were encountered.

Standard treatment for treatment of RPOC

21 patients with RPOC were randomised to standard treatment. 19 patients had one telephone consultation, one patient had two telephone consultations, six patients were invited for a face-to-face appointment and two patients had two face-to-face appointments. Another transvaginal ultrasound scan was performed in seven patients, one of whom had two ultrasound scans. 16 patients (76%) were recommended expectant management for their RPOC, one of whom required manual vacuum aspiration under local anaesthesia as expectant management failed. Five patients (24%) were recommended surgical management for their RPOC, of whom four underwent manual vacuum aspiration under local anaesthesia and one underwent surgical suction curettage under general anaesthesia as per patient choice. Histology was confirmed in all six patients who underwent surgical management; all of whom were originally diagnosed as having RPOC based on finding an endometrial mass at ultrasound scan. Three patients (21%) were given oral antibiotics for a lower genital tract infection, of whom one was given a prescription outside of the trial processes.

Clinical outcomes

Primary outcome - pregnancy

The four women who conceived before their post-miscarriage ultrasound scan, as displayed in Figure 1, had a live birth. Two women who were found to have an early viable pregnancy diagnosed at their post-miscarriage ultrasound also had a live birth.

Table 2 depicts the pregnancy outcomes of women with RPOC (according to their treatment) and women without RPOC. Both intention-to-treat and per-protocol analyses have been performed based on the inclusion/exclusion, respectively, of the three patients that were randomised to hysteroscopy but could not undergo this intervention as they fell pregnant beforehand.

Table 2 also shows women the proportion of women eligible for a hysteroscopy at 12 months and their hysteroscopic findings, as well as reasons for not undergoing the procedure in those that were eligible. The majority of intrauterine and/or isthmic/cervical canal adhesions that were found (n= 6/7; 86%) were in women randomised to standard treatment, of whom two had a manual vacuum aspiration and four had expectant management. The one woman with RPOC experienced two further miscarriages over the 12-month follow-up period.

Table 2: Pregnancy outcomes and 12 month hysteroscopy findings

			RPOC			No RPOC
			OPH (n=20) [ITT]	OPH (n=17) [PP]	ST (n=20)	(n=75)
Pregnant (n,%)			14 (70%)	11 (65%)	13 (65%)	60 (80%)
Mean time to conception in days (+/-SD)			142+/-95	171+/-85	153+/-106	143+/-102
Method of conception (n, %)	Natural		14 (100%)	11 (100%)	12 (92%)	57 (95%)
	IVF		0 (0%)	0 (0%)	1 (8%)	3 (5%)
Pregnancy outcome (n, %)	Ongoing		6 (43%)	6 (55%)	3 (23%)	16 (27%)
	Miscarriage		3 (21%)	3 (27%)	4 (31%)	19 (32%)
	Livebirth		5 (36%)	2 (18%)	6 (46%)	25 (42%)
	Ectopic		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean gestation of ongoing pregnancy in weeks (+/- SD)			24.3+/-8.4		14.7+/-11.7	24.4+/-10.8
12-month hysteroscopy	Eligible (N)		7/9[1]		9/11[2]	25/34[3]
	Declined (n/N)		5/7[4]		2/9[5]	6/25[6]
	Findings	Normal (n/N)	1/2		1/7	18/19
		Adhesions (n/N)†	0		6/7	1/19
		RPOC (n/N)	1/2‡		0	0

[1,2]2 patients who had miscarriages had ongoing pregnancies at 12 months
[3]6 patients who had miscarriages had ongoing pregnancies at 12 months, 1 who had a miscarriage had a copper coil inserted between their 6 and 12 month follow-up, 1 who had a miscarriage DNA their 12 month follow-up and 1 DNA their 12 month follow-up (the last 2 patients attended their 6 month follow-up)
[4]1 patient fell pregnant between follow-up and hysteroscopy, 1 declined hysteroscopy and 3 DNA
[5]1 patient fell pregnant between follow-up and hysteroscopy and 1 DNA
[6]1 patient fell pregnant between follow-up and hysteroscopy and 5 DNA

†Adhesions were present in at least one from the following (i) body of the uterus, (ii) uterine isthmus (iii) cervical canal
‡This was diagnosed on hysteroscopy, where morcellation of RPOC were confirmed histologically. This patient had two additional miscarriages over her 12-month follow-up period.

Legend
RPOC: retained products of conception, OPH: outpatient hysteroscopy, ST: standard treatment, SD: standard deviation, IVF: in-vitro fertilisation, RPOC: retained products of conception, MVA: manual vacuum aspiration, LA: local anaesthesia; ITT: intention-to-treat; PP: per protocol; DNA: did not attend

Secondary outcomes - symptoms, satisfaction, quality of life and healthcare resource use

Table 3 shows the symptom data collected at the 8-week post miscarriage diagnosis ultrasound scan as well as the symptom, quality of life, satisfaction and healthcare resource use data at the 14-week follow-up.

More women with RPOC had non-menstrual bleeding (13/42 (31%) vs 14/84 (17%)), vaginal discharge (5/42 (12%) vs 5/84 (6%)) and a positive urinary pregnancy test 3 weeks after miscarriage (15/42 (36%) vs 15/76 (20%)) compared to women without RPOC. More women without RPOC reported the return of menses following their miscarriage by the time they had their ultrasound scan when compared to women with RPOC (73/84 (87%) vs 29/42 (69%)).

Table 3: Secondary outcome data

DATA COLLECTED AT 8 WEEK ELIGIBILITY TRANSVAGINAL ULTRASOUND SCAN		RPOC (n=42)		No RPOC (n=84)
Symptoms	Non-menstrual bleeding (n (%))	13 (31.0%)		14 (16.7%)
	Abdominal cramping (n (%))	9 (21.4%)		19 (22.6%)
	Vaginal discharge (n (%))	5 (11.9%)		5 (6.0%)
Menstruation	Number of patients who had a period between their miscarriage and scan (n (%))	29 (69.0%)		73 (86.9%)
	Mean number of days to first menstrual period after miscarriage (+/-SD)	33.8+/-9.2		34.0+/-11.0
Urinary pregnancy test	Number of patients who had a positive UPT 3 weeks post-miscarriage	15 (35.7%)		15 (19.7%)†
DATA COLLECTED AT 14 WEEK FOLLOW-UP		**OPH (n=13)**	**ST (n=19)**	
Symptoms	Mean number of weeks to regularity of periods if menses returned (+/-SD)	8.4+/-3.2	8.6+/-3.5	
	Acceptable bleeding pattern in women whose menses have returned (n, %)	11 (84.6%)	16 (84.2%)	
	New vaginal discharge by 14w (n, %)	1 (7.7%)	5 (26.3%)	
	New abdominal pain (n, %)	2 (15.4%)	4 (21.1%)	
Quality of life	Mean overall health on 100-point scale (+/-SD)	81.9+/-13.9	74.8+/-17.1	
	Mean number of days off work (+/-SD)	10.4+/-11.9	11.9+/-19.4	
Satisfaction	Mean treatment pathway satisfaction on 100mm VAS (+/-SD)	89.9+/-13.3	89.3+/-14.5	
Healthcare resource use	Mean number of primary care attendances (+/-SD)	0.38+/-0.65	0.47+/-0.90	
	Mean number of emergency department attendances (+/-SD)	0	0.11+/-0.32	
	Mean number of early pregnancy unit attendances (+/-SD)	0.62+/-0.77	1.37+/-1.74	
	Number of patients admitted to hospital overnight (+/-SD)*	1 (7.7%)	2 (10.5%)	

*all patients admitted for one night
†8 patients did not perform a urinary pregnancy test

Legend
RPOC: retained products of conception, OPH: outpatient hysteroscopy, ST; standard treatment, SD: standard deviation, VAS: visual analogue scale, mm: millimetres, UPT: urinary pregnancy test

At 14 weeks, it was noted that whilst more women reported the presence of new vaginal discharge when randomised to standard treatment when compared to outpatient hysteroscopy (5/13 (26%) vs 1/13 (8%)), the mean number of weeks

to regularity of periods (8.4+/-3.2 vs 8.6+/-3.5), the proportion of women who had an acceptable bleeding pattern (11/12 (85%) vs 16/19 (84%)) and proportion of women with new abdominal pain (2/13 (15%) vs 4/19 (21%)) remained balanced between groups. Mean overall health on a 100-point scale (81.9+/-13.9 vs 74.8+/-17.1), mean number of days off work (10.4+/-11.9 vs 11.9+/-19.4), mean treatment pathway satisfaction on a 100mm VAS (89.9+/-13.3 vs 89.3+/-14.5) was also balanced between groups. Healthcare resource use across all parameters from the diagnosis of miscarriage to 14 weeks post-randomisation (mean number of primary care (0.38+/-0.65 vs 0.47+/-0.90), emergency department (0 vs 0.11+/-0.32) and early pregnancy unit admissions (0.62+/-0.77 vs 1.37+/-1.74) and number of patients admitted to hospital overnight (1 vs 2)) was higher in women randomised to standard treatment, although it must be noted that there was significant overlap in standard deviations across both groups.

CHAPTER 5: DISCUSSION

Main findings

158 eligible patients were identified for inclusion into this single centre study over a six-month period. Only 6% (9/158) of eligible patients declined participation and of those that agreed participation, only 15% (23/149) failed to attend an ultrasound scan. Randomisation was acceptable to all patients, with no loss-to-follow-up after group allocation except for those that fell pregnant before hysteroscopy who were excluded. As a result, per-protocol analysis was performed for pregnancy outcomes in addition to intention-to-treat analysis. Both trial interventions (post-miscarriage transvaginal ultrasound scan and outpatient hysteroscopy) were highly acceptable (>99%) to patients and were successful without any serious complications occurring (e.g. uterine perforation). Nearly a quarter (10/42; 24%) of randomised patients failed to provide secondary outcome data relating to symptoms, quality of life and health care resource use at 14 weeks. However, at 6 and 12 months, only 9% (11/126) of patients could not provide us with our primary clinical outcome i.e. pregnancy data.

This RCT was a feasibility study and as such the small number of patients randomised to each group meant that the study was not powered to show a clinical difference in terms of pregnancy rates, pregnancy outcomes and time to conception, which reinforces the need for a larger clinical study. It should be noted that, 8/28 (29%) of patients undergoing a follow up outpatient hysteroscopy because of a non-successful pregnancy outcome at 12 months had pathology (all in the form of intrauterine and/or isthmic/cervical canal adhesions) and 6/8 of these women with pathology were randomised to standard treatment. These findings are in agreement with existing systematic reviews of

observational data where the use of hysteroscopy is associated with less intrauterine adhesions (58). Women randomised to hysteroscopy attended the hospital fewer times than women randomised to standard treatment. Finally, clinicians should be aware that women diagnosed with RPOC have positive outcomes, regardless of the treatment they had, with 60% (n=24/40) of patients having an ongoing pregnancy or live birth at 12 months. In addition, all patients who became pregnant before attending their trial intervention ended with a live birth; four patients fell pregnant before their ultrasound scan and three patients fell pregnant prior to hysteroscopic treatment of their RPOC.

Strengths and limitations

This is the first RCT investigating hysteroscopy against a control for the treatment of RPOC to investigate pregnancy outcome. It provides important data in order to help determine the feasibility and design (including power calculations) of a full-scale, well-powered, substantive, multi-centre RCT. Although it is known that the risk of formation of intrauterine adhesions is greater in women who were treated with surgical management compared to hysteroscopy for RPOC (58), this is the first data available that points towards the reproductive implications of such adhesions.

Our sample size was too small to make strong clinical conclusions but was sufficient to test feasibility. Despite randomisation, there were imbalances between groups with respect to the type of miscarriage, management of miscarriage, the number of patients who had a previous miscarriage, the number

of patients who had previous uterine curettage in pregnancy, the description of RPOC at diagnosis. However, these imbalances reflected the small sample rather than deficiencies in the third-party randomisation schedule.

There was a relatively low proportion of histologically confirmed RPOC in women who underwent hysteroscopy (n=6/18; 33%) which could have been as a result of too low a threshold to diagnose RPOC at ultrasound scan using EEC. The follow-up questionnaire at 14 weeks had much higher loss-to-follow-up rates compared to the other trial follow-up processes which may have been due to the need to perform a face-to-face consultation in order to complete the questionnaire. Healthcare resource use questions were asked based on time since miscarriage rather than time since treatment of RPOC so it was difficult to ascertain if the reduction in healthcare visits (to primary care, the emergency department, secondary care etc.) was as result of baseline differences or as a result of randomisation.

Implications of findings on a future substantive trial

The high numbers of eligible patients in this single centre study in addition to the low attrition rates at each point, high acceptability of trial interventions and high follow-up rates for the primary clinical outcome demonstrate that a full-scale, well-powered, substantive, multi-centre RCT evaluating the management of RPOC after first trimester miscarriage with a focus on pregnancy outcomes is feasible.

There are, however, some considerations that should take place before such a trial is designed:

1. Randomisation led to imbalances in some baseline characteristics between groups and as the prevalence of RPOC is influenced by gestation at miscarriage, miscarriage type and initial treatment, impact of RPOC is influenced by size and vascularity, and future fertility is influenced by age, BMI and number of previous miscarriages. All of these factors cannot be controlled by stratification and so it may be prudent to exclude patients who have other contributing factors to adverse pregnancy outcome regardless of the presence of RPOC (e.g. age >40 years, BMI >35, women with recurrent miscarriage).
2. The low ratio of suspected to histologically confirmed RPOC at hysteroscopy has been previously identified across a number of studies (58). The lack of specific parameters to diagnose RPOC on ultrasound scan may have led to a higher number of false positive diagnoses; whilst we used a minimum EEC of 10mm, there is increasing literature to suggest that a cut-off of 15mm should be used. This study showed that in the 12 women who had positive histological diagnoses of RPOC (6 at hysteroscopy and 6 after surgical curettage), 11 were diagnosed after finding an endometrial mass and one was diagnosed due to a thickened EEC. It may therefore be worth redefining the criteria for RPOC based on an endometrial mass rather than a thickened EEC in order to achieve less false positive diagnoses of RPOC at ultrasound scan if this study is to be modified for a substantive trial in the future. In agreement with a randomised trial comparing loop resection to hysteroscopic morcellation for RPOC (56), which found a lack of uniformity between

hysteroscopic and histological diagnoses, it is clear that there needs to be agreement between the histopathologist and research team regarding the histological definition of RPOC, including the classification of decidua alone, in addition to chorionic villi, trophoblast, and fetal somatic tissue.

3. All patient-facing questionnaires should be clear in order to avoid reporter bias and should be available to complete online, with an email reminder, to reduce the attrition rates associated with the 14-week follow-up.
4. Questions regarding healthcare resource use should be specific to treatment allocation and further qualitative data should be ascertained to find out why patients sought healthcare outside of trial processes (e.g. primary care/emergency department attendances). In order to provide more contextual data regarding healthcare resource use, researchers should consider using contemporary cost-based analyses.
5. Since patients are most strongly influenced in their miscarriage management by the probability of success of the treatment and its influence on future pregnancy outcome (10), researchers must carefully consider what a future substantive study should be powered for when determining the primary clinical outcome. Based on the findings of this study, it may be worthwhile setting the primary clinical outcome as live births within a two year timeframe, especially as a number of patients had ongoing pregnancies at 12 months and between their 12 month follow-up and subsequent hysteroscopy.
6. There are many components of this study that ran smoothly based on the fact that this is a single-centre study with myself running the study on a day-to-day basis with a strong research team that has capacity to scan and organise hysteroscopies that are outside of standard clinical practice. If this

were to be developed into a multi-centre study at different NHS trusts, then the following considerations should take place:

a. Do trusts have the staffing, expertise, scan capacity and organisation to ensure that women who agree to participate receive an ultrasound scan 8 weeks after their miscarriage?
b. Do trusts have the staffing, expertise, hysteroscopy capacity and organisation to ensure that women who are randomised to hysteroscopy receive their hysteroscopy approximately as soon as possible (and ideally within two weeks) after randomisation?
c. How will trusts ensure that patients who agree to be scanned 8 weeks after their miscarriage as part of the trial do not receive any intervention (investigations or treatment) too early as part of local practice, therefore necessitating exit from the trial?
d. In order for there to be uniformity in how the standard management arm patients are treated across different centres, an algorithm-style approach should be considered. One proposal is that if patients are symptomatic or have RPOC ≥2cm then they should be offered either medical or surgical management unless they have symptoms suggesting of infection (e.g. offensive discharge, abdominal pain, pyrexia etc.) at which point surgical management should be offered. If patients are managed conservatively or medically then an ultrasound scan should be considered two weeks later to determine the efficacy of the treatment given. If RPOC are still present at this scan then surgical management could be offered.

e. Do trusts/the sponsor have the ability to allocate a researcher to call all included patients regarding pregnancy outcomes, bearing in mind that many patients will require more than one phone call due to unavailability? If not, then researchers should consider the use of timed emails sent to patients to register pregnancies/pregnancy outcomes, however, with the acceptance that completion rates may be lower.

CHAPTER 6: CONCLUSION

The results from this pilot RCT show that performing a full-scale, well-powered, substantive, multi-centre RCT investigating outpatient hysteroscopy against standard treatment in the future is feasible and clinically relevant, with high patient acceptability rates of proposed additional interventions. Consideration should be made regarding randomisation to ensure baseline and sonographic characteristics are balanced between groups. Not all parameters can be controlled by stratification and so eligibility criteria should be carefully considered to exclude patients who have other risk factors that would lead to potentially adverse pregnancy outcomes outside of a diagnosis of RPOC. The parameters used to diagnose RPOC at ultrasound scan should be carefully considered to reduce the risk of false positive diagnoses. Histological criteria for RPOC diagnosis should be uniform amongst gynaecologists and histopathologists to reduce false negative diagnoses at histopathology. Where possible, participants should be able to complete follow-up questionnaires online to reduce attrition rates. Women randomised to standard treatment should be offered a hysteroscopy to check for intrauterine adhesions if they have not had a successful pregnancy after 12 months, however, follow-up of ongoing pregnancies should continue past 12 months to ascertain their outcome. Should a substantive multi-centre RCT be performed in the future, researchers should consider the logistical challenges posed by additional scans and hysteroscopies which will be required within certain timeframes. Finally, researchers should consider adopting an algorithm for the management of patients randomised to standard treatment to ensure equity amongst centres.

PART 4: DISCUSSION

CHAPTER 1: SUMMARY OF FINDINGS AND IMPLICATIONS FOR CLINICAL PRACTICE

Introduction

This thesis constitutes a comprehensive body of research which utilises mixed methodologies in order to firstly, investigate the optimal method of undertaking outpatient hysteroscopy in order to provide safe, acceptable, and efficacious care for women and to secondly, investigate the novel role of outpatient hysteroscopy to treat retained products of conception following miscarriage as outlined by 'Part 1: Introduction'. In this chapter, the findings from 'Part 2: Best Practice in Outpatient Hysteroscopy' and 'Part 3: A Novel Application of Outpatient Hysteroscopy in the Management of Miscarriage' are summarised and their implications for clinical practice are discussed.

Best Practice in Outpatient Hysteroscopy

Chapter 1 outlined the need to provide a new evidence-based guideline for the provision of outpatient hysteroscopy in the UK since the last one was produced over a decade ago. Chapter 2 focused on the methodology used to answer questions explored by the guideline, outlining specific details of the searches used in the nine systematic reviews.

Chapter 3 identified the role of analgesic agents/adjuncts for the reduction of pain during outpatient hysteroscopy (24). This systematic review and meta-analysis showed that analgesia reduced pain both during and after the procedure. Non-steroidal anti-inflammatory drugs (NSAIDs) and transcutaneous electrical nerve stimulation (TENS) devices were the only agents to reduce pain both during and after hysteroscopy, without increasing the risk of side-effects, namely vasovagal episodes and drowsiness. Based on available evidence, we

therefore recommend clinicians to communicate to patients the importance of taking an oral NSAID (in standard doses which are readily available over the counter), one hour before their hysteroscopy appointment. Where NSAIDs are contraindicated, clinicians should consider using TENS devices instead, which are far less readily available.

Chapter 4 described the role of local anaesthesia for outpatient hysteroscopy (25). Whilst we demonstrated a reduction in pain both during and after hysteroscopy after the administration of local anaesthesia, meta-analysis did not take into account the vaginoscopic approach which has been demonstrated in chapter 5 to be superior to using a vaginal speculum as a minimum to perform hysteroscopy. Therefore, any potential benefits of local anaesthesia administration that involve a speculum may be offset by the use of smaller diameter hysteroscopes utilising a 'no touch' vaginoscopic technique. Injectable/topical local anaesthesia administration to the cervix is therefore recommended where cervical dilatation is anticipated, for example with the use of larger-diameter scopes (≥5mm) or in women with cervical stenosis. Intracornual fundal anaesthesia demonstrated a significant reduction in intraprocedural pain during endometrial ablation, although data were limited to one trial, and so this should be considered in this context (74).

Chapter 5 demonstrated the superiority of vaginoscopy to the traditional approach (which utilises a vaginal speculum as a minimum) to performing outpatient hysteroscopy, in terms of pain, operative time and risk of vasovagal episodes and so should be the gold-standard approach, with the use of a

speculum reserved for when vaginoscopy fails or local cervical anaesthesia is required.

Chapter 6 aimed to identify the optimal distension medium type, pressure and temperature for outpatient hysteroscopy (31). We found that higher quality trials provided evidence that pain was reduced with the use of saline compared to carbon dioxide. Using normal saline also led to a lower chance of unsatisfactory images, shorter procedural times, fewer side-effects and the ability to perform operative hysteroscopy to allow for a “see-and-treat” service, and so was recommended over carbon dioxide as the distension medium of choice. Lower uterine distension pressures invariably caused less pain, however led to a higher risk of unsatisfactory views and we concluded that the minimum distension pressure to achieve a satisfactory view should be used. Warming saline may be considered as it left women feeling more satisfied with their hysteroscopy, although there was no demonstrable reduction in pain.

Chapter 7 identified an absence of data regarding the routine use of cervical dilatation in order to reduce the pain associated with outpatient hysteroscopy and found that although cervical preparation using vaginal prostaglandins reduced pain during outpatient hysteroscopy, it was associated with a significant increase in side-effects, namely abdominal pain and genital tract bleeding (32). In addition, one trial investigating the timing of administration found that pain was only significantly reduced when vaginal prostaglandins were given 12 rather than 3 hours prior to hysteroscopy (75). It is therefore difficult to recommend their use in the context of smaller-diameter scopes (<5mm) which allow for the

vaginoscopic approach. Where vaginoscopy fails, the use of injectable or topical local anaesthesia and cervical dilatation is recommended instead of cervical preparation which is associated with significantly more side-effects when compared to placebo and involves logistical barriers to their administration.

Chapter 8 outlined the role of conscious sedation for the reduction of pain associated with outpatient hysteroscopy (33). Intravenous conscious sedation showed no benefit compared to their controls with regards to pain and led to a higher risk of adverse events, including dizziness and vasovagal episodes. Although inhaled conscious sedation showed a reduction in pain in one study (76), the incidence of side-effects were not reported. The lack of high-quality data available and the lack of benefit exemplified by available studies could not allow us to recommend the use of conscious sedation for outpatient hysteroscopy, especially when the risks of oversedation can lead to potentially life-threatening complications.

Chapter 9 identified the equipment used for operative outpatient hysteroscopy that conferred the least pain (34). We showed that mechanical, rather than electrical energy, conferred less pain and so we recommend the use of hysteroscopic tissue retrieval systems and inactivated ancillary instruments (e.g. cold scissors) rather than miniature bipolar electrosurgery to remove intrauterine pathology (e.g. endometrial polyps) in the outpatient setting.

Chapter 10 consists of the updated national, evidence-based ‘green-top’ guideline regarding how outpatient hysteroscopy services should be organised

and how hysteroscopy should be conducted in the outpatient setting. The guideline features previously published systematic reviews found in chapters 3-9, with additional articles cited where applicable that have been published since the searches were performed. Novel changes that were made since the last guideline and were not contained within the previous chapters encompassed minimum staffing recommendations, pre-procedural care (information, consent, safety checklist), post-procedural care (information, facilities), training & standards, the role of antimicrobial prophylaxis, documentation and auditable topics.

A Novel Application of Outpatient Hysteroscopy in the Management of Miscarriage

Chapter 1 defined the author roles for the HYsteroscopic Miscarriage MaNagement (HYMMN) trial that formed this part of the PhD thesis.

Chapter 2 identified the burden of retained products of conception (RPOC) following miscarriage and the lack of evidence regarding how best they should be diagnosed and treated. It highlighted the potential role of hysteroscopy, only investigated thus far in observational studies, which have highlighted that hysteroscopy leads to a shorter time to conception, higher rates of complete evacuation and lower rates of intrauterine adhesion formation.

Chapter 3 outlined the design of a pilot randomised controlled trial, the HYsteroscopic Miscarriage MaNagement (HYMMN) trial, investigating the use of

outpatient hysteroscopy against standard treatment options for the treatment of RPOC following diagnosis on routine ultrasound 8 weeks post-miscarriage.

Chapter 4 depicted the results of the HYMMN trial. Although the trial was not powered to detect significant differences in time to pregnancy, pregnancy outcomes and clinical pregnancy rates, it did, however, show that a full-scale, substantive, multi-centre trial is feasible due to the high number of eligible and willing participants within 6 months of recruitment, high acceptability of trial interventions and low rates of attrition.

Chapter 5 summarised the main findings from the HYMMN trial before discussing its strengths and limitations and providing recommendations if the trial were to be modified as a full-scale, multi-centre, substantive trial. There are some important considerations that should be made regarding the eligibility criteria, potential stratification, criteria for diagnosis of RPOC sonographically and histologically, how patients should be followed-up to reduce attrition rates, primary clinical outcome and follow-up duration. Further considerations were recommended based on upscaling the trial; these included resource and staffing availability with regards to ultrasound facilities and hysteroscopy, and the protocolisation of the standard management arm to ensure equity of treatment amongst centres.

CHAPTER 2: RECOMMENDATIONS FOR FUTURE RESEARCH & DEVELOPMENT

Analgesia

There is a lack of availability of transcutaneous electrical nerve stimulation (TENS) machines in outpatient hysteroscopy units in the UK (12). Further qualitative data is required to understand the reason for this with regards to feasibility, expense and acceptability.

Local anaesthesia

Conventional pair-wise meta-analysis was utilised multiple times to provide multiple pooled effect estimates, with comparisons provided between local anaesthetic agents against nil or placebo. Future research in evidence synthesis for local anaesthesia in outpatient hysteroscopy should consider utilising network meta-analysis in order to provide head-to-head comparisons of agents that were compared against nil or placebo in their original randomised controlled trials, in order to provide a hierarchy of routes and/or agents.

Vaginoscopy

Although the superiority of vaginoscopy to the use of a speculum and local injectable cervical anaesthesia has been demonstrated by only one randomised controlled trial (77), the role of local anaesthesia which is instilled into the distension medium and administered through to the uterus transcervically and vaginoscopically requires further exploration.

Distension media

There was insufficient data to show a clinically meaningful reduction in pain when warmed saline was administered compared to room temperature saline, although satisfaction was improved. Further higher-quality, large randomised trials are required to definitively determine the role of warming saline to body temperature, a simple and easily implementable intervention, for the reduction of pain and improvement in satisfaction associated with outpatient hysteroscopy.

Cervical preparation

Further research is required to determine the specific agent, dose and timing of administration of cervical preparation in women who have a failed procedure due to severe cervical stenosis, because this is the only context in which a cervical preparation may be beneficial in contemporary practice.

Conscious sedation

Inhalational agents are commonplace in the Emergency Department, where Methoxyflurane (78) has been used as an important adjunct in pain management for traumatic injuries, such as fractures and dislocations, with promising effects (79). This simple device is safe, patient-administered, handheld, disposable and does not require the presence of an anaesthetist due to the inability to over-sedate. This may have a promising role in reducing the procedural pain associated with operative hysteroscopic procedures such as endometrial ablations which are known to have higher pain scores than diagnostic procedures alone (5).

Instrumentation for diagnostic hysteroscopy

Off-set angle lenses allow for the angle of view to be manipulated without moving the hysteroscope, which may be advantageous in women who have distorted anatomy due to factors such as obesity, fibroids, uterine anomalies etc. Using such lenses requires variation in technique compared to that when using a more intuitive 0º lens in order to avoid causing trauma to the cervical canal and endometrium which can cause additional pain during insertion and removal of the hysteroscope. Further research is required to compare the use of an off-set angle against a 0º lens with regards to operator and patient-reported outcomes.

Instrumentation for operative and therapeutic hysteroscopy

Endometrial ablation devices that have been trialled are no longer up-to-date because many of those evaluated are no longer commercially available (34). Research is urgently needed to compare the newer so called “third generation”, smaller diameter, faster ablative devices that have been designed to confer less pain where outcomes related to pain, satisfaction and feasibility should be reported in addition to efficacy with regards to alleviating heavy menstrual bleeding.

Antimicrobial prophylaxis

There are still some clinicians that advocate for the use of antibiotic prophylaxis for endometrial ablation (12), for which there are no data available. Endometrial ablation has the highest rate of post-procedural infection at 4.8% (95% CI 0.6%-16.1%) (80). Further research is required to ascertain up-to-date figures in light

of contemporary ablative devices and the role of prescribing antibiotics at the time of ablation to reduce this risk.

Hysteroscopic management of retained products of conception

A pilot RCT of 42 women comparing outpatient hysteroscopic mechanical tissue removal against standard treatment for retained products of conception after first trimester miscarriage demonstrated that a full-scale, well-powered, substantive, multicentre randomised controlled trial is feasible. Such a study is urgently required in order to determine if hysteroscopy leads to a higher conception and live birth rate, shorter time to subsequent conception and lower rates of intrauterine adhesions in women who fail to have a positive pregnancy outcome at the end of follow-up.

CHAPTER 3: CONCLUSION

Research and technical innovation in outpatient hysteroscopy are rapidly evolving and the application of hysteroscopy in ambulatory gynaecology is widening. The National Institute of Health and Care Excellence (NICE) has recently published guidance in 2018 on the management of heavy menstrual bleeding which affects up to 25% of women of reproductive age and accounts for 12% of all gynaecology referrals in the UK (81,82). This guidance states that outpatient hysteroscopy should now take precedence over ultrasound where endometrial pathology is suspected, allowing for diagnosis and treatment to occur at the same sitting (81). This change in guidance has predicted to require a huge investment in outpatient hysteroscopy services in the UK, increasing the number of annual hysteroscopies three-fold, from 5000 to 15000 (82). It is therefore timely that the first half of this doctoral thesis accrued and critically appraised all relevant and up-to-date randomised trial data investigating the provision and performance of outpatient hysteroscopy in order to inform a highly-coveted, national, 'green-top' evidence-based guideline on behalf of the Royal College of Obstetricians & Gynaecologists (RCOG) and the British Society for Gynaecological Endoscopy (BSGE) in the UK. Where there were gaps in research to answer important clinical questions, these were addressed through the acquisition of expert opinion from members of the BSGE Ambulatory Care Network (ACN) (12). The work in this doctoral thesis has resulted in the production of an evidence-based clinical guideline for one of the most common surgical interventions in contemporary gynaecology and has therefore concretely and meaningfully impacted clinical practice on a large scale.

This thesis also identified a paucity of evidence for the care of women who have retained products of conception (RPOC) following miscarriage. Due to advances in the miniaturisation of hysteroscopes and the emergence of mechanical hysteroscopic tissue retrieval systems (mHTRS), this thesis showed that hysteroscopic treatment of RPOC is a safe, effective and feasible method of removing RPOC in the outpatient setting. The latter half of this doctoral thesis that comprises the pilot RCT, shows that a substantive, well-powered, multicentre RCT comparing outpatient hysteroscopy against standard treatment in order to improve subsequent pregnancy outcomes, is clinically relevant and highly feasible.

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APPENDICES

APPENDIX 1: SEARCH STRATEGIES FOR THE SYSTEMATIC REVIEWS

A1.1: Search strategy for the systematic review and meta-analysis of analgesia for pain control during outpatient hysteroscopy

1.1a Medline (1950 to August 2019)

1. HYSTEROSCOPY/
2. (hysteroscop*).ti,ab
3. (vaginoscop*).ti,ab
4. (1 OR 2 OR 3)
5. exp ANALGESIA/
6. exp ANALGESICS/
7. (analges*).ti,ab
8. (5 OR 6 OR 7)
9. (4 AND 8)
10. (outpatient OR office OR ambulatory).ti,ab
11. (9 AND 10)

1.1b EMBASE (1980 to August 2019)

1. HYSTEROSCOPY/
2. (hysteroscop*).ti,ab
3. (vaginoscop*)

4. (1 OR 2 OR 3)

5. exp ANALGESIA/

6. exp ANALGESIC AGENT/

7. (analges*).ti,ab

8. (5 OR 6 OR 7)

9. (4 AND 8)

10. (outpatient OR office OR ambulatory).ti,ab

11. (9 AND 10)

1.1c CINAHL (1981 to August 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*)

4. (1 OR 2 OR 3)

5. ANALGESIA/

6. “ANALGESICS, OPIOID”/

7. “ANALGESICS, NONNARCOTIC”/

8. ANALGESICS/

9. (analges*).ti,ab

10. (5 OR 6 OR 7 OR 8 OR 9)

11. (4 AND 10)

12. (outpatient OR office OR ambulatory).ti,ab

13. (11 AND 12)

1.1d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND “analgesia”

A1.2: Search strategy for the systematic review and meta-analysis of local anaesthesia for pain control during outpatient hysteroscopy

1.2a Medline (1950 to October 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. exp “ANESTHETICS, LOCAL”/

6. exp “ANESTHESIA, LOCAL”/

7. (local anesthe*).ti,ab

8. (local anaesthe*).ti,ab

9. (local infiltrat*).ti,ab

10. (5 OR 6 OR 7 OR 8 OR 9)

11. (4 AND 10)

12. (outpatient OR office OR ambulatory).ti,ab

13. (11 AND 12)

1.2b EMBASE (1980 to October 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. exp “LOCAL ANESTHETIC AGENT”/

6. exp “LOCAL ANESTHESIA”/

7. (local anesthe*).ti,ab

8. (local anaesthe*).ti,ab

9. (local infiltrat*).ti,ab

10. (5 OR 6 OR 7 OR 8 OR 9)

11. (4 AND 10)

12. (outpatient OR office OR ambulatory).ti,ab

13. (11 AND 12)

1.2c CINAHL (1950 to October 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. exp “ANESTHESIA, LOCAL”/

6. TETRACAINE/

7. PROCAINE/

8. PRILOCAINE/

9. LIDOCAINE/

10. “ETHYL CHLORIDE”/

11. “EMLA CREAM”/

12. COCAINE/

13. BUPIVACAINE/

14. BENZOCAINE/

15. “ANESTHETICS, LOCAL”/

16. (local anesthe*).ti,ab

17. (local anaesthe*).ti,ab

18. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17)

19. (4 AND 18)

20. (outpatient OR office OR ambulatory).ti,ab

21. (19 AND 20)

1.2d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND “anaesthesia”

A1.3: Search strategy for the systematic review and meta-analysis of hysteroscopic approach for pain control during outpatient hysteroscopy

1.3a Medline (1950 to December 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (no*touch*)ti,ab

5. (1 OR 2)

6. (3 OR 4)

7. (5 AND 6)

8. (outpatient OR office OR ambulatory).ti,ab

9. (7 AND 8)

1.3b EMBASE (1980 to December 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (no*touch*)ti,ab

5. (1 OR 2)

6. (3 OR 4)

7. (5 AND 6)

8. (outpatient OR office OR ambulatory).ti,ab

9. (7 AND 8)

1.3c CINAHL (1950 to December 2019)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (no*touch*)ti,ab

5. (1 OR 2)

6. (3 OR 4)

7. (5 AND 6)

8. (outpatient OR office OR ambulatory).ti,ab

9. (7 AND 8)

1.3d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND “vaginoscopy”

A1.4: Search strategy for the systematic review and meta-analysis of the effect of distension media on pain control during outpatient hysteroscopy

1.4a Medline (1950 to January 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “SODIUM CHLORIDE”/

6. “CARBON DIOXIDE”/

7. GLYCINE

8. “GLYCINE AGENTS”/

9. MANNITOL/

10. SORBITOL/

11. exp “SALINE SOLUTION, HYPERTONIC”/

12. GLUCOSE/

13. DEXTRANS/

14. (distension medi*).ti,ab

15. (saline).ti,ab

16. (sodium chloride).ti,ab

17. (carbon dioxide).ti,ab

18. (glycine).ti,ab

19. (mannitol).ti,ab

20. (sorbitol).ti,ab

21. (dextrans).ti,ab

22. (glucose).ti,ab

23. (dextrose).ti,ab

24. (uter* AND disten*).ti,ab

25. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24)

26. (4 AND 25)

27. (office OR outpatient OR ambulatory).ti,ab

28. (26 AND 27)

1.4b EMBASE (1980 to January 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “SODIUM CHLORIDE”/

6. “CARBON DIOXIDE”/

7. GLYCINE/

8. “GLYCINE AGENTS”/

9. MANNITOL/

10. SORBITOL/

11. GLUCOSE/

12. DEXTRAN/

13. (distension medi*).ti,ab

14. (saline).ti,ab

15. (sodium chloride).ti,ab

16. (carbon dioxide).ti,ab

17. (glycine).ti,ab

18. (mannitol).ti,ab

19. (sorbitol).ti,ab

20. (dextrans).ti,ab

21. (glucose).ti,ab

22. (dextrose).ti,ab

23. (uter* AND disten*).ti,ab

24. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23)

25. (4 AND 24)

26. (office OR outpatient OR ambulatory).ti,ab

27. (25 AND 26)

1.4c CINAHL (1950 to January 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “SODIUM CHLORIDE”/

6. “CARBON DIOXIDE”/

7. “NORMAL SALINE”/

8. GLYCINE/

9. “GLYCINE AGENTS”/

10. MANNITOL/

11. SORBITOL/

12. ‘HYPERTONIC SOLUTIONS”/

13. GLUCOSE/

14. DEXTRANS/

15. (distension medi*).ti,ab

16. (saline).ti,ab

17. (sodium chloride).ti,ab

18. (carbon dioxide).ti,ab

19. (glycine).ti,ab

20. (mannitol).ti,ab

21. (sorbitol).ti,ab

22. (dextrans).ti,ab

23. (glucose).ti,ab

24. (dextrose).ti,ab

25. (uter* AND disten*).ti,ab

26. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25)

27. (4 AND 26)

28. (office OR outpatient OR ambulatory).ti,ab

29. (27 AND 28)

1.4d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND “distension media”

A1.5: Search strategy for the systematic review and meta-analysis of the effect of cervical dilatation and cervical preparation on pain control during outpatient hysteroscopy

1.5a Medline (1950 to March 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “CERVICAL RIPENING’/

6. exp PROSTAGLANDINS/

7. exp ESTROGENS/

8. exp PROGESTINS/

9. exp LAMINARIA/

10. exp MIFEPRISTONE/

11. (prostaglandin).ti,ab

12. (oestrogen).ti,ab

13. (estrogen).ti,ab

14. (progest*).ti,ab

15. (laminaria).ti,ab

16. (mifepristone).ti,ab

17. (dilapan).ti,ab

18. (cervi* AND prep*).ti,ab

19. (cervi* AND ripe*).ti,ab

20. (cervi* AND dilat*).ti,ab

21. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20)

22. (4 AND 21)

23. (outpatient OR office OR ambulatory).ti,ab

24. (22 AND 23)

1.5b EMBASE (1980 to March 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. exp “UTERINE CERVIX DILATATION”/

6. “UTERINE CERVIX RIPENING”/

7. exp PROSTAGLANDIN/

8. exp ESTROGEN/

9. exp GESTAGEN/

10. exp LAMINARIA/

11. exp MIFEPRISTONE/

12. exp DILAPAN/

13. (prostaglandin).ti,ab

14. (oestrogen).ti,ab

15. (estrogen).ti,ab

16. (progest*).ti,ab

17. (laminaria).ti,ab

18. (mifepristone).ti,ab

19. (dilapan).ti,ab

20. (cervi* AND prep*).ti,ab

21. (cervi* AND ripe*).ti,ab

22. (cervi* AND dilat*).ti,ab

23. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 23)

24. (4 AND 23)

25. (outpatient OR office OR ambulatory).ti,ab

26. (24 AND 25)

1.5c CINAHL (1950 to March 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “CERVIX DILATATION AND EFFACEMENT”/

6. exp PROSTAGLANDINS/

7. exp PROGESTERONE/

8. exp ESTROGENS/

9. exp MIFEPRISTONE/

10. (prostaglandin).ti,ab

11. (oestrogen).ti,ab

12. (estrogen).ti,ab

13. (progest*).ti,ab

14. (laminaria).ti,ab

15. (mifepristone).ti,ab

16. (dilapan).ti,ab

17. (cervi* AND prep*).ti,ab

18. (cervi* AND ripe*).ti,ab

19. (cervi* AND dilat*).ti,ab

20. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19)

21. (4 AND 20)

22. (outpatient OR office OR ambulatory).ti,ab

23. (21 AND 22)

1.5d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND “cervical”

A1.6: Search strategy for the systematic review and meta-analysis of the effect of conscious sedation on pain control during outpatient hysteroscopy

1.6a Medline (1950 to October 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. exp “CONSCIOUS SEDATION’/

6. exp “HYPNOTICS AND SEDATIVES”/

7. (sedati*).ti,ab

8. (hypno*).ti,ab

9. (5 OR 6 OR 7 OR 8)

10. (4 AND 9)

11. (office OR outpatient OR ambulatory).ti,ab

12. (10 AND 11)

1.6b EMBASE (1980 to October 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “CONSCIOUS SEDATION’/

6. exp “HYPNOTIC SEDATIVE AGENT”/

7. (sedati*).ti,ab

8. (hypno*).ti,ab

9. (5 OR 6 OR 7 OR 8)

10. (4 AND 9)

11. (office OR outpatient OR ambulatory).ti,ab

12. (10 AND 11)

1.6c CINAHL (1950 to October 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. “CONSCIOUS SEDATION’/

6. exp “HYPNOTIC SEDATIVE AGENT”/

7. (sedati*).ti,ab

8. (hypno*).ti,ab

9. (5 OR 6 OR 7 OR 8)

10. (4 AND 9)

11. (office OR outpatient OR ambulatory).ti,ab

12. (10 AND 11)

1.6d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND “conscious sedation”

A1.7: Search strategy for the systematic review and meta-analysis of the effect of different diagnostic hysteroscopes on pain control during outpatient hysteroscopy

1.7a Medline (1950 to December 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. HYSTEROSCOPES/

5. (rigid).ti,ab

6. (flex*).ti,ab

7. (diameter).ti,ab

8. (size).ti,ab

9. (angle).ti,ab

10. (1 OR 2 OR 3 OR 4)

11. (5 OR 6 OR 7 OR 8 OR 9)

12. (10 AND 11)

13. (office OR outpatient OR ambulatory).ti,ab

14. (12 AND 13)

1.7b EMBASE (1980 to December 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. HYSTEROSCOPE/

5. ‘RIGID HYSTEROSCOPE’/

6. ‘FLEXIBLE HYSTEROSCOPE’/

7. (rigid).ti,ab

8. (flex*).ti,ab

9. (diameter).ti,ab

10. (size).ti,ab

11. (angle).ti,ab

12. (1 OR 2 OR 3 OR 4)

13. (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11)

14. (12 AND 13)

15. (office OR outpatient OR ambulatory).ti,ab

16. (14 AND 15)

1.7c CINAHL (1950 to December 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. (1 OR 2 OR 3)

5. (rigid).ti,ab

6. (flex*).ti,ab

7. (diameter).ti,ab

8. (size).ti,ab

9. (angle).ti,ab

10. (5 OR 6 OR 7 OR 8 OR 9)

11. (4 AND 10)

12. (office OR outpatient OR ambulatory).ti,ab

13. (11 AND 12)

1.7d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. “hysteroscopy”

A1.8: Search strategy for the systematic review and meta-analysis of the effect of different therapeutic interventions on pain control during outpatient hysteroscopy

1.8a Medline (1950 to January 2021)

1. HYSTEROSCOPES/

2. HYSTEROSCOPY/

3. (hysteroscop*).ti,ab

4. “ENDOMETRIAL ABLATION TECHNIQUES”/

5. (endometri* AND ablation).ti,ab

6. (outpatient OR office OR ambulatory).ti,ab

7. (1 OR 2 OR 3 OR 4 OR 5)

8. (6 AND 7)

1.8b EMBASE (1980 to January 2021)

1. HYSTEROSCOPY/

2. HYSTEROSCOPE/

3. (hysteroscop*)ti,ab

4. “ENDOMETRIUM ABLATION”/

5. (endometri* AND ablation).ti,ab

6. (outpatient OR office OR ambulatory).ti,ab

7. (1 OR 2 OR 3 OR 4 OR 5)

8. (6 AND 7)

1.8c CINAHL (1950 to January 2021)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. “ENDOMETRIAL ABLATION TECHNIQUES”/

4. (endometri* AND ablation).ti,ab

5. (outpatient OR office OR ambulatory).ti,ab

6. (1 OR 2 OR 3 OR 4)

7. (5 AND 6)

1.8d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscop*

2. endometri* AND ablation

3. outpatient OR office OR ambulatory

4. #1 OR #2

5. #3 AND #4

A1.9: Search strategy for the systematic review and meta-analysis of the effect of antimicrobial prophylaxis on the prevention of infection attributed to outpatient hysteroscopy

1.9a Medline (1950 to December 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. exp “PELVIC INFECTION’/ OR INFECTION/ OR SEPSIS/

5. exp ENDOMETRITIS/

6. exp “REPRODUCTIVE TRACT INFECTIONS’/

7. (infection).ti,ab

8. (endometritis).ti,ab

9. exp “ANTI-BACTERIAL AGENTS’/

10. (antibiotic*).ti,ab

11. exp PYOMETRA/

12. (pyometra).ti,ab

13. (office OR outpatient OR ambulatory).ti,ab

14. (1 OR 2 OR 3)

15. (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12)

16. (13 AND 14 AND 15)

1.9b EMBASE (1980 to December 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. INFECTION/ OR exp “INTRAUTERINE INFECTION”/ OR SEPSIS/ OR exp UROGENITAL TRACT INFECTION”

5. (infection).ti,ab

6. exp ENDOMETRITIS/

7. (endometritis OR pyometra).ti,ab

8. exp “FEMALE GENITAL TRACT INFECTION”/

9. exp PYOMETRA/

10. exp “ANTIBIOTIC AGENT”/

11. (antibiotic*).ti,ab

12. (office OR outpatient OR ambulatory).ti,ab

13. (1 OR 2 OR 3)

14. (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11)

16. (12 AND 13 AND 14)

1.9c CINAHL (1950 to December 2020)

1. HYSTEROSCOPY/

2. (hysteroscop*).ti,ab

3. (vaginoscop*).ti,ab

4. INFECTION/ OR SEPSIS/

5. exp PYOMETRA/

6. (infection OR endometritis OR pyometra).ti,ab

7. exp ANTIBIOTICS/

8. (antibiotic*).ti,ab

9. (office OR outpatient OR ambulatory).ti,ab

10. (1 OR 2 OR 3)

11. (4 OR 5 OR 6 OR 7 OR 8)

12. (9 AND 10 AND 11)

1.9d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscop*

2. infection OR antibiotic

3. #1 AND #2

APPENDIX 2: QUESTIONS AND ANSWERS TO THE VIRTUAL POLLS FROM THE BRITISH SOCIETY FOR GYNAECOLOGICAL ENDOSCOPY (BSGE) AMBULATORY CARE NETWORK (ACN) MEETING HELD ON 2021

1. **Regarding preoperative information, should all patients receive written information? (n=116)**
    - It is mandatory (hysteroscopy should not go ahead if information was not provided) – 42% (n=49)
    - It is ideal (hysteroscopy can still proceed if not provided) – 54% (n=63)
    - It is not necessary as all information can be given on the day – 3% (n=4)

2. **Regarding patient consent: (n=116)**
    - All patients should give written consent – 69% (n=80)
    - All patients should give written OR verbal consent – 31% (n=36)

3. **Regarding safety checks, units should use a checklist e.g. specifically adapted WHO surgical safety checklist in all patients: (n=116)**
    - Yes – 85% (n=99)
    - No – 15% (n=17)

4. **How many support workers should there be as a minimum for diagnostic OPH? (n=140)**
    - 1 – 14% (n=19)
    - 2 – 83% (n=116)
    - 3 – 4% (n=5)
    - 4 – 0%
    - >4 – 0%

5. **How many support workers should there be as a minimum for operative OPH? (n=140)**
    - 1 – 6% (n=8)
    - 2 – 63% (n=88)
    - 3 - 29% (n=41)
    - 4 – 2% (n=3)
    - >4 – 0%

6. **Should there be at least one registered nurse present? (n=140)**

- Yes – 91% (n=128)
- No – 9% (n=12)

7. **Regarding documentation, are you using: (n=126)**
    - A standardised written proforma – 45% (n=57)
    - A standardised computerised/digital proforma – 28% (n=35)
    - Free-text written documentation – 17% (n=21)
    - Free-text computerised/digital proforma – 10% (n=13)

8. **Should the guideline make recommendations regarding caseload for hysteroscopists (i.e. the number of cases done per year): (n=62)**
    - Yes – 69% (n=43)
    - No – 31% (n=19)

9. **What is the acceptable minimum caseload: (n=62)**
    - A minimum caseload is not required – 21% (n=13)
    - 0-50 – 16% (n=10)
    - 50-99 – 40% (n=25)
    - 100+ - 13% (n=21)
    - The minimum threshold should be higher than what is stated – 2% (n=1)

10. **After giving local anaesthesia, do you then remove the speculum and/or tenaculum, to allow for vaginoscopy? (n=106)**
    - Yes routinely – 42% (n=45)
    - Yes often – 21% (n=22)
    - Yes rarely – 11% (n=12)
    - No – 25% (n=27)

11. **Do you administer antibiotics for endometrial ablation? (n=102)**
    - Yes, routinely – 18% (n=18)
    - Yes, in selected cases – 14% (n=14)
    - No – 68% (n=70)

12. What should be documented at hysteroscopy? (Answers below collated from free-text / verbal responses)

a. Pre-procedurally:
    i. Confirm 3 identifiers
    ii. Chaperone
    iii. Date of clinic
    iv. Consent
    v. Indication
    vi. Has GA been offered?
    vii. Analgesia taken?
    viii. UPT?
    ix. Allergies
    x. Anxiety scale at the beginning and discussion with the patient how to minimise this prior to proceeding with the procedure

b. Procedural:
    i. Diagnostic or therapeutic?
    ii. Size and type of scope
    iii. Distention medium used
    iv. Angle of scope
    v. Pain score
    vi. Cervical dilatation?
    vii. Local anaesthesia?
    viii. Approach (Vaginoscopy or speculum)
    ix. Biopsy done?
    x. Whether coil fitted?
    xi. Whether switched to operative and details of this
    xii. Abx?
    xiii. Complications
    xiv. Fluid balance

c. Post-procedurally
    i. Findings including whether ostia seen and any abnormalities

ii. Pictures including ostia
iii. Combination of images and simple diagrams
iv. Impression
v. Print out to GP/patient
vi. Option of electronically download images which can be stored directly in the patient record electronically
vii. Digital format of documentation to be standardized by BSGE which can be used nationally which can be shared for research and audit
viii. Pain score should be collected and to be reliable we discussed this should be done by a nurse/HCA away from the hysteroscopist to avoid bias
ix. Assessment of pain score and tolerability

APPENDIX 3: SUPPLEMENTAL FIGURES FOR PART 2, CHAPTER 3 – ANALGESIA

A2.1: Supplemental Table 1. Pain scores and timing of administration of analgesic agents prior to hysteroscopy

Supplementary Table 1

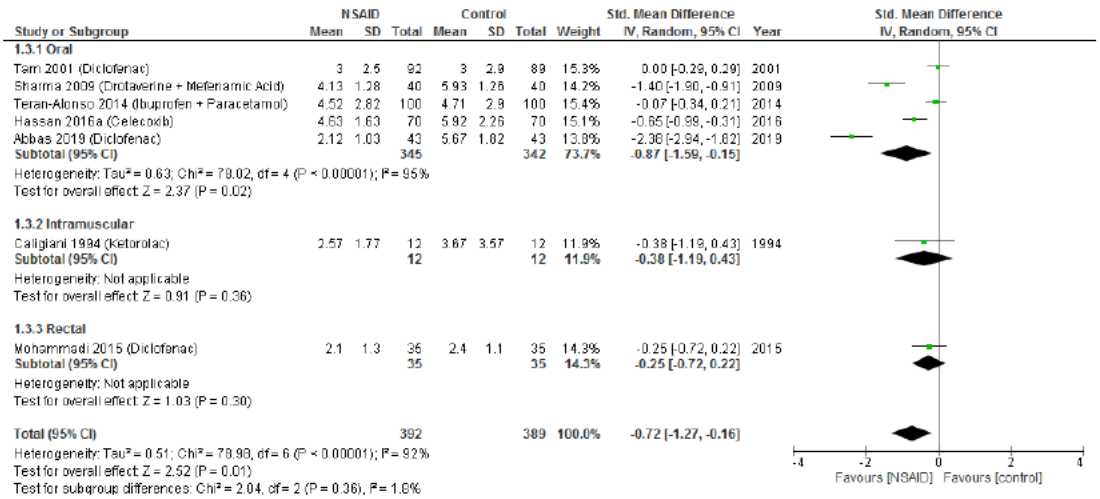
*TOA = Timing of Administration = ntraprocedural P = Postprocedural SD = Standard Deviation QR = nter-Quartile Range n = number of women = group not used as control

Study	Group 1	TOA	Pain (I)	SD/ IQR	Pain (P)	SD/ IQR	n	Group 2	TOA	Pain (I)	SD/ IQR	Pain (P)	SD/ IQR	n	Group 3	TOA	Pain (I)	SD/ IQR	Pain (P)	SD/ IQR	n	Post-Procedure Pain Score Timing
Caligiani et al 1994 [20]	Nil	N/A	3.67	3.57	3.33	3.57	12	30mg IM ketorolak (NSAID)	45 min	2.57	1.77	1.79	2.01	12	N/A							5 min
Nagele et al 1997 [9]	500mg PO mefenamic acid (NSAID)	1h prior	5.00	2.5-7.5	1.00	0-4.5	49	Placebo	1h prior	5.00	4-8.5	2.00	0-4	46	N/A							Immediately after
Bellati et al 1998 [21]	100mg IM tramadol (opioid)	50 min prior	3.00	2.01	N/A	N/A	40	4ml of 2% intracervical mepivacaine	N/A	4.34	1.89	N/A	N/A	40	Nil	N/A	4.59	1.87	N/A	N/A	40	N/A
Tam et al 2001 [22]	50mg PO diclofenac (NSAID)	81min prior	3	2.5	1.1	1.3	92	Placebo	82 min prior	3	2.9	1.2	1.7	89	N/A							30 min
Mercorio et al 2002 [10]	25mg PO dexketoprofen (NSAID)	1h prior	6	4.2-7.2	4	1.8-4.9	148	5ml of 2% intracervical mepivacaine	During	6	3.3-6.6	5	1.8-6.9	150	N/A							30 min
De Angelis et al 2003 [24]	TENS	During	3.71	2.06	N/A	N/A	71	Nil	N/A	5.07	2.03	N/A	N/A	71	N/A							N/A
Lin et al 2005 [23]	0.2mg SL buprenorphine (opioid)	40 min prior	3.3	1.1	N/A	N/A	80	Placebo	40 min prior	3.2	1.3	N/A	N/A	84	N/A							N/A
Floris et al 2007 [11]	100mg IV tramadol (opioid)	50 min prior	4.58	2.39	0.53	1.2	25	Placebo	50 min prior	6.49	2.7	2.22	2.03	25	N/A							15 min
Sharma et al 2009 [25]	80mg PO drotaverine (antispasmodic) and 250mg PO mefenamic acid (NSAID)	1h prior	4.13	1.28	1.78	0.89	40	10ml of 1% paracervical lignocaine	5 min prior	5.93	1.26	2.53	0.81	40	IV sedation	10 min prior	5.58	1.51	2.23	0.94	40	30 min
Thiel et al 2011 [26]	IV sedation with fentanyl (2mg/kg and midazolam (2mg and PO placebo	PO 1 hour prior, IV immediately pre-procedure	3.89	2.82	N/A	N/A	42	5mg PO oxycodone (opioid) and 50/mg PO naproxen (NSAID) and IV placebo	PO 1 hour prior, IV immediately pre-procedure	4.36	2.73	N/A	N/A	42	N/A							N/A
Hassa et al 2013 [14]	200µg misoprostol PV and PR placebo	PV 6h prior and PO 45-60 min prior	4.75	N/A	N/A	N/A	51	PV placebo and 100mg PR diclofenac (NSAID)	PV 6h prior and PO 45-60 min prior	5.01	N/A	N/A	N/A	50	PV placebo and PR placebo	PV 6h prior and PO 45-60 min prior	4.15	N/A	N/A	N/A	51	N/A
Issat et al 2014 [17]	PV placebo and IV placebo	4h prior and 30 min prior	4	2.75-5.25	0	0	50	PV placebo and IV ketoprofen (NSAID)	4h and 30min prior	3	2-5	0	0	50	400µg PV misoprostol and IV placebo	4h and 30min prior	3	2-4	0	0	50	15 min
Teran-Alonso et al 2014 [27]	1g PO paracetamol and 600mg PO ibuprofen (NSAID)	1h prior	4.52	2.82	1.14	1.87	100	Nil	N/A	4.71	2.9	1.33	2.04	100	N/A							5 min
Mohammadi et al 2015 [28]	5ml of 2% transcervical intrauterine lidocaine	3 min prior	2.4	1.1	N/A	N/A	35	100mg PR diclofenac (NSAID) and 5ml of transcervical intrauterine normal saline	30 min and 3 min prior	2.1	1.3	N/A	N/A	35	N/A							N/A
Kadrogulian et al 2016 [16]	100mg PO tramadol (opioid)	1h 30m prior	3.6	N/A	5.1	N/A	44	Placebo	1h 30m prior	5.9	N/A	5.4	N/A	44	N/A							15 min

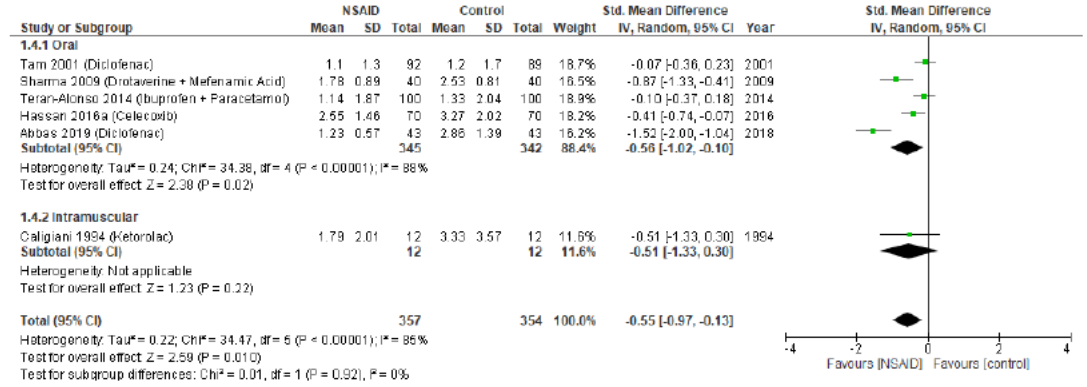
Senturk et al 2016 [15]	PR and intrauterine placebo	45 min before and during	2	1	1	1	68	1000ml intrauterine distension medium containing 18ml lidocaine per 250ml (20mg at 2%)[†]	45 min before and during	1	1.75	0	1	76	**100mg PR indomethacin (NSAID)** and intrauterine placebo	45 min before and during	1	1	1	1	62	10 min
Hassan et al 2016 (a) [29]	**100mg PO tramadol (opioid)**	1h prior	4.37	1.77	2.18	1.46	70	**200mg PO celecoxib (NSAID)**	1h prior	4.63	1.63	2.55	1.46	70	PO placebo	1h prior	5.92	2.26	3.27	2.02	70	Immediately after
Hassan et al 2016 (b) [13]	**50mg PO tramadol (opioid)**	1h prior	5	N/A	3	N/A	70	Placebo	1h prior	6	N/A	4	N/A	70	N/A							Immediately after
Asgari et al 2017 [30]	General anaesthesia[†]	N/A	N/A	N/A	1.21	2.04	28	PO diazepam 10mg and **100mg diclofenac PR (NSAID)** and paracervical 10cc 2% lidocaine	60 min prior	1.81	1.52	0.85	1.06	27	IV sedation	10 min prior	1.1	1.32	0.68	1.33	29	In recovery
Schneider et al 2017 [12]	Placebo pills and **inhalational N2O/O2** to max conc 70%/30%	30 min prior and during	2.28	2.76	2.2	N/A	34	**5/325mg PO hydrocodone/acetaminophen (opioid)** and 1mg PO lorazepam and inhaled O2	30 min prior and during	5.45	3.27	5.5	N/A	30	N/A							3-5 min
Lisón et al 2017 [31]	Nil[†]	Nil	3.92	2.88	1.05	1.38	46	Placebo TENS	Nil	3.06	2.11	0.93	1.81	46	**Active TENS**	5 mins prior and for duration of hysteroscopy	0.86	0.86	0.21	0.5	46	5 min
Abbas et al 2019 [32]	**50mg PO diclofenac (NSAID)**	1h prior	2.12	1.03	1.23	0.57	43	**20mg PO hyoscine-N-butyl-bromide [buscopan] (antispasmodic)**	1h prior	3.02	1.55	1.56	0.73	43	PO placebo	1h prior	5.67	1.82	2.86	1.39	43	Immediately after

A3.2: Supplemental Fig. 1. (A) Effect of NSAIDs on pain control during office hysteroscopy according to the route of administration. (B) Effect of NSAIDs on pain control after office hysteroscopy according to the route of administration.

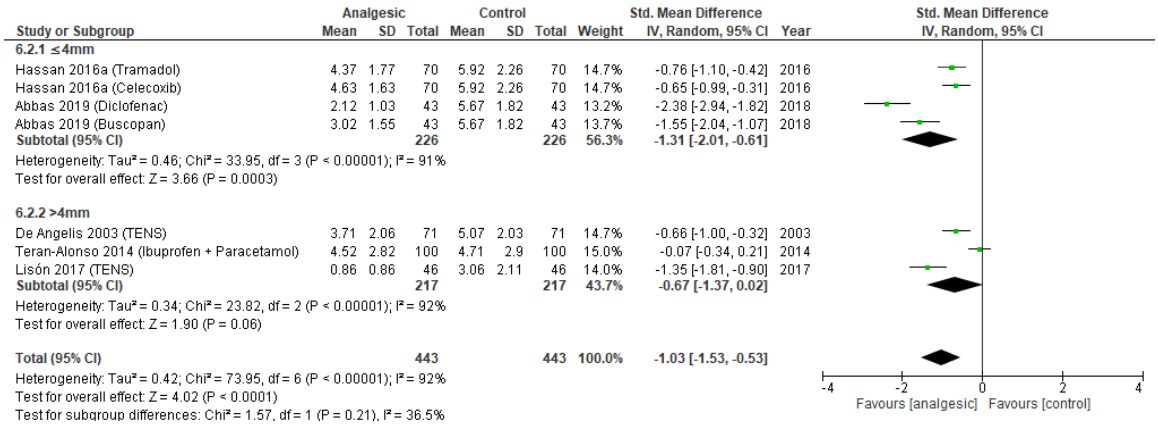
1a



1b



A3.3: Supplemental Fig. 2. Effect of vaginoscopy on pain control during office hysteroscopy according to the hysteroscope's diameter



APPENDIX 4: SUPPLEMENTAL FIGURES FOR PART 2, CHAPTER 4 – LOCAL ANAESTHESIA

A4.1: Supplemental Table 1. Study characteristics: details of the interventions, data presented and control variables for all included studies.

PCB: paracervical block, ICB: intracervical block, TC: transcervical instillation, TOP: topical cervical application, ICOB: intracornual block, CO2: carbon dioxide, NS: normal saline, PO: oral, SL: sublingual, IV: intravenous, IM: intramuscular, PR: rectal, PV: vaginal, He: Hegar number, h= hour, mmHg: millimeters of Mercury, Y: yes, N: not used, SD: standard deviation, SE: standard error, IQR: interquartile range, *Italics*: not used as control

Year	First Author	Study population	Group 1	Group 2	Group 3	Group 4	Data Presented	Conscious Sedation	Analgesia	Cervical Preparation	Vaginoscopy	Cervical Dilatation	Additional Local Anaesthesia	Distension Medium	Instrument Diameter (mm)
1992	Finikiotis	Not reported	16-20ml 1% lidocaine PCB	2ml 2% lidocaine with 1:80,000 adrenaline USB			Grouped	N	N	N	N	N	N	Not reported	Not reported
1992	Broadbent	Nulliparous, parous, premenopausal and postmenopausal women	10ml 1% lidocaine with 1:200,000 adrenaline ICB	Placebo			Grouped	N	N	N	N	N	N	CO2	5.5
1994	Vercellini	Premenopausal women	10ml 1% mepivacaine hydrochloride PCB	Nil			Mean (SD)	N	N	N	N	N	N	1.5% glycine at 80mmHg	5
1995	Zupi	Not clear	5ml 2% mepivacaine TC	Placebo			Mean only	N	N	N	N	N	N	CO2	Not reported
1996	Clark	Nulliparous, parous, premenopausal and postmenopausal women	10ml 2% lidocaine gel TC	Placebo			Dichotomous	N	N	N	N	If required	1% lignocaine with 1:80000 adrenaline ICB given, if required (9 in each group)	CO2	5
1997	Davies	Nulliparous, parous, premenopausal and postmenopausal women	10 metered doses of 10% lidocaine spray TOP and TC	Placebo			Median (IQR)	N	N	N	N	If required	2.2ml 2% lignocaine with epinephrine 1:80000 ICB, if required (9 in Group 1 and 10 in Group 2)	CO2 (NS used if bleeding or poor view)	5.5
1997	Cicinelli	Postmenopausal women	2ml 2% mepivacaine TC	Placebo			Mean (SD)	N	N	N	N	N	N	CO2	3.5
1998	Costello	Nulliparous, parous, premenopausal and postmenopausal women	5ml 2% lidocaine TC	Placebo			Mean (SD)	N	550mg PO naproxen 1-hour prior (43 (88%) in Group 1, 48 (96%) in Group 2)	N	N	N	5 doses of 10% lignocaine TOP for tenaculum	CO2 (NS used if poor view; 9 in each group)	5
1998	Cicinelli	Postmenopausal	10ml 1.5%	Placebo			Mean (SD)	N	N	N	N	N	N	CO2	3.5

		women	mepivacaine PCB											
1998	Bellati	Not reported	4ml 2% mepivacaine hydrochloride ICB	Nil	*100mg IM tramadol*	Raw Data	N	N	N	N	N	N	CO2 to 40ml/min and 50mmHg	5
1999	Lau	Nulliparous, parous, premenopausal and postmenopausal women	10ml 2% lidocaine PCB	Placebo		Mean (SD)	N	N	N	N	N	N	CO2 at 100mmHg	5
1999	Zullo	Nulliparous, parous, premenopausal and postmenopausal women	3ml 5% EMLA TOP cream (25mg lidocaine and 25mg prilocaine per g)	20mg lidocaine TOP spray		Descriptive	N	N	N	N	N	N	CO2 <80mmHg	5
2000	Giorda	Postmenopausal women	20ml 1% mepivacaine PCB	Nil		Mean (SE)	N	N	N	N	N	N	CO2 at 30ml/min <80mmHg	5
2000	Lau	Nulliparous, parous, premenopausal and postmenopausal women	5ml 2% lidocaine TC	Placebo		Mean (SD)	N	N	N	N	N	N	CO2 at 40-50ml/min and 100mmHg	5
2000	Soriano	Nulliparous, parous, premenopausal and postmenopausal women	30mg 5% lidocaine spray TOP	Placebo		Mean (SD)	N	N	N	N	If required (7 in Group 1, 11 in Group 2)	N	NS	2.7
2000	Wong	Nulliparous, parous, premenopausal and postmenopausal women	4ml 2% lidocaine gel TOP	Placebo		Mean (SD)	N	N	N	N	If required (74 in Group 1, 84 in Group 2) to He 5	N	CO2	5

2001	Makris	Nulliparous, parous, premenopausal and postmenopausal women	9ml 3% mepivacaine hydrochloride ICB	Placebo	[redacted]	Mean only	N	PO 20mg buscopan and 500mg mefenamic acid 2 h prior	N	N	N	N	CO2	3.5-4
2002	Mercorio	Postmenopausal women	5ml 2% mepivacaine ICB	25mg PO dexketoprofen		Median (IQR)	N	N	200 microg PV misoprostol 2-3h prior	N	If required to He 5	N	CO2 to 45 ml/min up to 100 mmHg	5
2002	Esteve	Nulliparous, parous, premenopausal and postmenopausal women	8ml 2% lidocaine hydrochloride ICB	Placebo		Mean (SD)	N	N	N	N	N	N	CO2	4
2003	Guida	Premenopausal women	10ml 1% mepivacaine hydrochloride PCB	Conscious sedation with IV atropine, fentanyl and midazolam		Mean (SD)	Y, in group 2	If requested post-op (5 in Group 1 and 4 in Group 2)	N	N	N	N	NS	5.5
2004	Shankar	Nulliparous, parous, premenopausal and postmenopausal women	40ml 2% lidocaine in 500ml NSTC	Placebo	*CO2*	Mean (SD)	N	N	N	N	Y to He 8	0.2–0.5 mL of 4% prilocaine hydrochloride ICB for vulsellum	NS to 150-200mmHg	3.5
2006	Hong	Nulliparous, parous, premenopausal and postmenopausal women	10ml 0.25% bupivacaine PCB	Placebo		Mean only	Y	30mg IM ketolorac if required postop (4 in Group 2)	N	N	N	N	Glycine solution at 100mg	8.5
2007	Al-Sunaidi	Premenopausal women	8ml 0.5% bupivacaine hydrochloride PCB	Nil		Mean (SD)	Lorazepam 10mg PO 30 min prior	N	N	N	N	2ml 0.5% bupivacaine hydrochloride ICB	NS	3.5
2008	Kabli	Premenopausal women	18ml 1% lidocaine in 250ml NSTC	Placebo		Median (SD)	Lorazepam 10mg PO 30 min prior	N	N	N	N	2ml 1% lidocaine ICB	NS	3.5

2009	Sharma	Nulliparous, parous, premenopausal and postmenopausal women	10ml 1% lidocaine PCB	PO 80mg drotaverine and PO 250mg mefenamic acid	*IV sedation*	[redacted]	Mean (SD)	Y, in group 3	Y, in group 1	N	N	If required (3 in Group 1, 2 in Group 2, 3 in Group 3)	N	NS hung at 6ft with pressure bag inflated to 300mmHg	5
2010	Chapa	Premenopausal women	1% 30ml mepivacaine with 20ml NS PCB	100 micrograms/h fentanyl patches from 12-14h prior	[redacted]	[redacted]	Median (range)	400mg PO celecoxib QDS from 2 days prior and 30mg SL ketolorac pre-procedure and 800mg PO motrin PRN post-procedure	N	N	N	Not reported	N	Not reported	4.5
2010	Gupta	Premenopausal women	5ml 2% lidocaine TC	Nil	[redacted]	[redacted]	Mean (SD)	N	N	400 microg PV misoprostol 3 h prior	N	If required; 2 in Group 1 and 3 in Group 2	N	Not reported	5
2010	Chudnoff	Premenopausal women	11ml 1% lidocaine PCB	Placebo	[redacted]	[redacted]	Mean (SD)	N	60mg IM ketolorac prior	N	N	N	N	NS	5
2012	Isley	Premenopausal women	5ml 4% lidocaine TC	Placebo	[redacted]	[redacted]	Median (Range)	2mg PO lorazepam 30-45 min prior	800mg PO ibuprofen 30-45 min prior	N	N	If required (16 in Group 1, 13 in Group 2)	9ml 1% lidocaine PCB	Not reported	5
2013	Esin	Premenopausal women	SL placebo and 60mg 10% lidocaine pump spray TOP	200 microg misoprostol SL and placebo spray TOP	[redacted]	[redacted]	Mean (SD)	N	N	N	Y	If required (2 in Group 1, 1 in Group 2)	N	Not reported	4
2013	Arnau	Nulliparous, parous, premenopausal and postmenopausal women	3mg 5% EMLA cream TOP	Placebo	[redacted]	[redacted]	Mean (SD)	5mg PO diazepam 2h prior	600mg PO ibuprofen or 1g paracetamol 2 h prior	200microg PV misoprostol 6h prior for postmenopausal women only	Y	If required (7 in Group 1, 5 in Group 2)	Y, with PCB in 3 in Group 2 only	NS at 100-150mmHg	5.5
2014	Kokanali	Nulliparous, parous, premenopausal and postmenopausal	10m 1% prilocaine ICB	Nil	[redacted]	[redacted]	Mean (SD)	N	N	N	Y	N	N	1.5% glycine	3

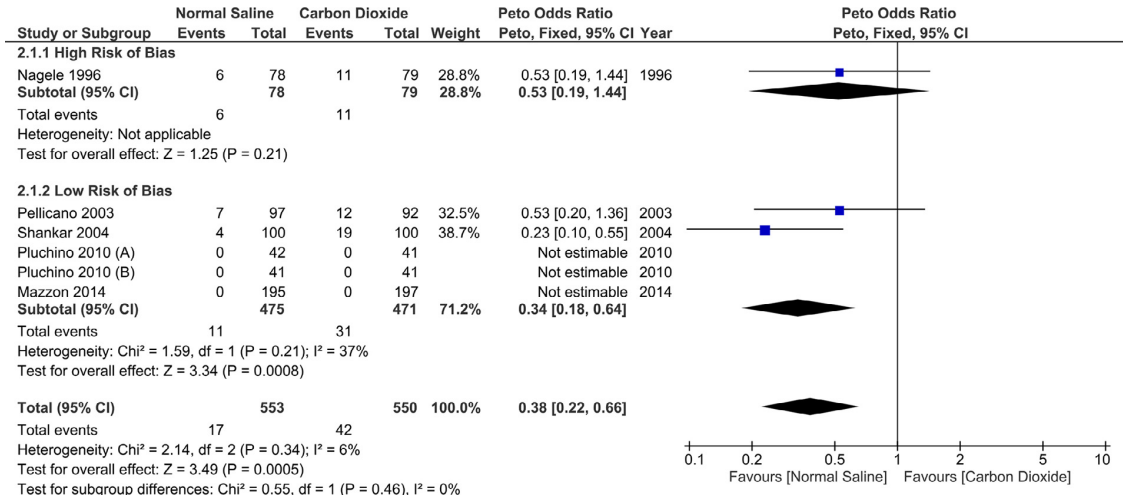
		women													
2014	Karakus	Premenopausal women	5ml 2% lidocaine TC	2% lidocaine spray TOP	5ml 2% lidocaine TC and 2% lidocaine spray TOP	Placebo	Mean (SD)	N	N	400 microg PV misoprostol 2 h prior	N	Y	N	Not reported	Not reported
2015	Lukes	Premenopausal women	37ml 1% lidocaine and 0.25% bupivacaine ICB and PCB and lidocaine 1% TOP	22ml 1% lidocaine and 0.25% bupivacaine ICB			Mean (SD)	10mg diazepam 1 h prior	800mg ibuprofen the night before. 10mg hydrocodone/acetaminophen and IM 30mg keterolac and 0.4% atropine 1 h prior	N	N	Y to He 6	N	Sterile saline	6.25
2015	Mohammadi	Nulliparous, premenopausal women	5ml 2% lidocaine TC	100mg PR diclofenac and placebo TC			Mean (SD)	N	Y, if in group 2	N	N	N	1% lidocaine ICB	Not reported	3.5
2016	Kumar	Premenopausal women	1ml 3% mepivacaine and 1ml 0.5% bupivacaine ICOB	Placebo			Mean (SD)	N	50mg PO diclofenac and 20mg/1g co-dydramol	N	N	N	6.6ml 3% mepivacaine ICB	Not reported	4.5-8
2016	Senturk	Nulliparous, parous, premenopausal and postmenopausal women	18ml of 20mg 2% lidocaine per 250ml NS TC	PR and intrauterine placebo	*PR indomethacin and intrauterine placebo*		Median (IQR)	N	Y, in Group 3	N	Y	N	N	0.09% NS to 70-80mmHg	3.5

APPENDIX 5: SUPPLEMENTAL FIGURES FOR PART 2, CHAPTER 6 – DISTENSION MEDIUM TYPE, PRESSURE AND TEMPERATURE

A5.1: Supplemental Fig 1. Forest plot of unsatisfactory hysteroscopic examinations for studies randomising women according to distension media type.

Supplemental Fig. 1

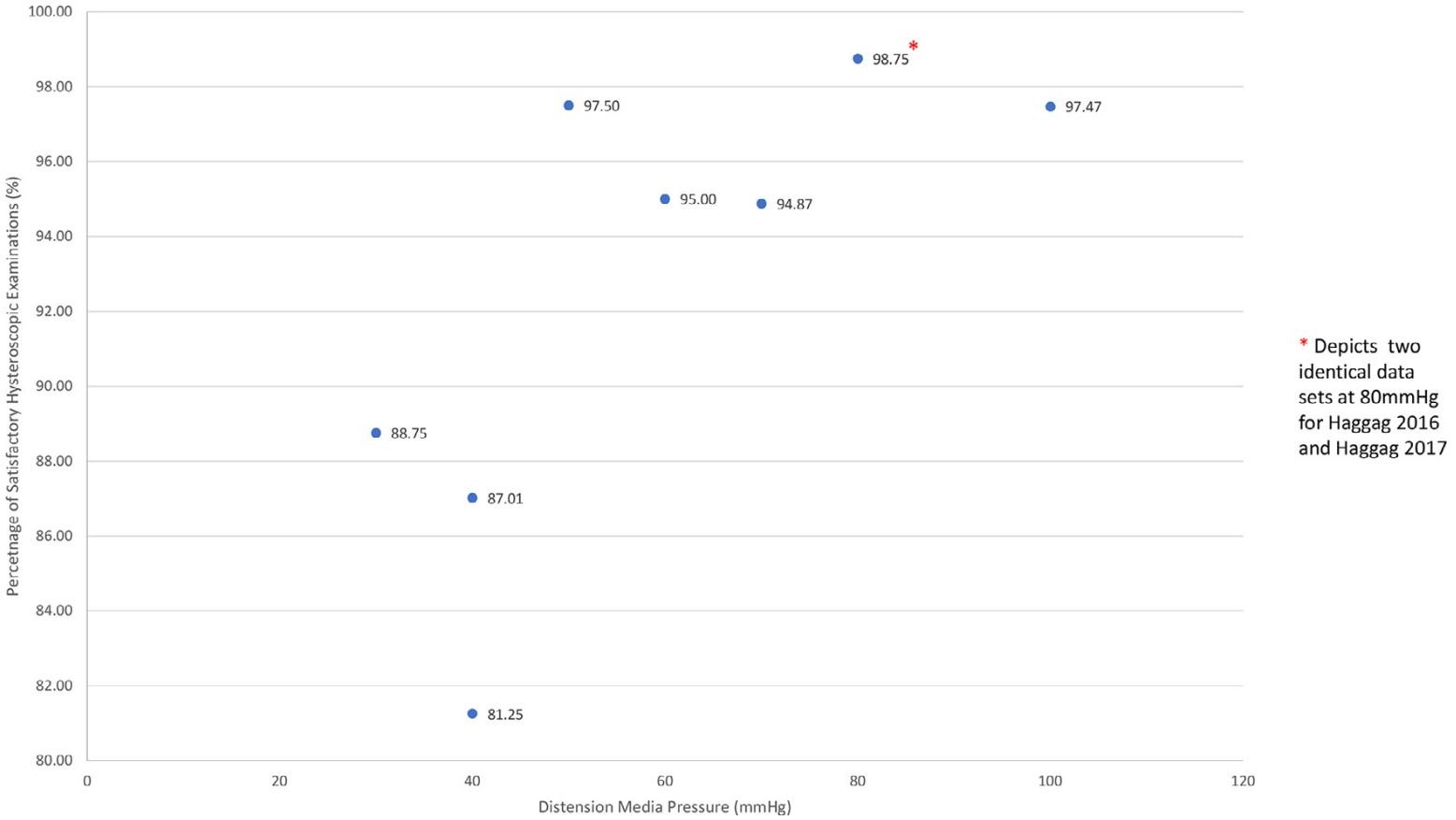
Forest plot of unsatisfactory hysteroscopic examinations for studies randomizing women according to distension media type.



A5.2: Supplemental Fig 2. Graph of the percentage of satisfactory hysteroscopic examinations at specified distension media pressures for studies randomizing women according to distension media pressure.

Supplemental Fig. 2

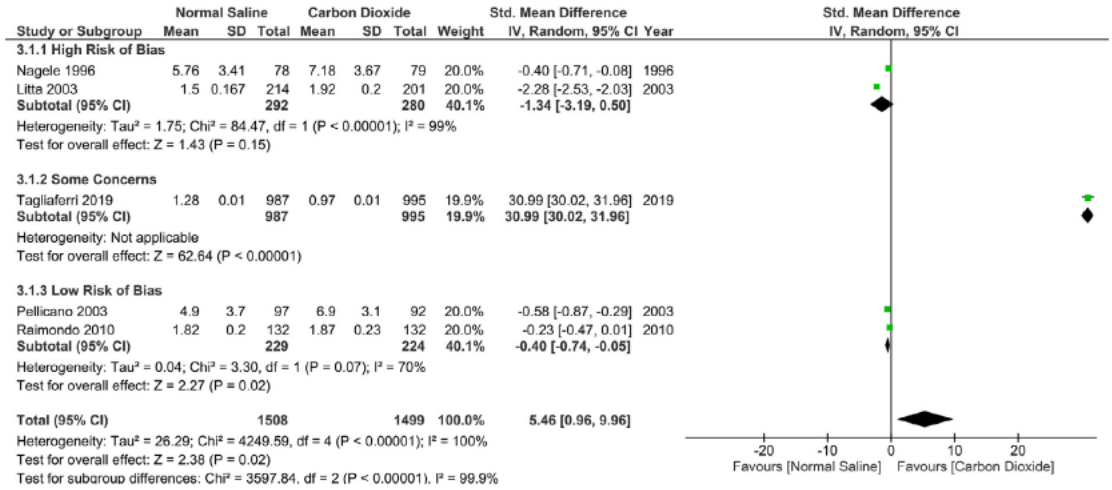
Graph of the percentage of satisfactory hysteroscopic examinations at specified distension media pressures for studies randomizing women according to distension media pressure.



A5.3: Supplemental Fig 3. Forest plot of procedural time for studies randomizing women according to distension media type.

Supplemental Fig. 3

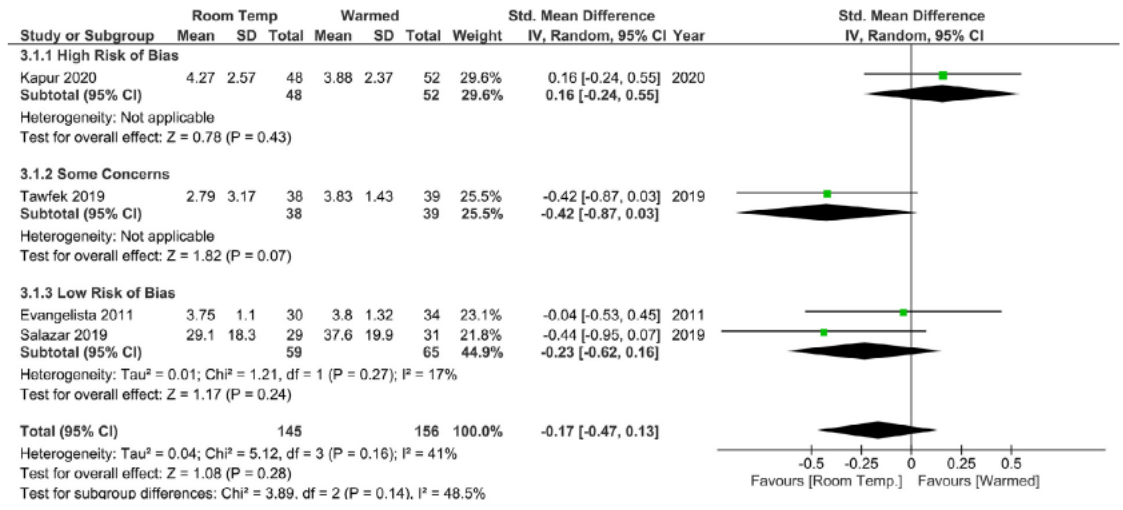
Forest plot of procedural time for studies randomizing women according to distension media type.



A5.4: Supplemental Fig 4: Forest plot of procedural time for studies randomizing women according to distension media temperature

Supplemental Fig. 4

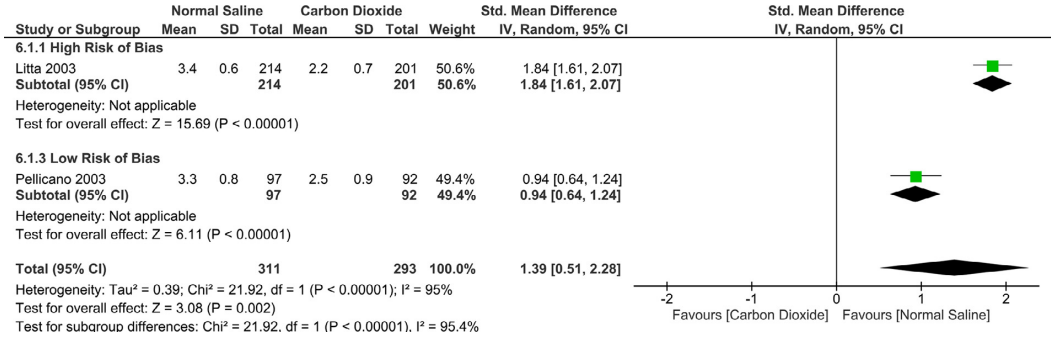
Forest plot of procedural time for studies randomizing women according to distension media temperature.



A5.5: Supplemental Fig 5: Forest plot of patient satisfaction scores for studies randomizing women according to distension media type

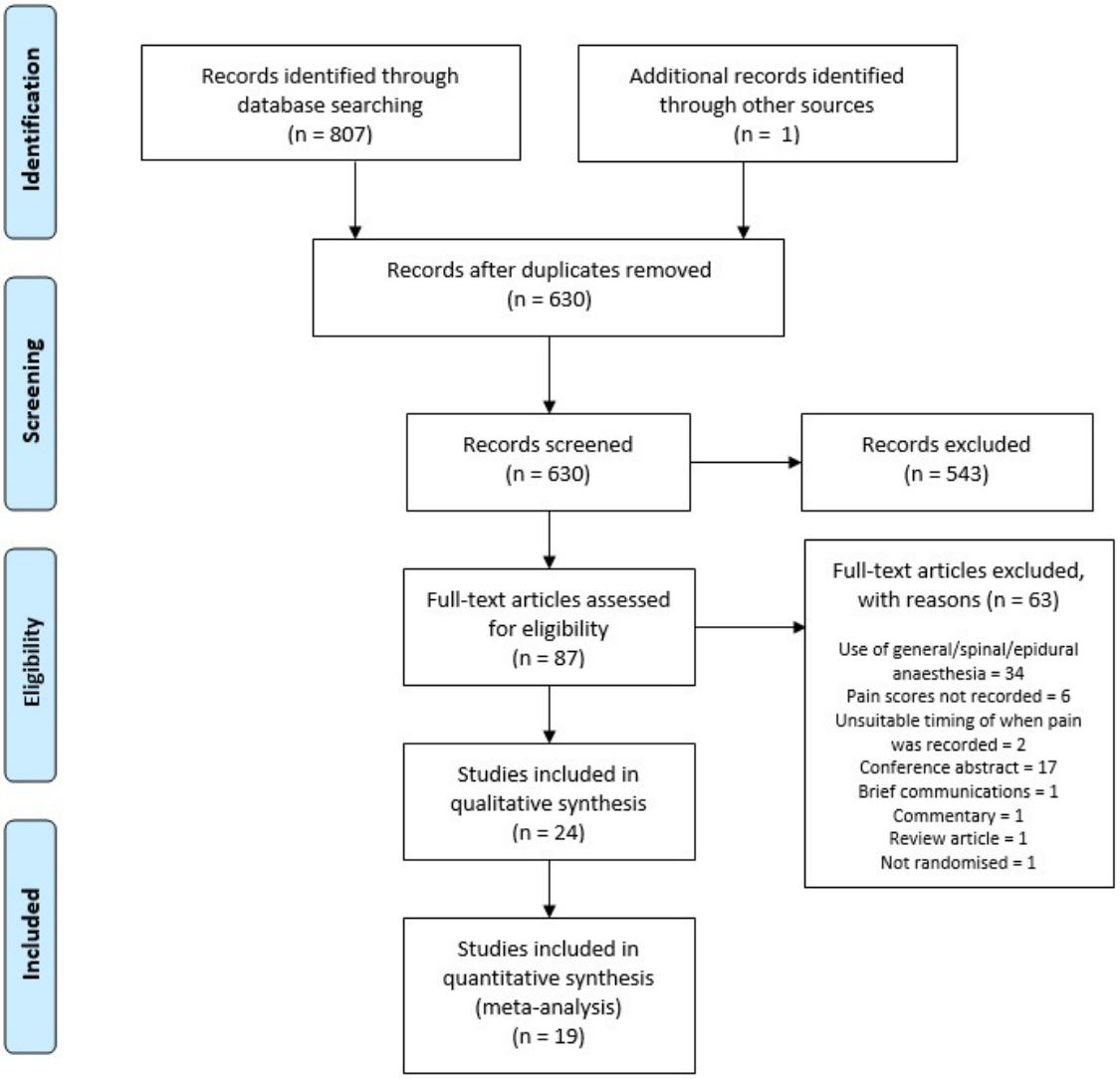
Supplemental Fig. 5

Forest plot of patient satisfaction scores for studies randomizing women according to distension media type.

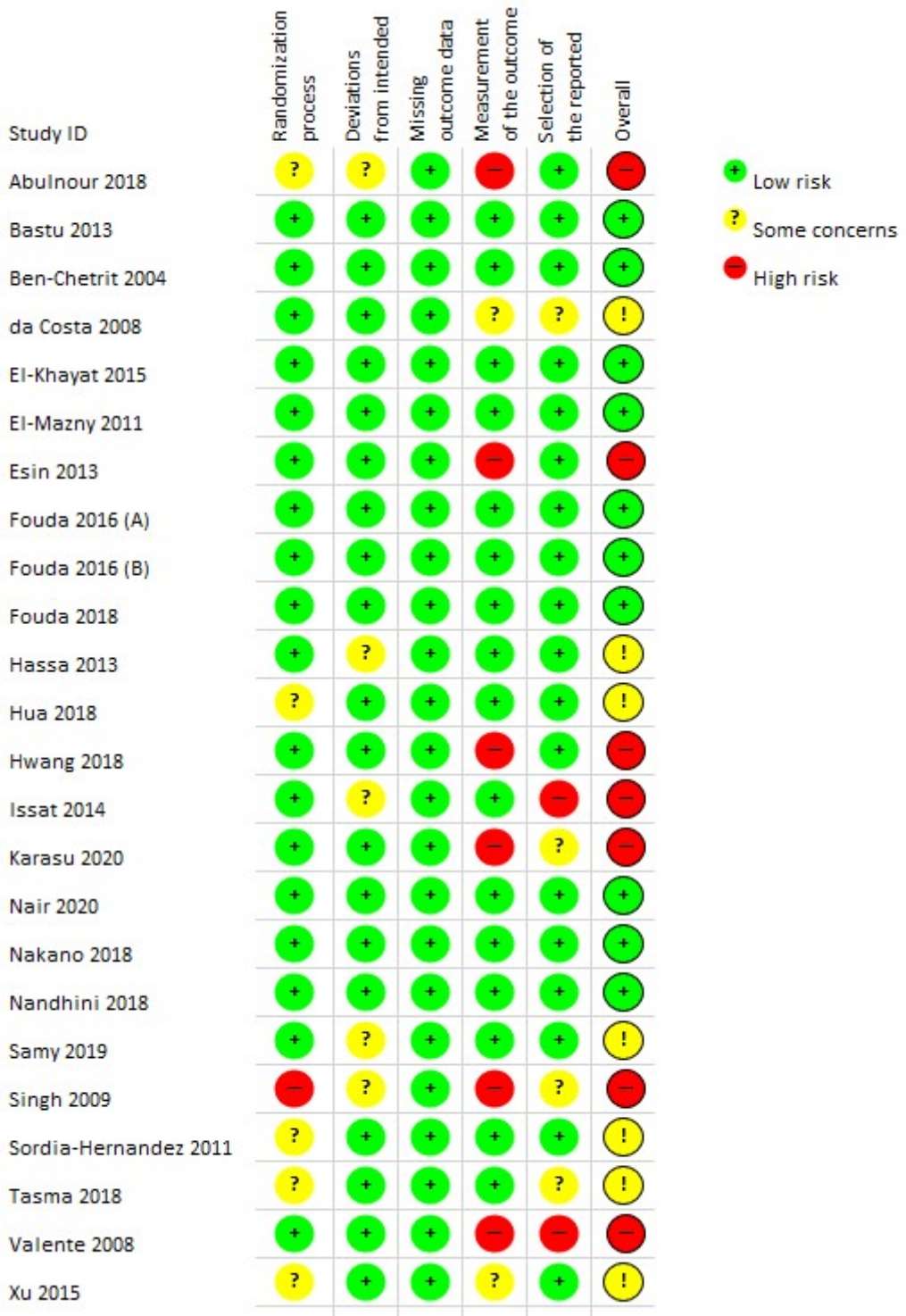


APPENDIX 6: SUPPLEMENTAL FIGURES FOR PART 2, CHAPTER 7 – CERVICAL DILATATION AND PREPARATION

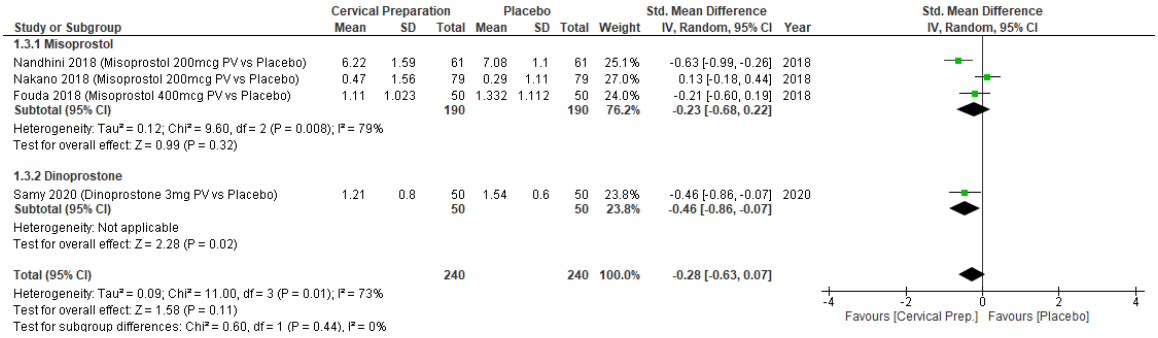
A6.1: Supplemental Fig 1. PRISMA flow diagram depicting the study selection process.



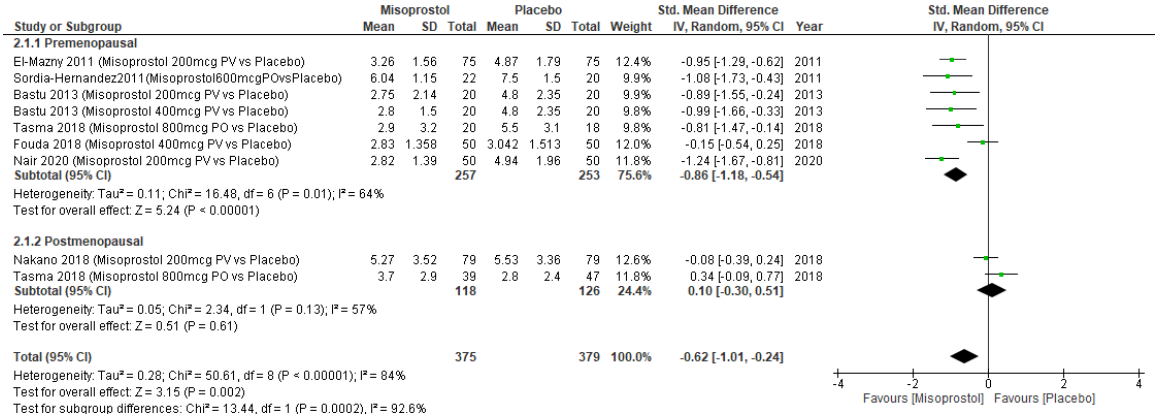
A6.2: Supplemental Fig 2. Study quality of included studies, based on the Risk of Bias 2 (RoB 2) tool.



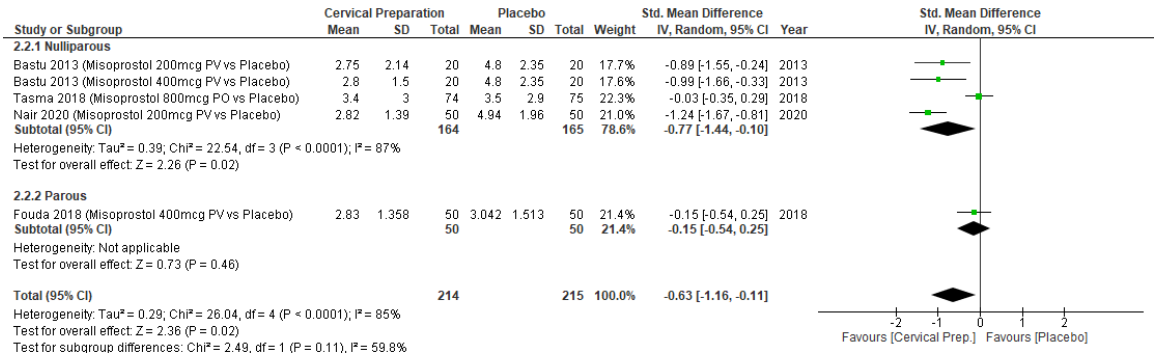
A6.3: Supplemental Fig 3. Effect of cervical preparation on post-procedural pain, according to the agent administered.



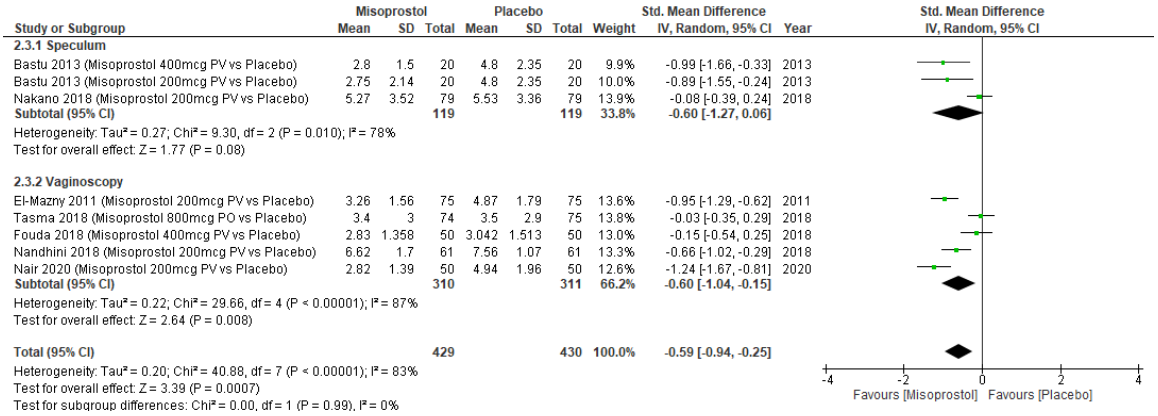
A6.4: Supplemental Fig 4. Effect of misoprostol on intra-procedural pain, according to menopausal status.



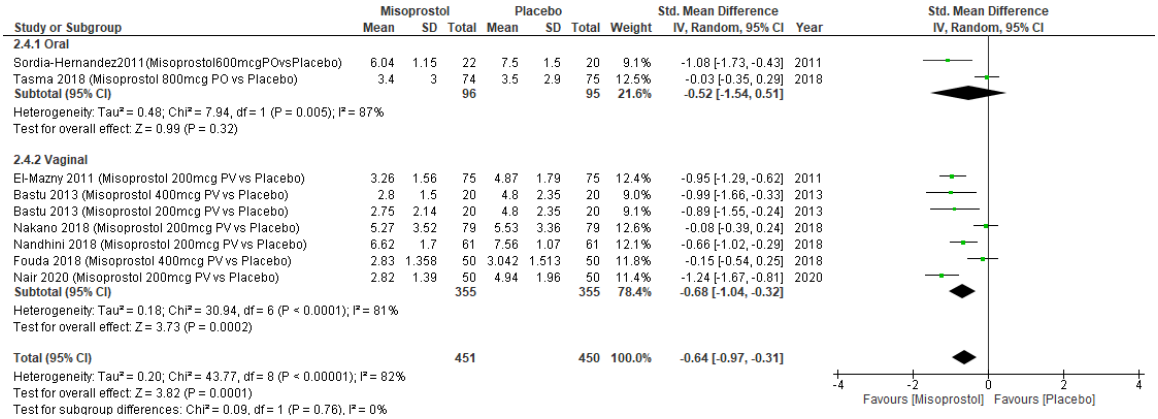
A6.5: Supplemental Fig 5. Effect of misoprostol on intra-procedural pain, according to parity.



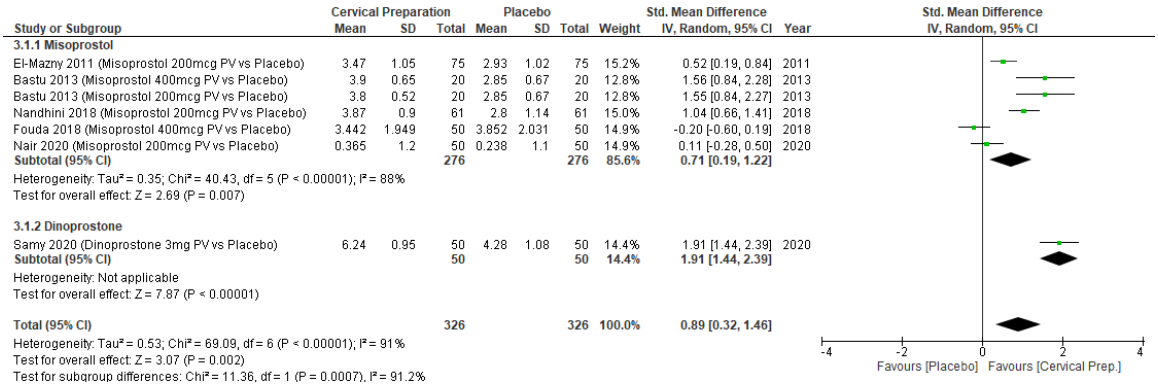
A6.6: Supplemental Fig 6. Effect of misoprostol on intra-procedural pain, according to approach.



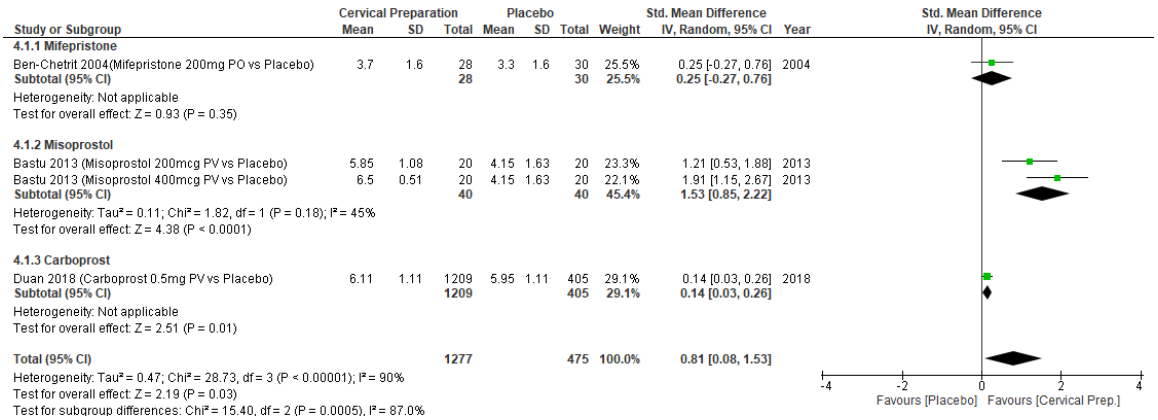
A6.7: Supplemental Fig 7. Effect of misoprostol on intra-procedural pain, according to route of administration.



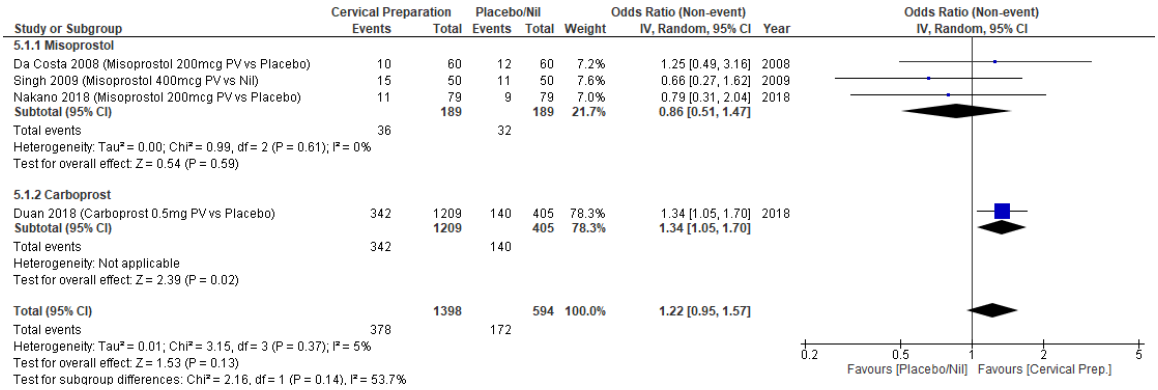
A6.8: Supplemental Fig 8. Effect of cervical preparation on the ease of hysteroscopic entry, according to the agent administered.



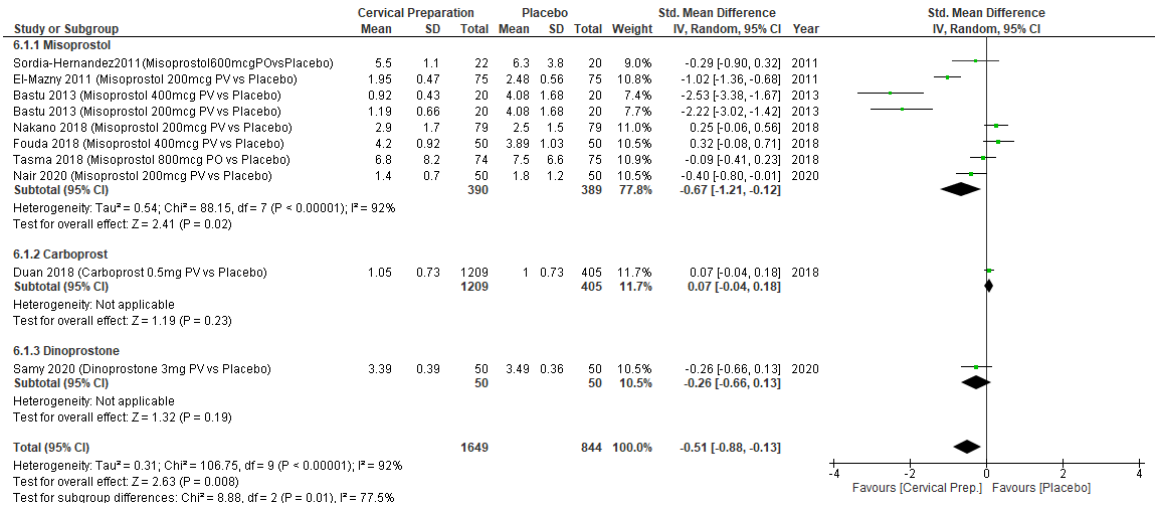
A6.9: Supplemental Fig 9. Effect of cervical preparation on cervical dilatation achieved prior to hysteroscopy, according to the agent administered.



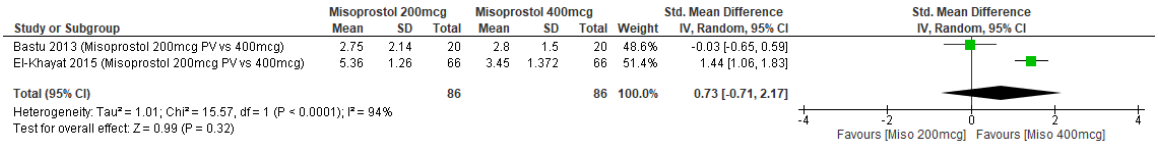
A6.10: Supplemental Fig 10. Effect of cervical preparation on the need for additional cervical dilatation prior to hysteroscopy, according to the agent administered.



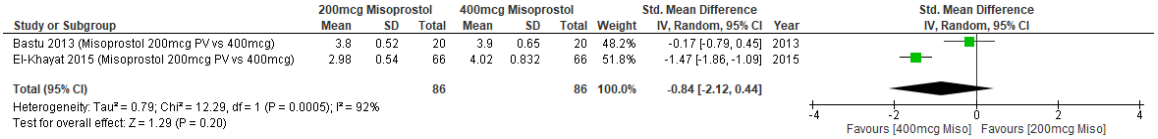
A6.11: Supplemental Fig 11. Effect of cervical preparation on procedural time, according to the agent administered.



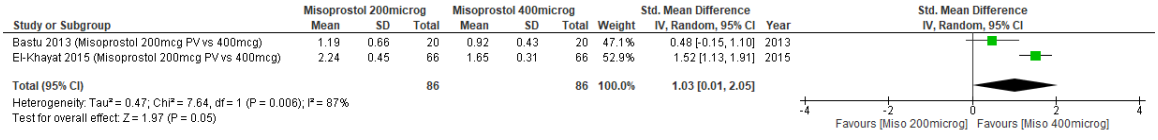
A6.12: Supplemental Fig 12. Effect of 200 micrograms vs 400 micrograms vaginal misoprostol, given as a cervical preparation, on intra-procedural pain.



A6.13: Supplemental Fig 13. Effect of 200 micrograms vs 400 micrograms vaginal misoprostol, given as a cervical preparation, on ease of hysteroscopic entry.



A6.14: Supplemental Fig 14. Effect of 200 micrograms vs 400 micrograms vaginal misoprostol, given as a cervical preparation, on procedural time.



A6.15: Supplemental Table 1. Detailed summary of included study characteristics.

Table S1. Detailed summary of included study characteristics

Study	Group 1	Group 2	Group 3	Menopausal Status	Parity	Procedure Type	Pain Score Data Type	Timing of Recorded Pain		Conscious Sedation	Pre-procedural Analgesia	Local Anaesthesia	Approach	Cervical Dilatation	Distension Medium	Instrument Diameter
								During	After							
Abulnour 2018	Misoprostol 400microg PV 6h prior	Dinoprostone 3mg PV 6h prior	N/A	Mixed	Nulliparous	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Only if required	Not specified	Not specified	Not specified	5mm
Bastu 2013	Misoprostol 200microg PV 12-15h prior	Misoprostol 400microg PV 12-15h prior	VE 12-15h prior	Premenopausal	Nulliparous	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Nil	Speculum	Yes to 5mm	0.09% saline	5mm rigid
Ben-Chetrit 2004	Mifepristone 200mg PO 30h prior	Placebo PO 30h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean+/-SD	Uterine cavity inspection	N/A	Nil	Nil	Nil	Speculum	No	Not specified	2.9mm rigid
Da Costa 2008	Misoprostol 200microg PV 8h prior	Placebo PV 8h prior	N/A	Postmenopausal	Mixed	Diagnostic	Median	During	15 min	Nil	Nil	Nil	Speculum	Only if required	CO2 (23 in Group 1 and 19 in Group 2)	4mm rigid
Duan 2018	Carboprost 0.5mg PV 1.5h prior	Placebo PV 1.5h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Nil	Speculum	Yes to He 7	NS between 80-100mmHg at 260-300ml/min	5.5mm
El-Khayat 2015	Misoprostol 200microg PV 3h prior	Misoprostol 400microg PV 3h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Nil	Vaginoscopy	No	NS at 100-120mmHg	4mm rigid
El-Mazny 2011	Misoprostol 200microg PV 3h prior	VE 3h prior	N/A	Premenopausal	Mixed	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Nil	Vaginoscopy	No	NS at 100-120mmHg	4mm rigid
Esin 2013	Misoprostol 200microg SL 2h prior and placebo TOP 5 min prior	SL Placebo 2h prior and lidocaine spray 60mg TOP 5 min prior	N/A	Premenopausal	Mixed	Diagnostic & Therapeutic (IUD removal, polypectomy, myomectomy, septoplasty)	Mean+/-SD	Greatest pain during	10 min	Nil	Nil	Nil	Vaginoscopy	Only if required	NS at 70-80mmHg	4mm rigid
Fouda 2016 (A)	Misoprostol 400microg PV 12h prior	Bladder distension (1l water 2h prior)	N/A	Postmenopausal	Parous	Diagnostic	Mean+/-SD	During	30 min	Nil	Nil	Nil	Vaginoscopy	No	NS at 60-100mmHg	5mm rigid
Fouda 2016 (B)	Misoprostol 400microg PV 12h prior and placebo PV 3h prior	Placebo PV 12h prior and Misoprostol 400microg PV 3h prior	N/A	Premenopausal	Nulliparous	Diagnostic	Mean+/-SD	During	30 min	Nil	Nil	Nil	Vaginoscopy	No	NS at 60-100mmHg	5mm rigid

Fouda 2018	Misoprostol 400microg PV 12h prior	Placebo PV 12h prior	N/A	Premenopausal	Parous	Diagnostic	Mean+/-SD	During	30 min	Nil	Nil	Nil	Vaginoscopy	No	NS between 60-80mmHg	5mm rigid
Hassa 2013	Misoprostol 200microg PV 6h prior and placebo PR 60min prior	Placebo PV 6h prior and Diclofenac 100mg PR 60 min prior	Placebo PV 6h prior and placebo PR 60 min prior	Premenopausal	Nulliparous	Diagnostic	Median (IQR)	During	N/A	Nil	Nil	Nil	Vaginoscopy	No	NS at 100-120mmHg	4mm rigid
Hwang 2018	Misoprostol 200microg PV 8h prior	Misoprostol 400microg PV 8h prior	N/A	Mixed	Mixed	Therapeutic (polypectomy, myomectomy)	Median (range)	N/A	<2h	Yes	Nil	Nil	Speculum	Yes	Not specified	10mm
Issat 2014	Misoprostol 400microg PV 4h prior and 100ml 5% IV glucose 30 min prior	Placebo PV 4h prior and Ketoprofen 50mg/ml in 100ml 5% glucose 30 min prior	Placebo PV 4h prior and 100ml 5% IV glucose 30 min prior	Mixed	Mixed	Diagnostic & Therapeutic (polypectomy, myomectomy, directed biopsy)	Median (IQR)	During	5 min	Nil	Yes, in Group 2	Nil	Vaginoscopy	No	NS at 120mmHg	3.2mm rigid
Karasu 2020	Misoprostol 200microg PR 2h prior	Buscopan 20mg PR 2h prior	Rectovaginal examination 2h prior	Premenopausal	Mixed	Therapeutic (polypectomy, myomectomy)	Median+/- not specified	N/A	1h	IV propofol (1 5mg/kg)	Nil	Nil	Speculum	Yes, to 8.5mm	NS	9mm
Nair 2020	Misoprostol 200microg PV 4h prior	Placebo PV 4h prior	N/A	Premenopausal	Nulliparous	Diagnostic	Mean+/-SD	Uterine cavity inspection	N/A	Nil	Nil	Nil	Vaginoscopy	No	NS	3.2mm
Nakano 2018	Misoprostol 200microg PV 6h prior	Placebo PV 6h prior	N/A	Postmenopausal	Mixed	Diagnostic	Mean+/-SD	During examination	1h	Nil	Nil	Nil	Speculum	Only if required	CO2 <100mmHg at 50-60mmHg flow	2.9mm rigid
Nandhini 2018	Misoprostol 200microg PV 3h prior	VE 3h prior	N/A	Mixed	Mixed	Diagnostic	Mean +/-SD emailed	Introduction of scope into cervical canal	Immediately after	Nil	Nil	If vaginoscopy failed, PCB given	Vaginoscopy	No	NS at 100mmHg at 500ml/min	4mm rigid
Samy 2020	Dinoprostone 3mg PV 12h prior	Placebo PV 12h prior	N/A	Postmenopausal	Mixed	Diagnostic	Mean+/-SD	During	30 min	Nil	Nil	Nil	Vaginoscopy	No	NS at 50mmHg	4mm rigid
Singh 2009	Misoprostol 400microg PV 4-6h prior	Nil	N/A	Mixed	Nulliparous	Diagnostic	Median+/-SD	During	N/A	1ml IV pentazocin and 1ml IV diazepam if required	75mg IM diclofenac if required	Nil	Not specified	Only if required	Not specified	4mm rigid

Sordia-Hernandez 2011	Misoprostol 200microg PO every 8 hours for 24h prior (600microg total)	Misoprostol 200microg PV every 12 hours for 24h prior (400microg total)	PO placebo every 8 hours for 24h prior	Premenopausal	Mixed	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Nil	Not specified	No	NS at 100mmHg at 25-30ml/min	5mm
Tasma 2018	Misoprostol 400microg PO at 24h and 12h prior (800microg total)	Placebo PO 24h and 12h prior	N/A	Mixed (pain scores given according to parity)	Nulliparous	Diagnostic & Therapeutic (polypectomy)	Mean+/-SD	Introduction of scope into cervical canal	N/A	Nil	500mg Naproxen PO 1h prior	Nil	Vaginoscopy	No	NS between 80-100mmHg at 0.15 bar	5.5mm
Valente 2008	Misoprostol 400microg PV 6h prior	Placebo PV 6h prior	N/A	Premenopausal	Mixed	Diagnostic	Dichotomous	Most severe pain during	15 min	Nil	Nil	Nil	Speculum	No	NS	4mm rigid
Xu 2015	Misoprostol 400microg PO 2h prior	Phloroglucinol 80mg IM 30 min prior	N/A	Premenopausal	Mixed	Diagnostic	Mean+/-SD	During	N/A	Nil	Nil	Nil	Speculum	No	NS at 80-100mmHg	7mm

Legend: microg = microgram(s), mg = milligrams, mm = millimetre(s), ml = millilitre(s), l = litre(s), mmHg = millimetres of mercury, h = hour(s), min = minute(s), IQR = interquartile range, SD = standard deviation, N/A = not applicable, PO = oral, PV = per vagina, PR = per rectum, SL = sublingual, NS = normal saline, CO2 = carbon dioxide

*no previous vaginal deliveries; did not exclude Caesarean sections

A6.16: Supplemental Table 2. Distribution of specific side-effects according to the cervical preparation administered.

Table S2. Distribution of specific side-effects according to the cervical preparation administered

	Genital Tract Bleeding	Abdominal Pain/Cramping	Nausea	Diarrhoea	Pyrexia/Fever	Vomiting	Unspecified GI Symptoms	Vasovagal	Shivering	Blurred vision	Total
Misoprostol	68	50	42	22	8	7	6	3	4	0	210
Dinoprostone	0	7	5	2	3	0	0	0	0	0	17
Placebo	29	38	30	5	1	3	2	4	1	1	114

GI = gastrointestinal

APPENDIX 7: SUPPLEMENTAL MATERIAL FOR PART 3, CHAPTER 2 - THE HYSTEROSCOPIC MISCARRIAGE MANAGEMENT (HYMMN) PILOT RANDOMISED-CONTROLLED TRIAL

A7.1: Trial Protocol

Tommy's Together, for every baby

UNIVERSITY OF BIRMINGHAM

NHS Birmingham Women's and Children's NHS Foundation Trust

The HYsteroscopic Miscarriage MaNagement (HYMMN) Trial Protocol

HYMMN Trial Study Management Group

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Contents

1. Summary of Proposal

Pregnancy t ssue can be found rema n ng n the womb n up to 20% of women fo ow ng a m scarr age. These “reta ned products of concept on” (RPOC), wh ch are d agnosed by transvag na u trasound, can cause pro onged b eed ng, pa n, nfect on, mpa red fert ty and therefore further psycho og ca d stress.

Ineffect ve med ca and surg ca ntervent ons p ace cons derab e burden on affected women and ut se scarce hea th care resources. Add t ona y, surgery s performed ‘b nd y’ us ng a suct on tube or meta curette where r sks nc ude perforat on of the womb and scarr ng of the womb n ng, both of wh ch ead to de ayed fert ty and n the worst c rcumstances, nfert ty.

New surg ca equ pment a ows RPOC remova under v s on, us ng a spec a y des gned te escope p aced ns de the womb; a procedure known as hysteroscopy. Th s prec se techn que may more successfu y and ess traumat ca y remove RPOC, m n m s ng ongo ng b eed ng, the r sk of womb perforat on and scar t ssue format on, thereby reduc ng the r sk of nfert ty.

There s no current gu dance on how to best nvest gate and manage RPOC. We propose a p ot random sed contro ed tr a us ng rout ne transvag na u trasound to d agnose RPOC and random s ng affected women to e ther outpat ent hysteroscopy (to conf rm the d agnos s and surg ca y remove RPOC under d rect v s on) or standard management. Tr a process outcomes (e g b e popu at on, w ngness for random sat on, attr t on rates, comp eteness of fo ow up) and c n ca outcomes (c n ca pregnancy rates, uter ne evacuat on, b eed ng, qua ty of fe) w be co ected to nform the feas b ty and des gn of a future, substant ve, fu sca e tr a .

2. Introduction

2.1 Background

As many as 1 n 4 pregnanc es end n m scarr age [1]. Management compr ses expectant, med ca or surg ca opt ons. Surg ca treatment s nvar ab y performed under genera anaesthes a and nvo ves d atat on of the cerv ca cana fo owed by b nd curettage or vacuum asp rat on of reta ned products of concept on (RPOC) w th n the uter ne cav ty. The b nd nature of th s procedure r sks ncomp ete remova of t ssue, as we as ser ous comp cat ons such as uter ne perforat on and damage to the hea thy endometr um. For these reasons, most women choose n t a non surg ca (expectant or med ca) treatment opt ons. However, rates of comp ete uter ne evacuat on are est mated to be between 52% 85% for non surg ca management compared to 91 100% for surg ca management [2]. Add t ona y, t has been found that as many as 1 n 5 pat ents are found to have RPOC 4 weeks after expectant management [3].

RPOC after m scarr age may be asymptomat c but more often affected women present w th pro onged uter ne b eed ng, pa n and nfect on requ r ng add t ona ntervent ons and use of hea th serv ce resources. There s a ack of consensus regard ng how best to manage RPOC after m scarr age because ev dence based gu dance s absent. Expectant management r sks de ayed return of fert ty and the presence of chron c RPOC may nduce oca nf ammatory responses mak ng the endometr um vu nerab e to adhes on format on wh ch may comprom se subsequent fert ty. Th s s thought to be espec a y true from trauma nduced by current, b nd surg ca management [4]. The preva ence of ntrauter ne adhes on format on assoc ated w th RPOC after m scarr age, whether managed surg ca y or non surg ca y, s however, unknown. In add t on, the mpact of adhes ons upon ong term reproduct ve outcomes fo ow ng m scarr age s unc ear [5].

Recent techno og ca advances n hysteroscopy a ow RPOC to be d rect y v sua sed and s mu taneous y removed w th greater prec s on and ess trauma to the endometr um w th prom s ng resu ts. These ‘hysteroscop c t ssue remova systems’ represent the atest advance n uter ne surgery. Th s techno ogy a ows comp ete exc s on and remova of ntrauter ne patho ogy under d rect v s on, nc ud ng remova of RPOC n the npat ent [6] and more recent y, the outpat ent sett ng [7] w th comp ete resect on and reso ut on of symptoms w thout apparent comp cat ons. A recent meta ana ys s, wh ch nc uded 326 pat ents from 5 stud es, showed comp ete remova of RPOC n a cases w th no pat ents requ r ng further treatment and on y 3 comp cat ons (uter ne perforat on, s gn f cant vag na b eed ng, system c nfect on) conf rm ng that hysteroscopy s a safe and effect ve ntervent on [8]. Current ev dence suggests that hysteroscop c resect on of RPOC s assoc ated w th the format on of ess ntrauter ne adhes ons, ower rates of ncomp ete evacuat on, and shorter t me to subsequent concept on, but s based on m ted numbers of stud es, too sma samp e s zes to stat st ca y detect d fferences between treatments, poor report ng of confounders and the absence of random sed stud es [9]. S nce women are most strong y nf uenced by the ke hood of success and the h ghest subsequent chance of fert ty, t s c ear that hysteroscop c remova requ res further exp orat on [10].

To date, there are no random sed contro ed tr a s nvest gat ng the use of outpat ent hysteroscopy n the management of RPOC aga nst standard treatment. We therefore a m to perform a p ot random sed contro tr a to assess the feas b ty of undertak ng a future

substant ve fu sca e tr a to compare th s new pathway aga nst current pract ce for the management of RPOC, to see f t s more effect ve n mprov ng fert ty and m n m s ng symptomat c morb d ty. Furthermore, hea th serv ce resource use w be eva uated aga nst c n ca outcomes to determ ne the cost effect veness of th s new pathway.

2.2 Rationale

The d agnos s of reta ned products of concept on (RPOC) fo ow ng m scarr age causes phys o og ca and emot ona stress to women and the r partners. Add t ona hosp ta v s ts, npat ent adm ss ons and non ev dence based treatments mpose an add t ona burden on women and hea thcare serv ces. Ineffect ve med ca and surg ca treatments can pro ong symptoms such as b eed ng, pa n and psycho og ca d stress wh ch mpacts adverse y on qua ty of fe. In add t on, future fert ty can be de ayed or worse, permanent y mpa red, because of damage and scarr ng of the womb n ng ar s ng from chron c nfect on or mechan ca trauma after convent ona 'b nd' mechan ca evacuat on of the uter ne cav ty. We propose a new management pathway based upon rout ne transvag na u trasound fo ow ng m scarr age and when RPOC s d agnosed, subsequent referra for an outpat ent hysteroscopy where prec se, atraumat c RPOC remova w be undertaken n women w th conf rmed RPOC.

2.3 Research Question

Is t feas b e to perform an RCT to eva uate the potent a eff cacy of outpat ent hysteroscopy n mprov ng fert ty fo ow ng non surg ca management of m scarr age?

3. Project Design

3.1 Study Type

P ot random sed contro ed tr a

3.2 Study Setting

S ng e centre study at a centra urban teach ng hosp ta n B rm ngham (B rm ngham Women's Hosp ta).

3.3 Objectives

We a m to assess var ous aspects of tr a management and des gn. In order to ach eve th s, the object ves of the p ot RCT w be sp t nto:

1) Process Ob ect ves
   - To determ ne the proport on of e g b e women that are screened and meet the nc us on cr ter a what s the proport on of women that had non surg ca management of f rst tr mester m scarr age?

- To determ ne the proport on of e g b e women that agree to be random sed of the women that were e g b e, how many agreed to part c pate n the tr a ?
- To determ ne the proport on of women that attend TVS and OPH (attr t on rate) what s the proport on of women that attended the hosp ta for ntervent on(s) and fo ow up?
- To determ ne the robustness of proposed data co ect on too s we wou d expect at east 90% of the forms to be f ed out

2) Acceptab ty
   - To determ ne why pat ents dec ne part c pat on or w thdraw after random sat on
   - To determ ne the acceptab ty and mpact of the proposed ntervent ons and data co ect on too s to pat ents

3) C n ca Ob ect ves
   - To determ ne the appropr ateness of the outcome measures
   - To der ve c n ca data to he p nform the samp e s ze for a future substant ve study

The feas b ty study shou d enab e us to come to one of the fo ow ng conc us ons:

- A substant ve study s not feas b e.
- A substant ve study s feas b e w th substant a mod f cat ons to the tr a protoco to mprove recru tment, comp ance and fo ow up.
- A substant ve study s feas b e w th m nor mod f cat ons to the tr a protoco to mprove recru tment, comp ance and fo ow up.
- The substant ve study s feas b e us ng the p ot protoco .

3.4 Plan of Investigation

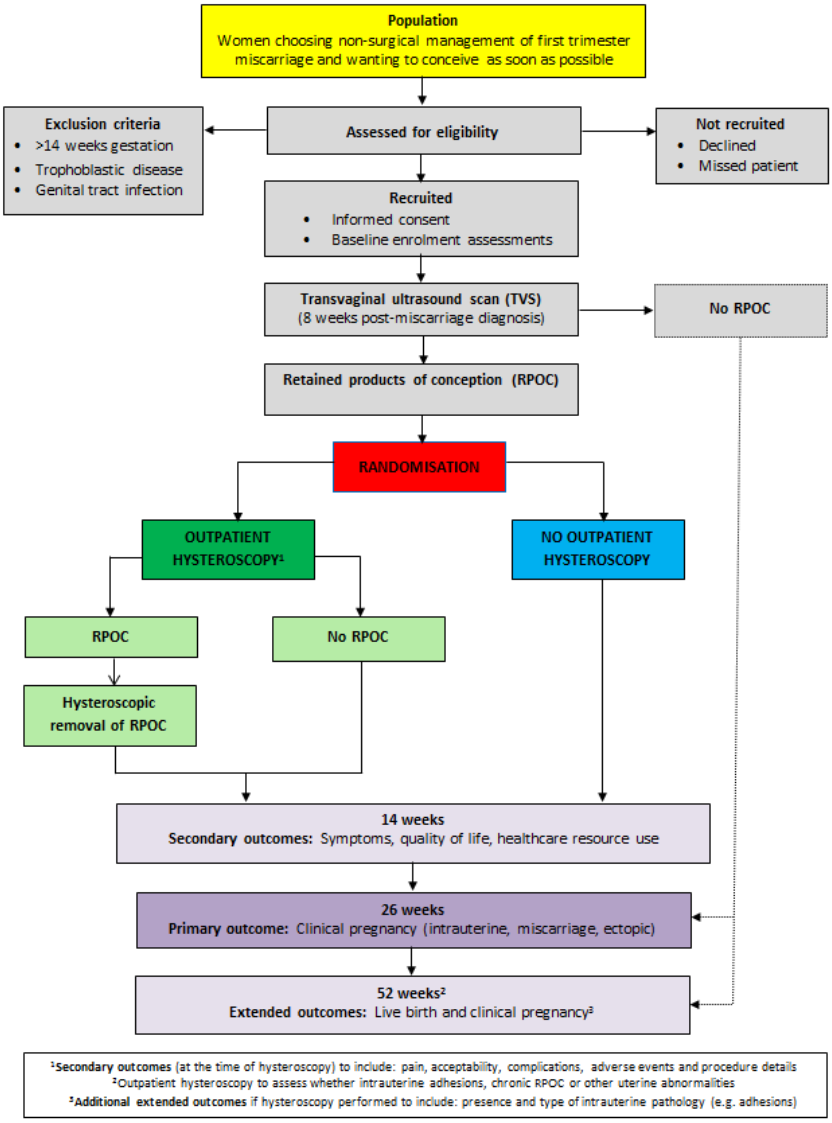
A women who choose non surg ca management of a f rst tr mester (≤14 weeks gestat on) m scarr age w be e g b e for recru tment nto the study, where nformed consent w be taken and base ne assessments w be conducted.

A pat ents who then have RPOC d agnosed on transvag na u trasound scan (TVS) at 8 weeks after the d agnos s of the r m scarr age w then be random sed (n a 1:1 rat o) to rece ve outpat ent hysteroscopy ('OPH') or no outpat ent hysteroscopy ('nOPH'). At 'OPH', f RPOC are present, then these w be removed on an ntent on to treat bas s. If random sed to the 'nOPH' arm, management w be based accord ng to current pract ce. Immed ate y after OPH, a women w be asked to comp ete a quest onna re exp or ng the acceptab ty of the procedure and c n c ans w be asked to comp ete a quest onna re exp or ng the eff cacy of OPH n d agnos ng and remov ng RPOC.

For those who had RPOC, regard ess of wh ch treatment they were random sed to, face to face consu tat ons w be performed at 14 weeks post random sat on. These w exp ore c n ca outcomes (symptoms and gener c qua ty of fe) and use of add t ona hea thcare resources (e.g. add t ona nvest gat ons / treatments / hosp ta sat ons). A pat ents, no matter whether they were d agnosed w th RPOC or not, w be fo owed up at 26 weeks and 52 weeks post random sat on to determ ne c n ca pregnancy rates and pregnancy outcomes, v a te ephone consu tat on. A pat ents who have had a m scarr age or have not fa en pregnant s nce enter ng the tr a w be offered the chance to undergo a hysteroscopy

to see f there s any scar t ssue, chron c RPOC or other cond t ons affect ng the womb n ng wh ch may be contr but ng to pregnancy fa ure; th s data w be co ected. At th s po nt, pat ents w d scharged from the tr a . Shou d any pat ent want to see us and d scuss any aspect of th s n person, th s can be arranged too.

A summary of the p an of nvest gat on s shown n the f ow d agram be ow:



3.5 Outcomes

Pr mary outcome: C n ca pregnancy rates and t me to next pregnancy

Secondary outcomes: Symptoms, qua ty of fe and hea thcare resource use. Pos t ve pred ct ve va ue (PPV) of TVS n d agnos ng RPOC. For pat ents undergo ng OPH, pa n and acceptab ty of the procedure and for c n c ans undertak ng OPH, f nd ngs at hysteroscopy and procedura success. For pat ents who do not get pregnant or have adverse pregnancy outcomes on y (m scarr age, ectop c pregnancy) by 56 weeks post random sat on, f nd ngs at hysteroscopy w a so be recorded.

3.6 Data Analysis

Th s w be carr ed out w th support from Pau Sm th at BWCH and Lee M dd eton at BCTU. The samp e s ze s too sma to a ow re ab e ana ys s of the effect of treatment of RPOC w th outpat ent hysteroscopy. Ana ys s of c n ca and feas b ty outcomes w pr mar y cons st of descr pt ve ana ys s (e.g. proport ons and nterquart e ranges, means and standard dev at ons) and where appropr ate, po nt est mates of effects s zes (e.g. mean d fferences and re at ve r sks) and assoc ated 95% conf dence nterva s.

4. Participant Selection & Enrolment

4.1 Eligibility

Inc us on Cr ter a

- Women above 18 years
- Women choos ng e ther expectant or med ca management of a f rst tr mester m scarr age ≤14 weeks gestat on
- Women want ng to conce ve as soon as poss b e after the r m scarr age
- Consent to tr a processes: (1) undergo fo ow up w th transvag na u trasound for the nvest gat on of RPOC; (2) be random sed to outpat ent hysteroscopy for conf rmat on and treatment or standard management; (3) accept tr a fo ow up procedures quest onna res, te ephone nterv ews

Exc us on Cr ter a

- Women be ow 18 years
- Women w th f nd ngs susp c ous of gestat ona trophob ast c d sease
- Women w th fever (≥38°C) or seps s secondary to gen ta tract nfect on/endometr t s
- Women who are unab e to understand spoken and wr tten Eng sh

4.2 Recruitment

Recru tment w be carr ed out n the Ear y Pregnancy Assessment Un t at the B rm ngham Women's Hosp ta . After d scuss on of the ava ab e treatment opt ons, women meet ng the

nc us on cr ter a w be approached to part c pate n the HYMMN tr a . Informed wr tten consent w be obta ned for part c pat on n the tr a .

Base ne cr ter a w be sought to determ ne prognost c parameters of RPOC such as age, par ty, gestat ona age at d agnos s of m scarr age, prev ous obstetr c h story, and surg ca ntervent ons on the uterus.

A recru ted women w undergo a transvag na u trasound scan (TVS) at 8 weeks post m scarr age d agnos s. If RPOC are found on TVS, endometr a th ckness and RPOC d mens ons w be measured and the woman w proceed to random sat on.

4.3 Randomisation

TVS at base ne w be performed. Women w th RPOC w be random sed fo ow ng TVS n a 1:1 manner to e ther 'OPH' (ntervent on) or 'nOPH' (contro). Random sat on w be performed v a a web based p atform (Sea ed Enve ope) w th support from Lee M dd eton (Sen or Stat st c an) at B rm ngham C n ca Tr a s Un t (BCTU) [11]. If a ocated to 'OPH', th s w be performed w th n two weeks of random sat on n the Ambu atory Gynaeco ogy Department of the B rm ngham Women's Hosp ta . Remova of RPOC w be carr ed out accord ng to a oca protoco .

4.4 Sample Size

The samp e s ze of a future substant ve study w part y be determ ned by the resu ts of th s study. Th s study w a m to recru t 200 women to g ve a better dea of the number of women w th RPOC and the numbers w ng to be recru ted. The Ear y Pregnancy Assessment Un t (EPAU) manages approx mate y 150 m scarr ages per month. A though we wou d expect ess than 1/3 of women to undergo surg ca management, we w conservat ve y assume that 600 women opt for non surg ca management over the t me per od of 6 months. After recru tment, we w a m to scan 200 women over the s x month per od (based upon a 50% part c pat on rate and a 33% attr t on rate). Pred cated upon a sonograph c RPOC rate of 20% [3], we expect 40 women to have RPOC; 20 women wou d be random sed to 'OPH' and 20 women to 'nOPH'. If the number of women ost to fo ow up before hav ng a hysteroscopy s h gher than expected or the number of women w th RPOC s ower than expected, we may ncrease the number of women scanned to 300 over a 9 month per od.

5. Follow-up

5.1 Interventions

1. Transvag na U trasound (TVS)
    - Used to determ ne progress on through the tr a . If RPOC are not found, women w be deemed ne g b e at 8 weeks post m scarr age d agnos s. If found, then they w be random sed to 'OPH' or 'nOPH'.

2. Outpat ent Hysteroscopy (OPH)
   - Used n pat ents who have RPOC on TVS f random sed to 'OPH' to remove RPOC.
   - The ma n r sks of outpat ent hysteroscopy are pa n, nfect on, vasovaga syncope and uter ne perforat on; a of wh ch are usua y secondary to d atat on of the cerv x.
   - A narrow hysteroscope <6mm w be used m n m s ng the need or degree of cerv ca d atat on. In order to fac tate d atat on, oca anaesthes a w th the oca anaesthet c, mep vaca ne, w be used where nd cated. Perform ng the procedure n the outpat ent sett ng avo ds the r sks of genera anaesthes a. Remova of ntrauter ne t ssue us ng mechan ca hysteroscop c t ssue remova systems have been shown to be both feas b e and safe [6,7,12].
   - If the procedure cannot be undertaken n the outpat ent sett ng, then the pat ent w be offered treatment under genera anaesthes a or standard management and w be exc uded from the tr a .
   - At 52 weeks post random sat on, f pat ents have not conce ved or had a m scarr age after random sat on, they w be offered an OPH to determ ne presence of ntrauter ne adhes ons, chron c RPOC or other uter ne abnorma t es, that may be contr but ng to the r subfert ty.

5.2 Questionnaires

1. Base ne
   - Pat ent enro ment quest onna re to be f ed n by recru t ng c n c an and consent to be s gned by pat ent and c n c an to determ ne base ne cr ter a to dent fy prognost c parameters of RPOC such as age, par ty, gestat ona age at d agnos s of m scarr age, prev ous obstetr c h story, and surg ca ntervent ons on the uterus.
2. At hysteroscopy
   - Pat ent quest onna re to nc ude V sua Ana ogue Score (VAS) for pa n and rat ng for acceptab ty To determ ne the acceptab ty of 'OPH' to pat ents random sed to th s ntervent on dur ng the procedure
   - C n c an quest onna re to determ ne feas b ty of RPOC remova f present. Comp cat ons (e.g. uter ne perforat on), s de effects (e.g. vasovaga symptoms) and reasons for fa ed hysteroscopy f procedure abandoned are a so to be noted. A standard sed proforma w be used to record the f nd ngs at hysteroscopy w th c ear def n t ons of RPOC and the type of ntrauter ne adhes ons.
   - Adverse effects quest onna re Used to determ ne t m ng and nature of any ser ous adverse events (SAE) re ated to the treatment pathway or spec f c treatments
3. 14 weeks post random sat on (Face to face consu tat on)
   - Symptom quest onna re Assessment to quant fy patterns and amount of abnorma uter ne b eed ng, pa n and vag na d scharge
   - Qua ty of fe quest onna re Qua ty of fe assessment to understand the mpact of the proposed versus the current treatment opt ons on burden to pat ents

- Use of hea thcare serv ces quest onna re Enqu r ng about the number of outpat ent appo ntments, npat ent stays, scans and treatments

4. 26 weeks post random sat on (Te ephone Interv ew)
   - Interv ew to ascerta n f pregnant. T me to next pregnancy after random sat on. Pregnancy outcome (ntrauter ne pregnancy, m scarr age, ectop c pregnancy). If fa ed pregnancy, treatment g ven (e.g. expectant, med ca , surg ca) and comp cat ons (e.g. repeat RPOC)
5. 52 week post random sat on (Te ephone Interv ew)
   - Interv ew as above repeated to ascerta n whether further pregnanc es occurred s nce ast te ephone nterv ew or f veb rths have occurred.
   - If pat ent has not conce ved or had pregnancy fa ure on y (m scarr age and/or ectop c pregnanc es) s nce random sat on, they w be offered an OPH to determ ne and co ect data regard ng the presence of ntrauter ne adhes ons, chron c RPOC or other uter ne abnorma t es that may be contr but ng to subfert ty.

6. Trial Management

6.1 Study Conduct

An ndependent overs ght comm ttee w rev ew study recru tment and safety data and w adv se on further enro ment.

The tr a w be managed from the B rm ngham Women's and Ch dren's Hosp ta . The study w be carr ed out n accordance w th the study protoco and to "Good C n ca Pract ce" standards a d out by the Med ca Research Counc . Pat ents w be nv ted to part c pate f they fu f *all* the nc us on cr ter a and do not have *any* exc us on cr ter a. They w be prov ded tr a nformat on eaf ets and the r consent obta ned. E g b e pat ents w be asked to f out an enro ment quest onna re.

6.2 Ethical Considerations

Eth ca approva for the protoco from the oca research eth cs comm ttees (LREC) s essent a pr or to the start of th s study.

6.3 Data Handling and Record Keeping

A data obta ned dur ng the course of the study w be recorded d rect y and eg b y on the case record forms. A entr es on the forms w undergo qua ty contro checks. For overs ght comm ttee reports, and on comp et on of the study, data w be c osed after reso ut on of a data quer es and t w be exported n text format for ana ys s.

Source Data

In order to a ow for the accurate reconstruct on of the tr a and c n ca management of the subject, source data w be access b e and ma nta ned. Source data s kept as part of the part c pants' med ca notes generated and ma nta ned at B rm ngham Women's and Ch dren's NHS Foundat on Trust.

Case Report Form (CRF) Comp et on

CRFs w be comp eted by the research team v a the e ectron c Remote Data Capture system (eRDC) system, hosted on the Un vers ty of B rm ngham server. Data reported on each form w be cons stent w th the source data and any d screpanc es w be exp a ned. A m ss ng and amb guous data w be quer ed. In a cases t rema ns the respons b ty of the Ch ef Invest gator to ensure that the CRF has been comp eted correct y and that the data are accurate. Where app cab e for the tr a th s w be ev denced by the s gnature of the s te's Ch ef Invest gator or de egate(s) on the CRF.

Data Management

Tr a data w be nputted d rect y nto the database by the s te from source data. A entr es on the forms w undergo qua ty contro checks. Any se f ev dent correct ons w be dent f ed and documented on a se f ev dent correct ons form. Perm ss on w be sought from the Ch ef Invest gator (CI) before any of these se f ev dent changes are made to the tr a data.

Data Secur ty

Any phys ca paperwork conta n ng dent f ab e data w be kept n an access contro ed, secured room ns de the B rm ngham Women's and Ch dren's NHS Foundat on Trust n a secure ocked off ce. Anonym sed data w be up oaded from the s te off ce to the e ectron c Remote Data Capture system (eRDC) system, hosted on the Un vers ty of B rm ngham server. The secur ty of the System s governed by the po c es of the Un vers ty of B rm ngham. The Un vers ty's Data Protect on Po cy and the Cond t ons of Use of Comput ng and Network Fac t es set out the secur ty arrangements under wh ch sens t ve data shou d be processed and stored. The Study Centre has arrangements n p ace for the secure storage and process ng of the study data wh ch comp y w th the Un vers ty of B rm ngham po c es.

The System ncorporates the fo ow ng secur ty countermeasures:

- Phys ca secur ty measures: restr cted access to the bu d ng, superv sed ons te repa rs and storages of back up tapes/d sks are stored n a f re proof safe.
- Log ca measures for access contro and pr v ege management: nc ud ng restr cted access b ty, access contro ed servers, separate storage of non dent f ab e data etc.
- Network secur ty measures: nc ud ng s te f rewa s, ant v rus software, separate secure network protected host ng etc.

- System Management: the System sha be deve oped, mp emented and ma nta ned by the Un vers ty of B rm ngham
- System Des gn: the system sha compr se of a database and a data entry app cat on w th f rewa s, restr cted access, encrypt on and ro e based secur ty contro s.
- Operat ona Processes: the data w be processed and stored w th n the Un vers ty of B rm ngham.
- Data process ng: Stat st c ans w on y have access to anonym sed data, f requ red
- System Aud t: The System sha benef t from the fo ow ng nterna /externa aud t arrangements:
    - Interna aud t of the system
    - Per od c IT r sk assessment
- Data Protect on Reg strat on: The Un vers ty of B rm ngham has Data Protect on Reg strat on to cover the purposes of ana ys s and for the c asses of data requested. The Un vers ty's Data Protect on Reg strat on number s Z6195856.

Arch v ng

It s the respons b ty of the CI to ensure a essent a tr a documentat on and source documents (e.g. part c pants' hosp ta notes, cop es of CRFs etc.) at the r s te are secure y reta ned for at east 25 years.

6.4 Adverse Event Reporting

Report ng Requ rements

The co ect on and report ng of Adverse Events (AEs) w be n accordance w th the UK Po cy Framework for Hea th and Soc a Care Research and the requ rements of the Hea th Research Author ty (HRA). Def n t ons of d fferent types of AEs are sted n the tab e of abbrev at ons and def n t ons. The Invest gator shou d assess the ser ousness and causa ty (re atedness) of a AEs exper enced by the tr a part c pant th s shou d be documented n the source data w th reference to the protoco .

Adverse Events (AE)

There are certa n AEs wh ch are common y expected n part c pants undergo ng surg ca management of m scarr age. As these events are we character sed, t s h gh y un ke y that th s tr a w revea any new safety nformat on re at ng to th s ntervent on. The record ng of se ected AEs w therefore not affect the safety of part c pants or the a ms of the tr a .

AE that w be recorded n the Case Report Form (CRF) w nc ude: uter ne perforat on, cerv ca trauma, b adder njury, comp cat ons of oca anaesthes a, anaphy ax s,

d ssem nated ntravascu ar coagu at on, b eed ng (as est mated b ood oss n m and those women requ r ng b ood transfus on), pe v c nfect on and unp anned hosp ta adm ss on.

Ser ous Adverse Advents (SAE)

A events wh ch meet the def n t on of ser ous w be co ected and recorded n the part c pant notes and the Case Report Form (CRF). SAEs w n add t on be reported to the tr a s off ce mmed ate y and w th n 24 hours of be ng made aware of the event.

An SAE s an untoward event wh ch:

Resu ts n death.

Immed ate y threatens the fe of the part c pant*.

Resu ts n hosp ta sat on or a onger than ant c pated stay n hosp ta .

Resu ts n a pers stent or s gn f cant d sab ty.

*L fe threaten ng n the def n t on of a Ser ous Adverse Event or Ser ous Adverse React on refers to an event n wh ch the part c pant was at r sk of death at the t me of the event. It does not refer to an event wh ch hypothet ca y m ght have caused death f t were more severe. Important adverse events/react ons that are not mmed ate y fe threaten ng or do not resu t n death or hosp ta sat on but may jeopard se the part c pant or may requ re ntervent on to prevent one of the other outcomes sted n the def n t on above, shou d a so be cons dered ser ous.

Report ng per od

The report ng per od for AEs s up to 6 weeks post ntervent on.

Record ng of AEs

Se ected AEs shou d be recorded n accordance w th the AE CRF. Records of AEs shou d be subm tted v a the tr a e ectron c Remote Data Capture system (eRDC) as soon as poss b e.

Record ng of SAEs

AEs def ned as ser ous and wh ch requ re report ng as an SAE shou d be reported on an SAE Form. When comp et ng the form, the PI w be asked to def ne the causa ty and the sever ty of the AE.

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship, however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship; there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

On becom ng aware that a part c pant has exper enced an SAE, the member of the research team shou d report the SAE to the s te off ce. Where an SAE Form has been comp eted by someone other than the CI, the or g na SAE form w be requ red to be counters gned by the CI to conf rm agreement w th the causa ty and sever ty assessments.

On rece pt of an SAE Form, the Ch ef Invest gator (CI) or de egate(s) w ndependent y determ ne the ser ousness and causa ty of the SAE. An SAE judged by the CI or members of the research team to have a reasonab e causa re at onsh p w th the ntervent on w be regarded as a re ated SAE. The causa ty assessment g ven by the members of the research team w not be downgraded by the CI. If there s d sagreement n causa ty assessment, the op n on of both part es w be documented, and where the event requ res further report ng, the op n on w be prov ded w th the report. A re ated SAEs w be assessed for expectedness. If the event s unexpected (.e. s not def ned n the protoco as an expected event) t w be c ass f ed as an unexpected and re ated SAE.

On rece pt of an SAE, the research team w a ocate each SAE form w th a un que reference number and enter th s onto the SAE form. The SAE reference number w be quoted on a correspondence and fo ow up reports regard ng the SAE and f ed w th the SAE n the Tr a Management F e.

<u>Prov s on of fo ow up nformat on</u>

Fo ow ng report ng of an SAE for a part c pant, the part c pants shou d be fo owed up unt reso ut on or stab sat on of the event. Once the SAE has been reso ved, a fo ow up nformat on has been rece ved and the paperwork s comp ete, the or g na SAE form that was comp eted at s te must be returned to the S te F e.

Report ng to the Research Eth cs Comm ttee

The research team w report a events categor sed as Unexpected and Re ated SAEs to the ma n Research Eth cs Comm ttee (REC) w th n 15 days. The ma n REC w be not f ed mmed ate y f a s gn f cant safety ssue s dent f ed dur ng the course of the tr a .

Invest gators

Deta s of a Unexpected and Re ated SAEs and any other safety ssue wh ch ar ses dur ng the course of the tr a w be reported to the CI. A copy of any such correspondence shou d be f ed n the s te f e and Tr a Management F e.

Tr a Overs ght

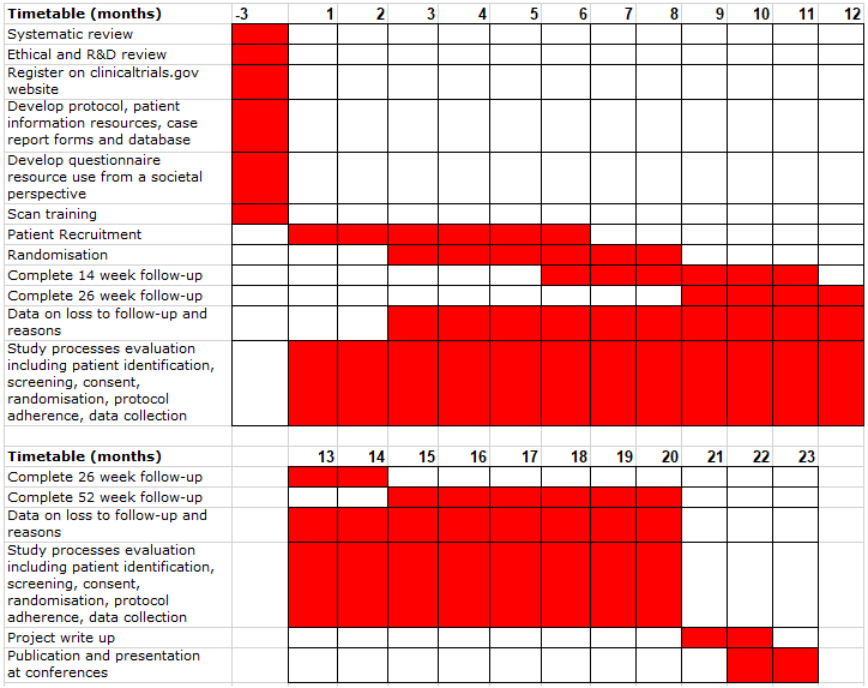
The sponsorsh p overs ght comm ttee (see be ow) w rev ew SAEs per od ca y. The tr a management group (page 2) w a so be convened to rev ew study recru tment and safety data and w adv se on further enro ment.

Sponsorsh p Overs ght Comm ttee

Matthew Boazman	Execut ve D rector for Strategy and Innovat on
Jeremy K rk	D rector of R & D (BCH)
F ona Reyno ds (CHAIR)	Ch ef Med ca Off cer
L z Adey	Head of R&D
He en W amson C n ca	Tr a s Pharmacy Lead
Sarah Hadf e d	R&D De very and Comp ance Manager
Andy Ewer	D rector of R & D (BWH)
Pame a Kearns	D rector of CRCTU

6.5 Timescales

P ease refer to the GANTT chart be ow to nform t me sca es based on 6 months of recru tment.



7. References

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A7.2: Patient Information Leaflet

Tommy's
Together, for every baby

UNIVERSITY OF BIRMINGHAM

NHS
Birmingham Women's and Children's
NHS Foundation Trust

The HYMMN Trial
(Hysteroscopic Miscarriage ManagemeNt)

Participant Information Sheet

Thank you for taking the time to read this information sheet. We understand that this will be a very difficult time for you. This leaflet will explain what is happening, about the treatments available and a research study that you can take part in to try and help us find out which is the best way to help women who are in this situation. Your doctor will also talk to you about the treatment options available.

Why am I being given this leaflet?

We are sorry that you have had a miscarriage. You have been given this leaflet because you have chosen non-surgical management of your miscarriage and desire another pregnancy. We are undertaking a study to see if we can improve non-surgical treatment of miscarriage, especially with regards to shortening the time taken to become pregnant again and reducing symptoms such as bleeding that may affect your quality of life.

Non-surgical management comprises:

1. Expectant management (involving waiting for your body to naturally pass the miscarriage)
2. Medical management (where medications are given to speed the miscarriage process up)

Unfortunately, these options do not guarantee complete removal of the miscarriage. Retained products of conception (RPOC) are found in up to 20% of women following a miscarriage. There is no agreed treatment for RPOC. Sometimes women are given medical drug treatment to induce a miscarriage or surgical management, which involves a small suction tube being passed vaginally into the womb to remove the miscarriage, usually under general anaesthetic i.e. with you asleep.

These treatment options may not be effective and prolong symptoms such as bleeding and pain, which impact upon quality of life. In addition, chronic infection due to the RPOC or repeated medical or surgical treatments may cause damage and scar the womb lining, leading to delayed or permanently impaired fertility.

We therefore want to make you aware of our research study that aims to improve how we recognise and treat these retained products of conception (RPOC) called the **H**ysteroscopic **M**iscarriage **M**anagemen**N**t (HYMMN) trial.

What is the purpose of this study?

We want to see if there is a role in routinely scanning women after miscarriage to see if RPOC are present. Based on the information you give us about yourself, this will help determine if some women are at higher risk of RPOC than others.

The next part of this study involves the introduction of a new treatment pathway for RPOC. Initial research suggests that using a specially designed miniature telescope placed inside the womb (hysteroscopy) to remove RPOC may be associated with lower rates of adverse bleeding, shorter time to the next pregnancy and higher pregnancy rates following miscarriage. Furthermore, due to the latest innovations in surgical equipment, this procedure can be done in the outpatient setting, without the need and risks of a general anaesthetic. It is therefore important that if you wish to be included in the trial, that you want to try for a pregnancy after your miscarriage.

We therefore intend to investigate the role of routine ultrasound after miscarriage for RPOC and intend to see how effective this new pathway using hysteroscopy is, when compared against current management.

What happens if I agree to participate in this study?

You will be asked to answer some questions about yourself, your medical history and any previous pregnancies. This information will determine whether or not you are eligible for the trial. If eligible and you would like to proceed, we will ask you to sign a consent form. You can have as much time as you need to consider whether you want to take part. This means you can take this leaflet home with you and contact us at any point during the next few weeks if you decide to participate. We will ask you to attend the hospital again at a time convenient to you to sign the study consent form.

We will then perform a transvaginal ultrasound scan 8 weeks after the diagnosis of your miscarriage to see if you have any RPOC. If there are RPOC present, you will be randomised to have a 50% chance of either receiving an outpatient hysteroscopy or being managed according to standard treatment, which may involve expectant, medical or surgical management. If randomised to outpatient hysteroscopy, this will be performed as soon as possible. You will be asked to fill in a questionnaire regarding your experience of hysteroscopy.

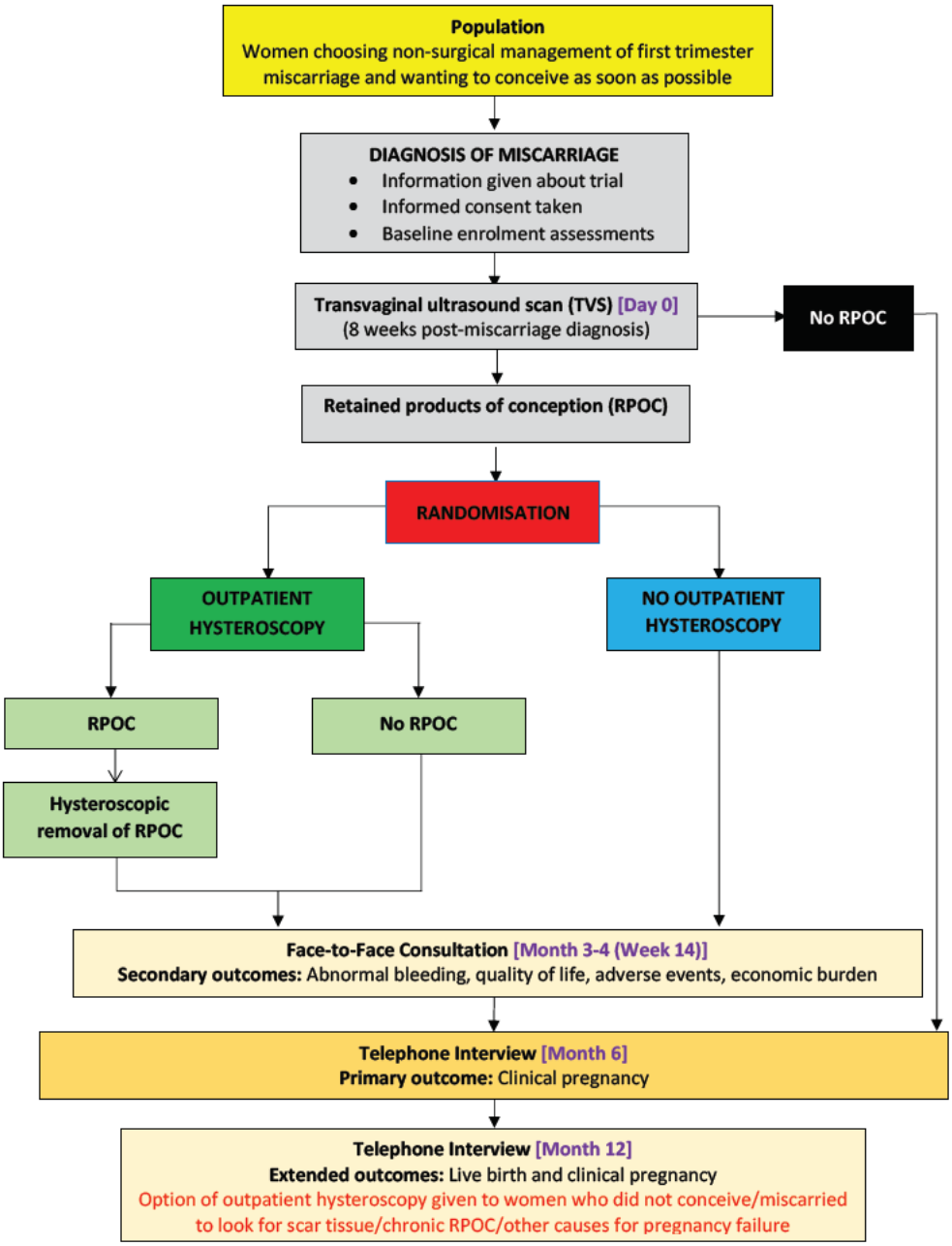
If you are found to have RPOC, you will be seen 14 weeks after your scan. We will ask about your symptoms, quality of life, and hospital/GP visits.

All patients who entered the trial, no matter if RPOC were found or not, will be telephoned at 6 months after their transvaginal ultrasound scan. Here, we will ask if you have become pregnant since your initial scan with us and ask you further questions based on your answer. We will finally call you 6 months after this to again ask you questions on any pregnancies that have occurred. Your answers will help us determine if women who had a hysteroscopy have a shorter time to pregnancy and resolution of adverse symptoms compared to women who did not.

At this point, if you have had a miscarriage or not fallen pregnant since you entered into the trial, no matter what treatment option you were originally given, you will be offered the chance to undergo another hysteroscopy to see if there is any scar tissue, chronic RPOC or other conditions affecting the womb lining which may be contributing to pregnancy failure. Following this, you will be discharged from the trial. Should you want to see us in person, this can be arranged too.

A summary of the study findings will be sent to you if you agree to this on the consent form.

Please refer to the diagram below which summarises the trial process:


Population
Women choosing non-surgical management of first trimester miscarriage and wanting to conceive as soon as possible
DIAGNOSIS OF MISCARRIAGE
Information given about trial
Informed consent taken
Baseline enrolment assessments
Transvaginal ultrasound scan (TVS) [Day 0]
(8 weeks post-miscarriage diagnosis)
No RPOC
Retained products of conception (RPOC)
RANDOMISATION
OUTPATIENT HYSTEROSCOPY
NO OUTPATIENT HYSTEROSCOPY
RPOC
No RPOC
Hysteroscopic removal of RPOC
Face-to-Face Consultation [Month 3-4 (Week 14)]
Secondary outcomes: Abnormal bleeding, quality of life, adverse events, economic burden
Telephone Interview [Month 6]
Primary outcome: Clinical pregnancy
Telephone Interview [Month 12]
Extended outcomes: Live birth and clinical pregnancy
Option of outpatient hysteroscopy given to women who did not conceive/miscarried to look for scar tissue/chronic RPOC/other causes for pregnancy failure

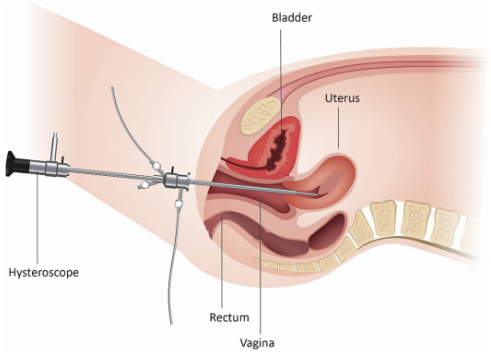
What does a transvaginal ultrasound scan involve?

A transvaginal ultrasound scan is a routine scan often used to identify early pregnancies. The procedure involves placing a plastic probe on your tummy, followed by a separate probe into the vagina, to identify whether there are RPOC inside the womb. The procedure will last between 5-10 minutes and whilst it will feel uncomfortable, you should not feel pain.

What does outpatient hysteroscopy involve?

Outpatient hysteroscopy is a simple technique that ***does not*** require you to be put to sleep under general anaesthetic in an operating theatre. For this reason you can eat and drink before arriving for your procedure. We recommend taking paracetamol and/or ibuprofen approximately 1 hour before your 30-minute appointment.

The procedure will be performed in a single-patient outpatient treatment room where you will be required to lie flat on a special couch where your legs will be placed apart in leg rests. In addition to a doctor, there may be up to 3 nurses/healthcare assistants. The doctor will place a tiny telescope (called a hysteroscope) into the vagina, through the cervix (entrance to the womb) and into the womb itself. Sometimes a speculum is placed into the vagina (similar to when a smear test is done) to help find the cervix. A speculum may also be used to give a local anaesthetic injection if the cervix is very narrow, in order to 'numb' it. If there are RPOC in the womb, then a slightly larger telescope is used, which has an instrument called a 'morcellator'. This 'morcellator' trims and retrieves RPOC under direct vision, minimising the damage to the womb lining. The tissue that is removed is sent for examination under a microscope to confirm the presence of RPOC.



It is not possible to 'numb' the entire womb so you may experience some abdominal discomfort during the procedure which most women describe as cramping period-like pain. The discomfort experienced varies from woman to woman but is usually described as mild to moderate although some women may experience more severe cramping pain. The procedure usually takes approximately 10 minutes to complete and you can request the treatment to be stopped at any time if the discomfort is not tolerable, although this situation is unusual.

Following the procedure you can sit in our recovery room where you will be encouraged to drink,

have light refreshments and be given pain killers if required, before going home. Any abdominal discomfort should settle over the next 24 hours and you will be given simple pain killers to control this. You may have some vaginal spotting, or fresh blood loss/watery discharge which can last a day or two. We advise that you shower rather than use a bath and refrain from sexual intercourse for a few days after the procedure and avoid swimming pools, tampons and vaginal douching for two weeks to avoid the risk of infection. Women can usually go to work the following day, if required.

What are the advantages of taking part?

If you are found to have RPOC, then removal of this by hysteroscopy may better remove the RPOC compared to other treatments, therefore reducing your risk of developing scarring of the lining of the womb and shortening the time to and improving the chances of your next pregnancy. If you have not fallen pregnant or had a miscarriage a year after being randomised into the trial, no matter what treatment option you have had, you will be offered a hysteroscopy. This can be used to see if there are any problems inside the womb that may be affecting your chances of getting pregnant.

What are the risks of participating in this study?

Any medical procedure has risks and benefits. Hysteroscopy is incredibly safe with a very low risk of complications. Minor risks include feeling sick, being sick, fainting. Other rare complications include excessive pelvic pain and severe or persistent bleeding. The risk of infection (which may include symptoms such as strong-smelling discharge, feeling unwell with shivers and a high temperature) is uncommon (1 in 400 women) and is easily treated with antibiotics. These symptoms may occur immediately or may take up to 14 days to develop. Although extremely rare, sepsis can occur following a hysteroscopy procedure, where symptoms include feeling extremely unwell within hours of the procedure - if this occurs, you should attend A&E immediately for an assessment.

The risk of damage to the wall of the womb is a more serious but rare (less than 8 in 1000 women) complication. You may need to stay in hospital overnight for close observation in case you develop complications. Usually nothing more needs to be done, and it will heal by itself but if there is significant bleeding or there are concerns about damage to other organs e.g. bladder or bowel, then you will need a further operation to correct the complication (less than 1 in 1000). In some cases, the procedure cannot be completed because it is impossible to insert the hysteroscope through the neck of the womb and inside the womb – this is very rare.

What are my rights?

You have the right to be given all-important information about your condition, your treatment, the HYMMN trial and what you will be asked to do if you decide to take part. You should only agree to take part if you feel happy that you know enough about all of these things. You do not have to take part in the study if you do not want to. If you decide not to take part in this research, your doctor will respect your decision and advise you of the current standard treatment options that are available. If you do agree to take part, **you are entitled to withdraw from the study at any time without having to give a reason**. This will not affect your medical care in any way either.

How will we use information about you?

We will need to use information from you for this research project. This information will include your initials. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What happens to my data?

Whether or not you take part in the study, you have the right to confidentiality of your medical records (although we will inform your GP that you are taking part in this study). The written data will be identified only by your initials and code number. Any physical paperwork containing identifiable data will be kept in an access-controlled, secured room inside the Birmingham Women's and Children's NHS Foundation Trust in a secure locked office.

Birmingham Women's and Children's NHS Foundation Trust will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Birmingham Women's and Children's NHS Foundation Trust will keep identifiable information about you from this study for up to 10 years after the study has finished.

Your written data will be anonymised and uploaded onto a secure password-protected electronic server, hosted by the University of Birmingham. Individuals from the University of Birmingham and/or regulatory organisations may look at your medical and research records to check the accuracy of the research study. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance. We will not share your data with any third party. No named information about you will be published in the trial report.

What are your choices about how your information is used?

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

How will my personal data be kept secure?

Electronic data will be kept on secure, encrypted IT servers within the University of Birmingham. The University takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Our staff receive regular data protection training, and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law.

The University has an Information Security Management System based on ISO27001 with a range of controls covering the protection of personal information. Annual security awareness training is

mandatory for staff and the University is accredited under the NHS Information Governance Toolkit, the Payment Card Industry Data Security Standard and is in the process of gaining Cyber Essentials Plus for defined services.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from [https://bwc.nhs.uk/research/]
- by asking one of the research team
- by sending an email to [bwc.research@nhs.net], or
- by ringing us on [0121 333 8751]

You can also contact our Data Protection Officer at Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH if you have any questions.

What support do I have available to me?

You should have been given a leaflet from the Miscarriage Association by one of our nursing staff, detailing the support available to you following the diagnosis of a miscarriage. Please call either the Early Pregnancy Assessment Unit (EPAU) on 0121 335 8090 during working hours (0815-1730 Monday-Friday, 0830-1230 Saturday-Sunday) or Ward 8 on 0121 335 8180 (24-hr service), in an emergency, who will be advice, or ask you to come in, for assessment by a doctor. Should you have any questions about the HYMMN trial, please contact the Tommy's Research Team on 07753421214.

Who can I contact for further details?

If you have any further questions related to the HYMMN study please contact:

Dr. Preth De Silva
Clinical Research Fellow to Professor Justin Clark
Birmingham Women's Hospital
[redacted]

If you have any concerns or problems with the care you have received as part of this trial, then please contact our Patient Advice and Liaison Service (PALS) service on:

0121 333 8403 / 0121 333 8505 (Monday-Friday 0830-1630) or bwc.pals@nhs.net

A7.3: Informed Consent Form

Participant trial number: ☐☐☐ — ☐☐☐

Tommy's
Together, for every baby

UNIVERSITY OF BIRMINGHAM

NHS
Birmingham Women's and Children's
NHS Foundation Trust

HYMMN: HYsteroscopic Miscarriage ManagemeNt Trial

PARTICIPANT CONSENT FORM

Chief Investigator: Professor T Justin Clark

	Initial each box to confirm consent
I confirm that I have read and understand the patient information leaflet (version _._, dated __/___/____) for the HYMMN trial. I have had the opportunity to ask questions and these have been answered satisfactorily.	☐
I understand that my participation in the trial is voluntary and I am free to withdraw my consent at any time without my treatment or legal rights being affected.	☐
I understand that the information collected will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that even if I withdraw from the study, information already collected about me may be included in the final study analysis after being anonymised.	☐
I understand that relevant sections of my medical notes (both paper and electronic) and data collected during the study may be looked at by individuals from the research team, representatives of the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have direct access to my records.	☐
I understand that the information held by the NHS may be used to keep in touch with me and follow up my status for the purposes of the study.	☐
I understand that researchers for the HYMMN Trial based at my hospital or at the University of Birmingham may contact me by telephone, mobile telephone, post or e-mail to request information.	☐
I agree for my General Practitioner to be informed about my participation in the study.	☐
I understand the information that I have been given about the HYMMN trial and I agree to take part.	☐
I agree to being contacted in the future to ask for my consent to future studies, and that I may be traced through the NHS databases and GP records. ☐ Yes ☐ No	☐
I agree to receive the end of study report, detailing the findings of the study. ☐ Yes ☐ No	☐

Name of Participant: _____ **Date:** _____ **Signature:** _____

Name of Researcher: _____ **Date:** _____ **Signature:** _____

For the translator (if required):
I confirm that I have interpreted the study information to the best of my ability and ensured the patient fully understands everything that has been given to them to read/verbally explained to them

Name of translator: _____ **Date:** _____ **Signature:** _____

Copy One for Patient, Copy Two for Notes, Copy Three for Trial Office

A7.4: Baseline Questionnaire

Baseline Questionnaire

Record ID	_____
Pat ent ID (pat ent n t a s, m ted to two e.g. "AB" fo owed by "-" and the subsequent enro ment number e.g. "001")	_____ (e.g. AB-001)
Date	_____
C n c an Name	◯ Preth De S va ◯ Oonagh P cker ng ◯ Nata e Woodhead ◯ Pau Sm th ◯ Just n C ark ◯ Other
If "other" p ease state c n c an name	_____

Before starting, please confirm eligibility criteria:	
Aged 18 or over	◯ Yes ◯ No
Gestat on ≤14 weeks	◯ Yes ◯ No
Pat ent want ng to conce ve as soon as poss b e	◯ Yes ◯ No
Are f nd ngs susp c ous of mo ar pregnancy or sept c m scarr age?	◯ Yes ◯ No
Pat ent choos ng expectant or med ca treatment?	◯ Yes ◯ No
Pat ent ab e to understand spoken and wr tten Eng sh	◯ Yes ◯ No

1. Introductory Questions	
Has the consent form been s gned nd cat ng that the pat ent agrees to part c pate n the tr a ?	◯ Yes ◯ No
If no, why has the pat ent dec ned enro ment?	◯ Does not want to be scanned n 8 weeks ◯ Does not want to undergo outpat ent hysteroscopy ◯ Does not want to part c pate n fo ow-up ◯ Does not fee comfortab e part c pat ng n a c n ca tr a ◯ Has concerns about data co ect on/storage ◯ Other ◯ Prefers not to say

If other, p ease state reason	_____

2. Patient Demographics

Pat ent age	_____
Ethn c ty	◯ As an or As an Br t sh (Inc udes any As an background, for examp e, Bang adesh , Ch nese, Ind an, Pak stan) ◯ B ack, Afr can, B ack Br t sh or Car bbean (Inc udes any B ack background) ◯ M xed or mu t p e ethn c groups (Inc udes any M xed background) ◯ Wh te (Inc udes any Wh te background) ◯ Another ethn c group (Inc udes any other ethn c group, for examp e, Arab) ◯ Prefer not to say
Body Mass Index (BMI)	_____

3. Miscarriage Details

Date of m scarr age d agnos s	_____ (Date of conf rmat on f had prev ous scan)
Gestat ona age at m scarr age d agnos s to the nearest week based on scan f nd ngs (type 0 f not recorded)	_____
If "0", gestat ona age from ast menstrua per od (LMP), to the nearest week	_____
M scarr age type	◯ M ssed ◯ Incomp ete ◯ Comp ete
Chosen m scarr age treatment	◯ Comp ete - does not requ re treatment ◯ Expectant ◯ Med ca
Concept on	◯ Natura ◯ Intrauter ne nsem nat on ◯ In-v tro fert sat on

4. Pregnancy History

Number of m scarr ages (nc ud ng th s one)	_____
Number of ve b rths	_____
Number of st b rths	_____
Number of ectop c pregnanc es/pregnanc es of unknown ocat on (PUL)	_____
Number of term nat ons of pregnancy (surg ca or med ca)	_____

5. Risk Factors

Prev ous d agnos s of reta ned products of concept on?	◯ Yes ◯ No
Has the pat ent ever been d agnosed w th any of the fo ow ng:	☐ Submucosa f bro d(s) ☐ Intramura f bro d(s) ☐ Subserosa f bro d(s) ☐ Intrauter ne adhes ons ☐ Uter ne septum ☐ B cornuate uterus ☐ Un cornuate uterus ☐ Uter ne d de phys ☐ Cerv ca nsuff c ency
Has the pat ent ever undergone any of the fo ow ng procedures:	☐ Myomectomy - hysteroscop c ☐ Myomectomy - aparoscop c ☐ Myomectomy - abdom na ☐ Myomectomy - vag na /cerv ca ☐ Intrauter ne adhes o ys s ☐ Uter ne septum resect on ☐ Cerv ca suture (vag na / aparoscop c/abdom na) ☐ LLE Z/cone b opsy
Number of prev ous surg ca evacuat ons of the uterus (nc ud ng manua vacuum asp rat ons (MVA))	_____
Number of prev ous surg ca term nat ons of pregnancy (S oP)	_____
Number of prev ous d atat on and curettage (D&C)	_____
Number of Caesarean sect ons	_____

6. Additional Comments

Add t ona comments

A7.5: Scan Questionnaire (to be filled by patient)

Ultrasound Scan

Thank you for agreeing to participate in the HYMMN trial. We would be grateful if you could fill in the following short questionnaire to help us improve how we diagnose retained products of conception.

Q1. Would you describe the procedure as (please tick one option only):

Very Acceptable ◯
Somewhat Acceptable ◯
Neither Acceptable or Unacceptable ◯
Somewhat Unacceptable ◯
Very Unacceptable ◯

Q2. In the future, would you recommend this scan to other women to check for the presence of retained pregnancy tissue following miscarriage treatment?

Yes ◯
Or
No ◯

Thank you for taking the time to complete this questionnaire

Patient Trial Number: Date completed:

A7.6: Scan Questionnaire (to be filled by clinician)

Ultrasound Scan

Thank you for agreeing to participate in the HYMMN trial. We would be grateful if you could fill in the following short questionnaire to help us improve how we diagnose retained products of conception.

Q1. Would you describe the procedure as (please tick one option only):

Very Acceptable ◯
Somewhat Acceptable ◯
Neither Acceptable or Unacceptable ◯
Somewhat Unacceptable ◯
Very Unacceptable ◯

Q2. In the future, would you recommend this scan to other women to check for the presence of retained pregnancy tissue following miscarriage treatment?

Yes ◯
Or
No ◯

Thank you for taking the time to complete this questionnaire

Patient Trial Number: Date completed:

A7.7: Hysteroscopy Questionnaire (to be filled by patient)

Outpatient Hysteroscopy

Thank you for agreeing to participate in the HYMMN trial. We would be grateful if you could fill in the following short questionnaire to help us improve how we treat retained products of conception.

Q1. We would like to assess how much abdominal pain you experienced during your treatment. Please place a mark (X) on the line below to indicate how much pain you had. The left end of the line represents "no pain at all" and the right end of the line represents "as much pain as you could possibly imagine".

No pain at all _____ Worst pain imaginable

Q2. Would you describe the procedure as (please tick one option only):

Very Acceptable ◯
Somewhat Acceptable ◯
Neither Acceptable or Unacceptable ◯
Somewhat Unacceptable ◯
Very Unacceptable ◯

Q3. Would you have the same treatment again?

Yes ◯
or
No ◯

Q4. If you were to have this procedure again, would you rather have had a general anaesthetic (i.e. be put to sleep for the procedure)?

Yes ◯
Or
No ◯

Q5. Please give any comments about your treatment experience:

_____

_____

_____

Thank you for taking the time to complete this questionnaire

Patient Trial Number: Date completed:

A7.8: Hysteroscopy Questionnaire (to be filled by clinician)

RPOC - Hysteroscopy Questionnaire

Record ID	_____
Introduction	
Pat ent ID	_____
D d the pat ent attend and consent to today's hysteroscopy?	◯ Yes ◯ No
If no, why not	◯ DNA ◯ Pregnant ◯ Does not want hysteroscopy ◯ Other
Date	_____
C n c an	◯ Preth De S va ◯ Pau Sm th ◯ Just n C ark
Details of Hysteroscopy (to be filled by clinician)	
Number of days s nce m scarr age conf rmed	_____
Has the pat ent had a per od s nce her scan?	◯ Yes ◯ No
Were you susp c ous of RPOC on today's hysteroscopy?	◯ Yes ◯ No
How easy on a sca e of 0-100 where 0 s mposs b e and 100 s ncred b y easy was morce at on of RPOC today?	Imposs b e (0) — Incred b y easy (100) *(Place a mark on the scale above)*
Was hysteroscop c morce at on successfu ?	◯ Yes ◯ No
If not, why not	_____
If not, what s the p an?	_____
How ong d d hysteroscopy take from nsert on of the hysteroscope nto the vag na/cerv x to remova of the hysteroscopy from the vag na/cerv x (n seconds)?	_____
D d you adm n ster oca anaesthes a?	◯ Yes ◯ No

D d you perform cerv ca d atat on?	◯ Yes ◯ No
D d you perform vag noscopy? (e ther w thout adm n ster ng or after adm n ster ng oca anaesthes a)	◯ Yes ◯ No
Do you have any add t ona comments about today's hysteroscopy?	_____
Were RPOC conf rmed at h sto ogy?	◯ Yes ◯ No

Please input the following data from the questionnaire filled in by the patient

Form comp eted?	◯ Yes ◯ No
PA IEN Q1. We wou d ke to assess how much abdom na pa n you exper enced dur ng your treatment. P ease p ace a mark (X) on the ne be ow to nd cate how much pa n you had. he eft end of the ne represents "no pa n at a " and the r ght end of the ne represents "as much pa n as you cou d poss b y mag ne".	No pa n at a (0) — Worst pa n mag nab e (100) *(Place a mark on the scale above)*
PA IEN Q2. Wou d you descr be the procedure as:	◯ Very Acceptab e ◯ Somewhat Acceptab e ◯ Ne ther Acceptab e or Unacceptab e ◯ Somewhat Unacceptab e ◯ Very Unacceptab e
PA IEN Q3. Wou d you have the same treatment aga n?	◯ Yes ◯ No
PA IEN Q4. If you were to have th s procedure aga n, wou d you rather have had a genera anaesthet c (.e. be put to s eep for the procedure)?	◯ Yes ◯ No
PA IEN Q5. P ease g ve any comments about your treatment exper ence:	_____

A7.9: Symptom, satisfaction of treatment pathway, quality of life and healthcare resource use questionnaire

14 Week Follow-Up Questionnaire

Thank you for agreeing to participate in the HYMMN trial. We would be grateful if you could fill in the following short questionnaire to help us improve how we treat retained products of conception.

Q1. Before your miscarriage, were your periods: Regular ◯ or Irregular ◯

Q2. Are your periods now:

Regular ◯ ----------> How soon after your miscarriage did they become regular? __ weeks

or

Irregular ◯

Q3. Before your miscarriage, did you have bleeding between your periods? No ◯ or Yes ◯

Q4. Since your miscarriage, are you having bleeding between your periods?

No ◯

or

Yes ◯ ----------> Is this bleeding either light ◯, heavy some days ◯, or heavy most days? ◯

Q5. Is your bleeding pattern now: Acceptable ◯ or Unacceptable ◯

Q6. Before your miscarriage, were your periods: Light ◯ or Normal ◯ or Heavy ◯

Q7. Since your miscarriage, are your periods: Light ◯ or Normal ◯ or Heavy ◯

Q8. Since your miscarriage, have you experienced any new vaginal discharge? No ◯ or Yes ◯

Q9. Since your miscarriage, have you experienced any new abdominal pain, requiring pain medication? No ◯ or Yes ◯

Q10. In the first month after being diagnosed with retained pregnancy tissue on ultrasound scan, were you ever given antibiotics for a urine or womb infection? No ◯ or Yes ◯

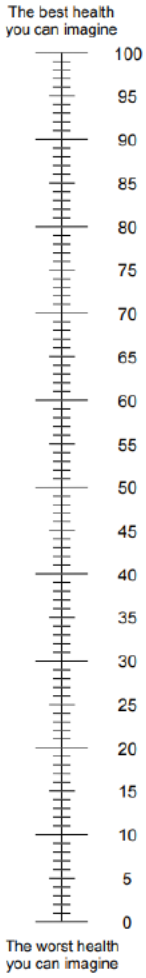
Q11. We would like to assess how satisfied you are with your treatment. Please place a mark (X) on the line below to indicate your level of satisfaction. The left end of the line represents “completely dissatisfied” and the right end of the line represents “totally satisfied”.

Completely DISSATISFIED _____ Totally SATISFIED

Please turn over (page 1/3) →

Patient Trial Number: Date completed:

Q12. We would like to know how good or bad your health is TODAY. The scale below is numbered from 0 to 100. 100 represents the best health you can imagine. 0 represents the worst health you can imagine. Please mark an X on the scale to indicate how your health is TODAY.



Now, please write the number you marked on the scale here: _____

Please turn over (page 2/3) →

Patient Trial Number: Date completed:

Q13. Since your miscarriage:

A) How many times have you seen your GP? __

B) How many times have you attended the early pregnancy unit? __

C) How many times have you attended accident and emergency? __

D) How many days have you taken off work? (Use 0.5 for half days) __

E) Have you been admitted to a hospital ward overnight?

No ◯
or
Yes ◯ ----------> How many nights did you spend in hospital, in total? __

Q14. Since you were diagnosed with retained pregnancy tissue, how many scans have you had? __

Q15. Since you were diagnosed with retained pregnancy tissue, have you had any additional treatment (not including hysteroscopy, if you were allocated this as part of the trial)? If you have had treatment, please indicate next to the ◯, in the __ provided, how many courses or times you received this treatment.

No ◯
or
Yes ◯ ----------> Antibiotics ◯ __
Miscarriage tablets (oral, vaginal or rectal) ◯ __
Surgery ◯ __

Thank you for taking the time to complete this questionnaire

Patient Trial Number: Date completed: