Practical guideline in office hysteroscopy
promoted by "Italian Society of Gynecological Endoscopy" (SEGI)

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EXECUTIVE SUMMARY OF RECCOMENDATIONS

PROCEDURAL ASPECTS

Setting

All gynaecology units should provide a dedicated ambulatory hysteroscopy service to aid management of women with abnormal uterine bleeding, infertility and suspicious of intracavitary abnormalities. The procedure performed in such setting is defined *"office hysteroscopy"*. There are clinical and economic benefits associated with this type of service **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION A).**

The physician has to have the necessary skills and expertise to carry out hysteroscopy **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

Patient information has to be provided before the procedure and her written consent must be taken **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

Diagnostic hysteroscopy and some operative hysteroscopic procedures should be conducted outside of the formal operating theatre setting in an appropriately equipped and staffed ambulatory guarantying patient's safety and privacy **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION B)**

Oral analgesia

Routine use of opiate analgesia before office hysteroscopy has to be avoided as it may cause adverse effects **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION A).**

The use of a standard dose of non-steroidal anti-inflammatory agents (NSAIDs) should be considered around 1 hour before the scheduled office hysteroscopy with the aim of reducing pain in the immediate post-procedural period **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION B).**

Topical anesthesia

Routine instillation of local anesthetic into the uterine cavity and topical application of local anesthetic on ectocervix should be avoided as it does not reduce pain during diagnostic hysteroscopy **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION B).**

Injectable local anesthetic

Application of local anesthetic into and or around the cervix is associated with a reduction of the pain experienced during office diagnostic hysteroscopy. Since the clinical significance of such reduction in pain is unclear it should not be routinely administered **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION B).**

Paracervical injection of local anesthetic is associated with a reduction of the pain experienced during office hysteroscopy, mostly in postmenopausal women. Technical and technological improvements may diminish any advantage of paracervical anesthesia. Therefore its routine use should only be considered in selected cases (i.e. when outer diameter greater than 5mm hysteroscopes are being employed) **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION B).**

Conscious sedation

Conscious sedation should not be routinely used in office hysteroscopic procedures as it confers no advantage in terms of pain control and the woman's satisfaction over local anaesthesia. **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION A).**

Life-threatening complications can result from the use of conscious sedation. Appropriate monitoring and staff skills are mandatory if procedures are to be undertaken using conscious sedation **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

Flexible versus rigid hysteroscope

Flexible hysteroscopes are associated with less pain during office hysteroscopy compared with rigid hysteroscopes. However, rigid hysteroscopes may provide better images, fewer failed procedures, quicker examination time and reduced cost. Thus, even though the choice of hysteroscope should be left to the discretion of the operator, for the above mentioned qualities we would recommend rigid instruments mostly when operative procedures need to be performed **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION B).**

Rigid hysteroscope has to be equipped with single or double sheaths according to the chosen distension medium (i.e. single sheath with carbon dioxide and double sheaths with fluid distension medium) **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A)**

Vaginoscopic approach

Vaginoscopy reduces pain during office hysteroscopy, thus reducing the need of sedation and/or anesthesia during office procedures and, increasing the patient compliance.**.** On this basis, vaginoscopy should be the standard technique for office hysteroscopy with fluid distension medium **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION A).**

The use of a vaginal speculum is indicated when anatomical and technological issues overcome the advantages of absence of vaginal instrumentation. **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

Cervical preparation

Routine cervical preparation before office hysteroscopy should not be used in the absence of any evidence of benefit in terms of reduction of pain, rates of failure or uterine trauma **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION A).**

Distensium medium

Uterine distension with normal saline appears to reduce the incidence of vasovagal episodes and

allows office diagnostic hysteroscopy to be completed more quickly. However, for routine office diagnostic hysteroscopy, the choice of distension medium between carbon dioxide and normal saline should be left to the discretion of the operator as neither is superior in reducing pain and in improving image quality **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION A).**

Operative office hysteroscopy, using electrosurgery, requires the use of fluid distension medium to act as both the distension and conducting medium (**LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

Antibiotic prophylaxis

Antibiotic prophylaxis should be avoided (as otherwise requested) before performing office hysteroscopic procedures, since the risk of infectious complications is extremely low and is not affected by the pre-treatment with antibiotics *(***LEVEL OF EVIDENCE III, STRENGH OF THE RECOMMENDATION B).**

USEFULNESS OF HYSTEROSCOPIC EVALUATION IN INFERTILITY WORK-UP

Hysteroscopy as a screening test in the diagnostic work up of infertile couple

Given the low invasiveness and the safety of office hysteroscopy and the desire for the infertile couple to shorten as much as possible he diagnostic period which is often a source of anxiety and uncertainty, it is reasonable to recommend the evaluation of uterine cavity by hysteroscopy in the diagnostic work up of infertile couples **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMMENDATION B).**

Wherever intrauterine diseases are detected, their removal should be performed in order to improve pregnancy outcome **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMMENDATION B)**.

Diagnostic and operative hysteroscopy before IVF and pregnancy rates

Hysteroscopy should be recommended for women with repeated implantation failure **(LEVEL OF EVIDENCE I, STRENGH OF THE RECOMMENDATION A).** Whether a similar beneficial effect applies for women who are going for the first or second IVF needs to be further investigated **(LEVEL OF EVIDENCE III)**. However, a "screening" hysteroscopy should be performed before including patients in an IVF program in order to minimize any negative intrauterine influence on IVF outcome **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMENDATION B).**

Hysteroscopy in women with recurrent miscarriage

Diagnosis and treatment by hysteroscopy of uterine malformations and intrauterine adhesions in such patients may improve live birth rate and ,therefore, their treatment could be recommended **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMENDATION B).**

Evaluating uterine cavity by hysteroscopy in women with recurrent miscarriage is strongly recommended **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMENDATION B)**.

USEFULNESS OF HYSTEROSCOPIC EVALUATION IN WOMEN UNDER TAMOXIFEN TREATMENT

Baseline endometrial evaluation by hysteroscopy

Since the prevalence of precancerous lesions is high in estrogen receptor-positive breast cancer patients before tamoxifen administration, we would suggest screening at baseline by hysteroscopy and, if it is necessary for a better diagnosis, endometrial biopsy **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION B).**

Regular endometrial evaluation by hysteroscopy in asymptomatic women during tamoxifen therapy

It seems reasonable to perform a single hysteroscopy annually in such women in order to reduce the incidence of endometrial lesions. However the lack of significant data on the cost-effectiveness of such innovative approach cannot allow to draw any definitive conclusion **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION C).**

Endometrial evaluation by hysteroscopy in abnormal uterine bleeding

Endometrial evaluation and sampling for histological evaluation are recommended in women receiving tamoxifen therapy with vaginal bleeding in order to recognize and, therefore, reduce the incidence of endometrial cancer as early as possible **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION B).**

Endometrial evaluation by hysteroscopy in asymptomatic women with increased endometrial thickness

Since increasing endometrial thickness is likely to be associated with precancerous endometrial lesions, in asymptomatic women receiving tamoxifen with endometrial thickness $\geq$ 8 mm hysteroscopy should be performed in order to detect endometrial polyp and/or cancer **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION B).**

USEFULNESS OF HYSTEROSCOPIC EVALUATION IN WOMEN WITH ABNORMAL UTERINE BLEEDING (AUB)

Hysteroscopy compared to other techniques in women with AUB

Sonohysterography, hysteroscopy and transvaginal ultrasound are accurate and feasible in diagnosing or excluding endouterine diseases. Hysteroscopy should be always performed in women presenting with AUB, in whom other tests (sonohysterography and/or transvaginal ultrasound) have already reported or have been unable to rule out endouterine pathologies). **(LEVEL OF EVIDENCE III, STRENGHT OF THE RECOMMENDATION B)**.

Postmenopausal women with abnormal uterine bleeding and negative ultrasound

Even though no studies are available on this topic, it is reasonable to recommend evaluation of endometrial cavity by hysteroscopy in case of repeated AUB in such women **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMMENDATION B)**.

Target biopsy during hysteroscopy and accuracy for detecting atypical lesions

Target-eye biopsy is more accurate than blind biopsy, and therefore hysteroscopy with multiple target biopsies should be used in place of blind techniques in the diagnostic work-up for atypical lesions **(LEVEL OF EVIDENCE II, STRENGH OF THE RECOMMENDATION B).**

The possible risk of the spreading of neoplastic cells to the abdominal cavity should not limit the use of hysteroscopy in favour of blind techniques **(LEVEL OF EVIDENCE II, STRENGH OF THE RECCOMENDATION A).**

CONTENTS

1. PURPOSE AND SCOPE

The aim of this guideline is to provide clinicians with up-to-date, evidence-based information regarding office hysteroscopy, both for what concern the ideal setting and the procedural aspects and for what concern the main clinical indications.

There is a part of physicians still unskilled and/or "self-made" on this topic, who started their hysteroscopic activity without any proper theoretical and practical training, but only after seeing a colleague or reading a book and/or few scientific works. Many of the conclusions reached by the present guideline will be found obvious and already routinely applied in daily practice by the most skilled hysteroscopists.

However, we believe that such guideline does represent a relevant platform to improve knowledge and diffusion of the most recent advances in terms of technology, techniques and clinical indications .

2. BACKGROUND

Hysteroscopy (from the greek terms hysteros=uterus, and; scopeo= to look) can be considered a real Copernican revolution of the modern gynaecology, since whilst laparoscopy simply modified the access to the abdominal cavity, hysteroscopy "enlightened" for first time a cramped and dark space, never directly explored until the mid-nineteenth century. The first hysteroscopy was performed in 1869 by Pantaleoni, an Italian doctor, with the aid of Desormeaux's endoscope.

In subsequent years, hysteroscopy remained a curiosity rather than a truly useful clinical technique. It took over 100 years for the clinical importance of hysteroscopy to become apparent, thanks to developments in optic systems and distension media, which made it possible to obtain satisfactory visualization of the uterine cavity.

In the early 1980s, several developments in the technical and instrumental areas made hysteroscopy even less invasive and painful and increased its widespread use reducing the number of hysteroscopies performed in operating room and increasing those performed in ambulatory setting (office hysteroscopy).

In a few years office hysteroscopy showed its definite advantages in comparison with the blind techniques (dilatation and curettage, Vabra, curette) and started to be considered the gold standard technique for the evaluation of uterine cavity.

In the mid-80s, a rapidly growing up of surgical hysteroscopy by means of resectoscope and electrosurgery took place allowing to treat many intrauterine pathologies in women complaining of bleeding, infertility and recurrent miscarriage.

The development of videocamera increased the feasibility of hysteroscopic approach allowing the physician to sit comfortably while performing a diagnostic or operative procedure. However the wide diameter of the resectoscope restricted its use to the operating room under anaesthesia.

In the mid-late 90s, the development of small-diameter hysteroscopes with continuous flow features and operative sheaths have provided the endoscopist not only to examine the cavity but also to take biopsy and treat several benign intrauterine pathologies in a relatively short time using miniaturized instruments without the need of general anaesthesia and operating room (operative office hysteroscopy).

In the last thirty years the rapid spread of endoscopic techniques together with a widening of the conditions for which office hysteroscopy seemed to be clinically relevant have led to:

i) an extreme variability in the mode of performing diagnostic and operative hysteroscopy in terms of set-up, techniques as well as specific instrumentations

ii) a worldwide variable over- or underuse of hysteroscopy due to an extreme confusion regarding its real clinical indications.

This guideline assesses these issues analysing what international literature produced in clinical-care, trying to identify the optimal hysteroscopy service to address the legitimate demands of women's health.

3. METHODS FOR EVIDENCE ASSESSMENT AND REACHING RECOMMENDATIONS

Definition of clinical questions

In a series of meeting conducted in 2011 and 2012 the editorial board composed by obstetricians and gynaecologists with high experience in performing hysteroscopy and by an epidemiologist developed the table of content of the guideline, defined the process of identifying and evaluating the relevant evidence for each chapter and developed clinically relevant questions for each chapter. The clinical questions formulated were developed according to the PICOS method (1, 2, 3)

P: patients characteristics

I: experimental intervention on which the question is focused

C: comparison intervention / control /reference group

O: outcome measure relevant for the clinical question

S: study design on which to base the evidence search

The PICOS components of each prioritized question were subsequently used by the epidemiologist to define specific key words which were then employed in comprehensive bibliographic searches. The results of these activities were reported back to the editors in subsequent workshops and electronically. This enabled the editors to provide continuous professional and scientific support to the process of identifying and analysing the relevant evidence.

Bibliographic search

The epidemiologist performed bibliographic searches on Medline and the Cochrane library databases from 2000 to December 2011 using Mesh terms and free text words. Published articles suggested by the authors and not retrieved by a systematic search were also considered. Only scientific publications in English, Italian, French and Spanish were included. Priority was given to recently published, high quality systematic reviews. If systematic reviews of high methodological quality were retrieved, the search for primary studies was limited to those published after the last search date of the most recently published systematic review (i.e. if the systematic review had searched primary studies until February 2006, primary studies published after February 2006 were sought). If no systematic reviews were found, a search for primary studies published since 2000 was performed.

For the chapter related to the procedural aspect of hysteroscopy the clinical questions and

the results of bibliographic search developed by the Royal College of Obstetricians and Gynaecologists and used to realise the guidelines "Best practice in Hysteroscopy" (4) have been acquired. The search strategies developed to answer to the questions have been asked to the authors of this guideline and updated to December 2011. The recommendations have been adapted to the Italian reality and the strength of the recommendation reassigned following the criteria used in the present guideline.

Inclusion criteria

The inclusion criteria applied were based on the elements of the PICOS and on the highest level of available evidence, taking into account study design. For primary studies, for each kind of question (e.g., effectiveness, diagnostic accuracy, acceptability and compliance) a hierarchy of the study designs and inclusion/exclusion criteria was developed by the epidemiologists. For example, for effectiveness studies randomised controlled trials (RCT) were initially searched. If RCTs were retrieved, no other types of study design were considered. If no, or few and small RCTs were retrieved, quasi-experimental studies were considered. If no quasi-experimental studies were found, prospective or retrospective cohort and case-control studies were considered. If studies with none of the above designs were retrieved, cross-sectional studies and case series were included. For diagnostic accuracy questions, cross-sectional studies with verification by reference standard were considered as the best source of evidence.

Quality assessment

The methodological quality of the publications retrieved was assessed using the following criteria obtained from published and validated check lists.

Systematic reviews: the following criteria drawn from the AMSTAR CHECKLIST were used (5).

i) Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place

ii) Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the

references in the studies found

iii) <u>Was the status of publication (i.e. grey literature) used as an inclusion criterion?</u> The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc

iv) <u>Was a list of studies (included and excluded) provided?</u> A list of included and excluded studies should be provided

v) <u>Were the characteristics of the included studies provided?</u> In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported

vi) <u>Was the scientific quality of the included studies assessed and documented?</u> A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

vii) <u>Was the scientific quality of the included studies used appropriately in formulating conclusions?</u> The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

viii) <u>Were the methods used to combine the findings of studies appropriate?</u> For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

ix) <u>Was the likelihood of publication bias assessed?</u> An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

Randomised controlled trials: we used the following criteria drawn from the criteria suggested by the Cochrane Handbook (6).

<u>Protection against selection bias</u>

Sequence generation:

Low risk: The investigators describe a random component in the sequence generation

process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization

High risk: The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention

Unclear risk: Insufficient information about the sequence generation process to permit judgment of low or high risk

Allocation concealment:

Low risk: Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

High risk: Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear risk: Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.

Protection against performance bias (blinding of providers and participants)

Low risk: Blinding of participants and providers and it is unlikely that the blinding could have been broken. No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding

High risk: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Unclear risk: Insufficient information to permit judgement of low or high risk

Protection against detection bias (blinding of outcome assessor)

Low risk: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken

High risk: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding;

Unclear risk: Insufficient information to permit judgment of low or high risk

Protection against attrition bias

Low risk: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;

High risk: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;

Unclear risk: Insufficient information to permit judgment of low or high risk (e.g. number randomized not stated, no reasons for missing data provided; number of drop out not reported for each group)

Observational studies:. We used the following criteria drawn from the Newcastle-Ottawa Scale (7).

Case control studies

<u>Selection</u>

1) Adequate definition of the cases

a) yes, with independent validation

b) yes, eg record linkage or based on self reports

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls

b) hospital controls

c) no description

4) Definition of Controls

a) no history of disease (endpoint)

b) no description of source

<u>Comparability</u>

5) Comparability of cases and controls on the basis of the design or analysis

a) study controls for the most important factor

b) study controls for any additional factor

c) no control or adjustment for potential confounders

<u>Exposure</u>

6) Ascertainment of exposure

a) secure record (e.g. surgical records)

b) structured interview where blind to case/control status

c) interview not blinded to case/control status

d) written self report or medical record only

e) no description

7) Same method of ascertainment for cases and controls

a) yes

b) no

8) Non-Response rate

a) same rate for both groups

b) non respondents described

c) rate different and no designation

Cohort studies

<u>Selection</u>

1) Representativeness of the exposed cohort:

a) truly representative of the average in the community

b) somewhat representative of the average in the community

c) selected group of patients

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record

b) structured interview

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes

b) no

<u>Comparability</u>

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for the most important factor

b) study controls for any additional factor

<u>Outcome</u>

1) Assessment of outcome

a) independent blind assessment

b) record linkage

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for

b) subjects lost to follow up unlikely to introduce bias - small number lost < 10% or description provided of those lost)

c) no statement

Diagnostic accuracy studies: we used the following criteria drawn from the QUADAS checklist (8):

Study design: cross sectional study with prospective or retrospective recruitment, case control study

Spectrum of patients representative of the individuals who will receive the test in practice

Patients selection criteria clearly described

Verification by reference standard of all or part of subjects (verification bias)

Execution of the index and comparator tests adequately described

Execution of the reference standard described

Independent and blind interpretation of index test and reference standard results

Un-interpretable /intermediate test results reported

Withdrawals from the study explained

Evidence tables and summary documents

The epidemiologist prepared the following documents for each clinical question or group of clinical questions. The documents were subsequently used by the authors in drafting respective chapters:

- an evidence table for each retrieved study with the main characteristics of the study (study design, objective of the study, comparisons, participant's characteristics, outcome measures, results, methodological quality, level of evidence);

- a summary document with a description of the bibliographic search, the number, types and characteristics of the retrieved studies, their overall methodological quality, a synthesis of the results of all included studies, the conclusions and the overall level of evidence.

Grading system

Level of the evidence

For grading the level of evidence the following domains have been considered (9, 10)

o   Study designs

o   Directness (differences in populations, tests, and outcomes of interest between the studies (existing evidence) and the scope of the recommendation (components of the PICO clinical question)..

o   Methodological quality

o   Consistency and precision of the results

These domains were considered together in an unstructured way to give an overall level of evidence grading for each question

Hierarchy of study designs

I: multiple randomized controlled trials (RCTs) of reasonable sample size, or systematic reviews (SRs) of RCTs

II: one RCT of reasonable sample size, or 3 or less RCTs with small sample size

III: prospective or retrospective cohort studies or SRs of cohort studies; diagnostic cross sectional accuracy studies or their SRs

IV: retrospective case-control studies, time-series analyses or their SRs

V: case series; before/after studies without control group, cross sectional surveys

VI: expert opinion

Strength of the recommendations

The strength of recommendations was graded according to the following scale:

A: intervention strongly recommended (it must be done with all patients)

B: intervention recommended (it should be done, but not necessarily with all patients)

C: intervention to be considered but with uncertainty about its impact (it could be considered on an individual basis but not at national policy level)

The level of evidence was assigned by the epidemiologist to each study results and to the conclusion of each summary documents reporting the highest level of evidence of the studies included .The strength of each key recommendation was determined by the editorial board.

Correspondence between level of evidence and strength of recommendation

This present grading of the strength of recommendations did not require a rigid correspondence with the levels of evidence. For example grade **A** was given to interventions for which there was evidence level **I** (multiple RCTs of good methodological quality or SR of RCTs)

but also to interventions that are not supported by level I because RCTs were considered not feasible for the kind of the intervention assessed, because the outcome is hardly evaluable by RCTs, RCTs have been judged unethical, or recommendations dealt with physician's behaviours which could impact to the psychological wellbeing of the patients (e.g., the importance of an accurate information to the patients, timeliness of diagnosis to reduce anxiety). Grade **B** was given to interventions with lower evidence level (**II** or **III**) but also for interventions with evidence level **I** but with uncertainty about their impact in the population or about practical implementation (e.g. lack of resources for implementation, social barriers, supposed lack of acceptability by the target population). Grade **C** level was given to interventions for which evidence was not available **(VI)** or was of low grade (i.e. **IV, V**) despite RCTs on the interventions could have been conducted for that type of intervention or outcomes.

Method to reach the consensus among the panellist and internal peer review

Each group of authors responsible of each subject received all the evidence tables and the summary documents relating to the clinical questions formulated. They elaborated the draft of their subject proposing the strength of the recommendation based on the results of the literature search and on their clinical experience. The subject's drafts and the proposed strength of the recommendations were sent for internal peer review to the other subject's authors. To reach consensus about the contents of the recommendations and their strength a modified DELPHI (11) approach was used. Eventually all the recommendations were discussed in informal way during a final meeting of the multidisciplinary editorial board and the authors of all subjects.

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4. PROCEDURAL ASPECTS

4.1.Introduction

For the chapter related to the procedural aspect of hysteroscopy the clinical questions, PICOS and bibliographic searches developed by the Royal College of Obstetricians and Gynaecologists (RCOG) to prepare the guidelines *"Best practice in Hysteroscopy"* have been obtained from the authors and used. The bibliographic searches were updated up to December 2011 searching on Medline and limiting the inclusion to the articles published in English, Italian, French, Spanish. A further clinical question related to antibiotic prophylaxis before hysteroscopy not considered by the RCOG guideline was added. Methodological quality of retrieved studies was assessed with the validated checklist reported in the method chapter of the guideline. The results of the RCOG guideline have been updated and the recommendations have been adapted to the Italian reality; the strength of the recommendation has been reassigned following the criteria used in the present guideline.

4.2.Background

The introduction of small diameter hysteroscopes with working channels and continuous flow features has largely contributed to stress the wide heterogeneity of attitudes in performing hysteroscopic procedures. Therefore, in the last twenty years there was a great debate about the better distension medium, as well as on the ideal setting where performing hysteroscopy, or the need to use analgesia or anaesthesia. The opportunity given by new scopes has also allowed to simultaneously diagnose and treat most benign endouterine pathologies in ambulatory setting, reserving the use of the resectoscope and the operative theatre to a few, selected cases. Nevertheless, also the use of the speculum and the tenaculum has begun to be judged as obsolete, as well as the use of local medications to reduce the patient discomfort associated with the traditional approach to the uterus. Finally, to further complicate the *"hysteroscopic debate"* there is also the development of new organizational models of care, by which one can diversify the appropriateness of providing health benefits for women. The role of the panel of experts in drafting these Italian Guidelines was to analyse and weigh the scientific literature produced in the medical field about *office hysteroscopy*. Thereby reducing the distance between the clinical experience of the single and the evidence-based medicine. Starting, of course, from the institutional situation of Italy.

4.3. Setting

4.3. 1. *What is the ideal setting for performing office hysteroscopy?*

An office hysteroscopy service offers a safe, convenient and cost-effective means of

diagnosing and treating abnormal uterine bleeding as well as aiding the management of other benign gynaecological conditions (e.g. fertility control, subfertility and miscarriage and abnormal glandular cervical cytology) (1). A randomised controlled trial reported more rapid mobilisation postoperatively (0 minutes [range 0–5] versus 105 minutes [range 80–120], $P < 0.001$) and quicker recovery to preoperative levels (2 days [range 1–2.7] versus 3 days [range 2–4], $P < 0.05$) favouring diagnostic office hysteroscopy compared with traditional day-case hysteroscopy under general anaesthesia (2). The same study demonstrated high and equivalent levels of women's satisfaction with office hysteroscopy in conscious women compared with day-case procedures under general anaesthesia. There were also economic benefits for women, the health service and society at large. Compared with day-case procedures under general anaesthesia, women undergoing office hysteroscopy required significantly less time off work compared with the day-case group (0.8 days versus 3.3 days, $P < 0.001$) and experienced reduced loss of income and reduced travel costs. Costs per woman to the National Health Service were estimated to be substantially less for office procedures (3).

Recommendations

All gynaecology units should provide a dedicated ambulatory hysteroscopy service to aid management of women with abnormal uterine bleeding, infertility and suspicious of intracavitary abnormalities. The procedure performed in such setting is defined *"office hysteroscopy"*. There are clinical and economic benefits associated with this type of service **(LEVEL OF EVIDENCE II, STRENGTH OF THE RECOMMENDATION A).**

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4.3.2. *What are the requirements for running an effective office hysteroscopy service?*

Office hysteroscopy should be performed in an appropriately sized and fully equipped treatment room. This may be a dedicated hysteroscopy suite or a multipurpose facility.

Office hysteroscopy can be associated with substantial anxiety, 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 onsite or offsite decontamination facilities of an appropriate standard is necessary. Office hysteroscopy should not be performed in a formal operating theatre setting because this environment is likely to provoke anxiety in the woman and negate the economic advantages associated with avoiding use of expensive operating theatres.

Thus, appropriate staffing levels are required; 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 up to three support staff consisting of at least one registered general nurse and healthcare assistants. When possible, one of the staff members should act as the woman's advocate during the procedure to provide reassurance, explanation and support. Communication with the woman in this way may help alleviate anxiety and divert their attention, thereby minimising pain and embarrassment (the so called 'vocal local').

Patient preparation is a key factor in ensuring a positive patient outcome. Ideally, patient preparation begins immediately after the patient and the physician have decided to proceed with an office hysteroscopy. It includes a clear explanation of the procedure, a thorough assessment of the patient's understanding of information given and a period of time for question and answers during which the doctor may discuss and address any patient's concerns about the procedure. Where simultaneous treatments are offered ('see and treat' services), it is important that this fact is reflected in the doctor's explanation to facilitate informed choice. It is good clinical practice to obtain formal consent for office hysteroscopy before the procedure.

Patient safety is the first and foremost domain of healthcare. For an ambulatory hysteroscopy service, a regular risk assessment will enable the identification of risks. A framework for performing risk assessment might involve mapping a patient's 'journey' through the hysteroscopy service, assessing the following areas for clinical and non-clinical risks:
- environment: equipment, medicines use, infection control
- staffing: number, training

- patient assessment: availability of medical records, documentation

- patient treatment: guidelines and consent

- discharge/follow-up arrangements.

When the procedure is broken down in this way, it is clear that errors or mistakes can happen at any stage. Specific areas for risk management in ambulatory hysteroscopy include: documentation, consent and adequate training before performing new procedures.

Recommendations

The physician has to have the necessary skills and expertise to carry out hysteroscopy **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

Patient information has to be provided before the procedure and its written consent must be taken **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

4.3.3 *Could some operative hysteroscopic procedures be moved from the operating theatre to an office setting?*

P. Women candidate to operative hysteroscopic procedures

I. Office (out-patient) hysteroscopic procedures (i.e. polipectomy; tubal sterilization; metroplasty, sinechiolysis)

C. In-patient hysteroscopic procedures (i.e. polipectomy; tubal sterilization; metroplasty, sinechiolysis)

O: Effectiveness; complication, adverse effects, safety (prevalence of cervical perforation; cervical laceration; pain after surgery; side-effects of surgery; hospitalization; acceptability);

S: RCTs, SRs of RCTs in first instance, all studies if not RCTs found

Bibliographic search

We Searched : Medline (1955- Dec 2011) with the following free text key words : ("office hysteroscopy" OR outpatients) AND (polypectomy OR "tubal sterilization" OR "hysteroscopic metroplasty" OR synechiolysis OR "Hysteroscopy/adverse effects"[Mesh]); we also performed a

Medline search with the following Mesh terms: Hysteroscopy AND (Polyps/surgery OR tissue adhesion/surgery OR uterine disease/surgery OR uterine neoplasms/surgery OR patient satisfaction OR ambulatory surgical procedures)

Assessment and synthesis of evidence

Only one randomized controlled trial which fulfilled the inclusion criteria was retrieved (1). Forty women with endometrial polyps were randomized to receive endometrial polypectomy in outpatient setting using grasping forceps or a bipolar electrode introduced down the operating channel of a rigid hysteroscope or in day-case setting under general anesthesia using a hysteroscopic, monopolar, electrosurgical resecting loop. More women in the outpatient cohort (58%) described themselves as pain free for the remainder of the day than in the day case cohort (28%) (P = 0.09). The day after the procedure, all women from the outpatient group described slight or no discomfort compared with only 41% of women from the day-case group (P = 0.02). No major complication were reported in either group. Only one woman in the outpatient setting had cervical stenosis and dilatation was unsuccessful in the outpatient setting. All women undergoing outpatient polypectomy had a significantly shorter mean time away from home (3.24 [1.5–5] hours) than women undergoing day-case polypectomy (7.42 [6–10.5] hours), P < 0.0005. Similarly, women from the outpatient cohort had a significantly faster mean return to preoperative fitness (1 [0–4] day versus 3.2 [1–13] days; P = 0.001) and required less postoperative analgesia than the day case cohort. Ninety-five percent of women from the outpatient cohort and 82% of women from the day case cohort stated they would prefer to undergo an endometrial polypectomy in the outpatient setting should they require a further polyp removal. Authors concluded that endometrial polypectomy can be successfully performed in the outpatient setting with minimal intra-operative discomfort, a significantly shorter time away from home and faster recovery and is preferred by women when compared with day case polypectomy.

Many uncontrolled case series have been published in the last years. The most relevant case series assessing the feasibility, tolerability and safety of office surgical hysteroscopic procedures were the following (2-5). Bettocchi 2002 (2) assessed the efficacy, safety and patient acceptability of office hysteroscopic procedures, without analgesia or anesthesia, for treating benign intrauterine pathologies by 5fr Versapoint electrodes: 445 endometrial polyps, 49 submucosal myomas < 2 cm and 21 partial intramural myomas <1.5 cm, No failure or major complications occurred. At three months follow up no recurrence were observed. Patients acceptability was good: no discomfort was reported by the 79.3% of patients with endometrial polyps , by the 63.3% of patients with

submucosal myomas and by the 47.6% of patients with intramural myomas. Bettocchi 2004 (3) reported the results of office hysteroscopic treatment , without analgesia or anaesthesia, of 4836 patients with 2306 endometrial polyps and 1996 cervical polyps ranging between 0.2 and 3.7 cm, 1450 anatomic impediments [stenosis, reduction in diameter of external (ECO) or internal cervical os (ICO), stenosis or adhesion of the cervical canal], and 771 intrauterine adhesions, making a total of 6523 pathologies treated. 90% of the patients with cervical polyps and 93.5% of patients with endometrial polyps smaller than or equal to the internal cervical os reported no discomfort as well as 89.6% of patients with synechiae or adhesions and 71.9 % of patients with anatomic impediments. Follow-up after 3 months showed recurrence of pathology in 364 patients (5.6%), mainly in those operated for cervical polyps. Alanis Fuentes 2007 (4) retrospectively reported the results of 641 office polypectomy; diagnostic and therapeutic hysteroscopy, at the same time, was performed in all the cases without major complications; only one patient had epileptic crisis during polypectomy and another one uterine perforation. Garuti 2008 (5) performed office hysteroscopic polypectomy on 101 consecutive women accomplished by mechanical or bipolar electrosurgical instrumentation. Nine patients were excluded because of severe pelvic pain arising in the diagnostic phase or the finding of an oversize polyp requiring an estimated time of more than 30 minutes to be removed in the office setting; Polypectomy was accomplished in 79 (85.8%) of 92 remaining patients. No major complications (i.e., uterine perforation, hemorrhage, distention fluid overloading syndromes, severe vasovagal syndrome, gas embolism, or postoperative infections) were recorded either intraoperatively or subsequently noticed after patient discharge. Authors concluded that office see-and-treat polypectomy represents a safe and effective alternative to resectoscopic polypectomy, leading to a complete polyp excision in about 80% of postmenopausal patients.

We also retrieved a recently published systematic review (6) which had the aim to describe the newest applications of office operative hysteroscopy, its efficacy, safety and acceptability. Authors underline that the available international literature from 1990 to 2002 has clearly demonstrated that such technique enables performance of hysteroscopically directed endometrial biopsy and treatment of uterine adhesions, anatomic disorders, polyps, and small myomas safely and successfully without cervical dilatation and the need for anesthesia. This review provides a comprehensive survey of further advancements of office operative hysteroscopy in the treatment of other gynecologic pathologic conditions that have not been included in the traditional schema of treatment indications for office procedures proposed in 2002 (3). The review performed a comprehensive bibliographic search from 2003 to 2009 on Medline, Embase, CINAHL, Cochrane Library. The review did not found any RCTs but included 18 observational studies: 7 case series and 2 comparative studies (3741 patients) on office-based hysteroscopic tubal sterilization, 1 case

series (260 patients) on office-based hysteroscopic metroplasty and 8 case report for other uncommon conditions. The review found that office-based procedures are effective and safe: for hysteroscopic tubal sterilization the rate of successful insertion ranged from :88.9% to 99%, the correct insertion confirmed at 3 months ranged from 93% to 99%, the complication rate ranged from 0% to 5%, and the patients' satisfaction ranged from 88% to 98%. For metroplasty the success rate was of 93% , the complication rate of 0% and patients discomfort of 0%.

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Recommendations

Diagnostic hysteroscopy and some operative hysteroscopic procedures should be conducted outside of the formal operating theatre setting in an appropriately equipped and staffed ambulatory guarantying patient's safety and privacy (**LEVEL OF EVIDENCE II, STRENGHT OF THE**

RECOMMENDATION B).

4.4 Oral analgesia

Do analgesics given before diagnostic hysteroscopy reduce the pain felt by women during the procedure?

P. Women undergoing diagnostic or operative hysteroscopy in the office setting i.e. without general anaesthesia.

I. Use of analgesics for pain relief during the procedure

C. No intervention or placebo.

O. Assessment of pain (primary outcome) and medication side effects (secondary outcome) associated with the procedure.

S. Randomised controlled trials (RCTs)

Bibliographic search

We searched: Medline (1950- Dec 2011) with the following key words: ,(HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscpopy. Ti,ab) AND (ANAESTHETICS, LOCAL/ OR LIDOCAINE/ OR BUPIVICAINE/ OR ANAESTHESIA, LOCAL/ OR PROCAINE OR "local anaesthetic".ti,ab OR (local AND anaesthe*).ti,ab) . Embase (1980 . Sept 2008) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR VAGINOSCOPY/ OR Vaginoscopy.ti,ab) AND (ANALGESIA/ OR ANALGESIC AGENT/ OR Analges*.ti,ab). CINAHL (1981 - Sept 2008) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy.ti,ab) AND (ANALGESIA/ OR analgesia.ti,ab OR analges*.ti,ab OR ANALGESICS/ OR ANALGESICS, OPIOID/ OR ANALGESICS, NONNARCOTIC/ OR NARCOTICS/ OR TRAMADOL/ OR ANTIINFLAMMATORY AGENTS, NON-STEROIDAL/). The Cochrane Library (Cochrane Central Register of Controlled Trials) with the following key words: hysteroscopy AND analgesia

Assessment and synthesis of evidence

Two systematic reviews were identified. The first (1) included six studies, which examine

the use of analgesics compared with controls before office hysteroscopy (2-7). All of these studies were randomised controlled trials. Three of the studies examined the use of opiate drugs (2-4) and three examined NSAIDs (5-7).

Two of the opiate studies examined the use of 100 mg tramadol administered approximately 50 minutes before the office hysteroscopy, one study giving the tramadol intramuscularly (2) and the second giving it as an intravenous infusion (3). The first study found that the women who had received tramadol had significantly less pain at the end of the procedure than women in the intracervical block group and the women who received no medication ($P = 0.001$ and $P < 0.001$, respectively) (2). Although this was a low-quality study, the result was supported by those from the second, high-quality study which reported significantly lower pain scores in the tramadol group compared with placebo both during ($P < 0.012$) and 15 minutes after ($P < 0.008$) the procedure (3). The third opiate study examined the use of sublingual buprenorphine 0.2 mg 40 minutes before the procedure compared with placebo. There was no significant pain reduction with the use of buprenorphine overall and when stratified for menopausal status and parity (7).

Two studies reported adverse effects (3,7). The tramadol study found no significant difference between the groups in terms of incidence of nausea, vomiting or bradycardia (3). Conversely, in the buprenorphine study there was a high incidence of adverse effects (nausea, vomiting and drowsiness) in the intervention group (38.8%) and none in the control group (7).

Three trials examined the use of NSAIDs before office hysteroscopy (5-7). One of these studies assessed the use of 50 mg oral diclofenac 1–2 hours before the procedure and found that it did not significantly reduce the pain experienced compared with placebo: mean (standard deviation) in the diclofenac group 3.0 (2.5) versus 3.0 (2.9) in the control group (7). Vasovagal reactions were not reduced in the diclofenac group compared with the placebo group (four reactions and five reactions, respectively). The only adverse effects were in the diclofenac treatment group, but these were mild and self-limiting (one woman reported drug rash and one complained of epigastric pain). The second NSAID study compared the use of 500mg oral mefenamic acid 1 hour before the procedure with placebo (6). This study found that mefenamic acid did not significantly reduce the pain of the hysteroscopy; however, it did significantly reduce the pain experienced at 30 minutes ($P < 0.01$) and 60 minutes ($P < 0.05$). Adverse effects were not reported for either group. The final study examined the use of ketorolac 30 mg intramuscularly given with an intracervical block 45 minutes before the procedure, compared with cervical block alone (5). The paper reports a significant reduction in pain with the addition of ketorolac; however, it does not report P values and there were only 12 women in each arm of the study, making it difficult to draw strong conclusions from the results.

The second systematic review assessed the efficacy of different types of pharmacological intervention for pain relief in office gynaecological procedures (8).

The systematic review was of good methodological quality. It included 15 trials but only two which assessed the efficacy of oral analgesics; one which compared opioid with placebo or no treatment (4) and one which compared diclofenac with placebo (7). Both studies had already been included in the systematic review by Cooper **(LEVEL OF EVIDENCE I).**

No studies were identified addressing the issue of timing of analgesia before office hysteroscopy. The onset of action of these drugs means that to be effective they need to be given in advance of the woman's appointment. Optimal timing depends upon the agent used (half-life, rate of absorption, etc.) and the route of administration, but in general simple, non opioid analgesics given orally, such as 1000mg paracetamol or 400mg ibuprofen, should be taken around 1 hour before the scheduled appointment time. Thus, it is likely to be more practical to advise women to take simple analgesics in advance of their appointment rather than administer them in hospital. Routine patient information leaflets posted to the woman with details of their appointment can advise them to consider taking simple analgesics before they attend their appointment, with the proviso that they have taken them before without ill effects. This approach is likely to be of more benefit in those units offering simultaneous hysteroscopic diagnosis and treatment (i.e. the 'see and treat' clinic), where the levels of discomfort experienced are likely to be increased **(LEVEL OF EVIDENCE VI).**

Recommendations

Routine use of opiate analgesia before office hysteroscopy has to be avoided as it may cause adverse effects **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION A).**

The use of a standard dose of non-steroidal anti-inflammatory agents (NSAIDs) should be considered around 1 hour before the scheduled office hysteroscopy with the aim of reducing pain in the immediate post-procedural period **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION B).**

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4.5 Local anesthetic

Should local anesthesia be administered before office hysteroscopy?

P. Women undergoing diagnostic or operative hysteroscopy in the office setting i.e. without general anesthesia.

I. Use of local anesthesia for pain relief during the procedure

C. No intervention or placebo

O. Assessment of pain (primary outcome) and medication side effects (secondary outcome) associated with the procedure.

S. Randomized controlled trials (RCT's)

Bibliographic search

We searched: Medline (1950- Dec 2011) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy. Ti,ab) AND (ANAESTHETICS, LOCAL/ OR LIDOCAINE/ OR BUPIVICAINE/ OR ANAESTHESIA, LOCAL/ OR PROCAINE OR "local anaesthetic".ti,ab OR (local AND anaesthe*).ti,ab) . Embase (1980 - Sept 2008) with the following search strategy: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR VAGINOSCOPY/ OR Vaginoscopy.ti,ab) AND (LOCAL ANAESTHETIC AGENT/ OR LOCAL ANESTHESIA/ OR BUPIVICAINE/ OR LIDOCAINE/ OR MEPIVICAINE/ OR ROPIVICAINE/ OR PRILOCAINE/ OR LEVOBUPIVICAINE/ OR TETRACAINE/ OR "local anaestehtic".ti,ab) . CINAHL (1981 - Sept 2008) with the following search strategy: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy.ti,ab) AND ANESTHESIA, LOCAL/ OR ANESTHETICS, LOCAL/ OR "local anaesthetic".ti,ab) . The Cochrane Library (Cochrane Central Register of Controlled Trials) with the following search strategy: hysteroscopy AND anaesthetic

Assessment and synthesis of the evidence

Three systematic reviews of good methodological quality (1, 2, 3) and two small RCTs (4, 5) not included in SRs were retrieved.

Topical Vaginal Agents: no studies were found that evaluated topical vaginal anesthesia as a prelude to the performance of the hysteroscopic procedure.

Topical Uterine Agents

Cervix Two reviews (1,3) identified three randomized controlled trials comparing the application of topical local anesthetic to the ectocervix vs placebo (6-8). Two of these studies were meta-analyzed (7, 8). One used lidocaine 5% spray on the ectocervix and canal (7), while the other used 2% lignocaine gel rubbed over the surface of the cervix (8); both used a placebo as a control. Meta-analysis of these two studies found that there was no significant pain reduction with the use of topical application of local anesthetic to the cervix (SMD –0.32, 95% CI –0.97 to 0.33) (1). Another randomized controlled trial using lignocaine 2% aerosol spray, which could not be included in the meta-analysis as it reported its results as medians rather than means, demonstrated a reduction in pain as measured on a 100 mm visual analogue scale when applying a cervical tenaculum as part of the hysteroscopy procedure using a rigid 5.5 mm diagnostic hysteroscope (visual analogue scale score 9 versus 18, P = 0.005), but no significant reduction in the pain associated with the hysteroscopic procedure itself (3). In summary, no significant difference in perceived pain was

observed when topical local anaesthetic is applied to the ectocervix compared with placebo (**LEVEL OF EVIDENCE II**).

Corpus

Two systematic reviews (1,3) identified seven randomized controlled trials comparing the intracavitary application of local anesthetic (9-15). There was wide variation in anesthetic technique, agent, concentration, and time from application to initiation of the procedure. Three trials injected the anesthetic through the cervical canal into the uterine cavity (10, 11, 13). In two of them (10, 13) the injection of anesthetic was done before ($\geq$5 minutes) the hysteroscopic procedure, while in the other study (11) the injection started after hysteroscope placement. Two of these studies used 5 ml of 2% lignocaine (11, 13), the other one used 2 ml of 2% mepivacaine (10). All three used normal saline as their control substance.

Other two studies mixed lignocaine with the distension medium. One used 18 ml of lignocaine (strength not stated) per 250ml of normal saline combined with an intracervical block and compared it with normal saline as the distension medium with an intracervical block (12). The second study used 40 ml of 2% lignocaine per 500ml of normal saline and compared it with normal saline as the distension medium (9). No significant reduction in pain during hysteroscopy was demonstrated (SMD -0.11, 95% CI -0.31 to 0.10) (1). Out of the two studies, included only in one systematic review (3), which did not performed a meta-analysis (14, 15), only one found statistical significant results in favor of the intervention.

Other two RCTs not included in the systematic reviews were identified (4, 5). The first one (5) compared 400 mg of vaginal misoprostol 3 hours prior to the procedure plus instillation of 5 ml of 2% lignocaine 2 minutes prior to procedure versus misoprostol only on pain score on 49 premenopausal women. The difference was not statistically significant for overall pain score, but it is not possible to exclude that the study is not powered to found a statistically significant difference. The other (4) compared the efficacy of gel with lidocaine instilled prior the procedure with gel without lidocaine on 132 patients. The study did not found significant difference in pain score.

In summary no significant reduction in pain was observed when transcervical application of topical anesthetic was compared with placebo although studies were heterogeneous (**LEVEL OF EVIDENCE I**).

Injectable Agents

Intracervical Block

Two systematic reviews (1, 3) identified five randomized controlled trials comparing the use of direct intracervical injection of local anesthetic before office hysteroscopy with control (placebo, vaginoscopy or nil) (16-20). No significant reduction in pain was noted in the four trials (16-19) included in the meta-analysis (SMD –0.05, 95% CI –0.71 to 0.60) (1). However, intracervical injection of local anesthetic was found to reduce pain with hysteroscopy (SMD –0.36,95% CI –0.61 to –0.10) when the trial comparing local anesthesia with vaginoscopy was excluded (20) **(LEVEL OF EVIDENCE I)**.

Paracervical Block

Two systematic reviews (1, 3) identified six randomized controlled trials comparing the use of paracervical injection of local anesthetic before office hysteroscopy with control (placebo or nil) (21-26). Meta-analysis showed a significant reduction in pain (SMD –1.28, 95% CI –2.22 to –0.35) although the studies were heterogeneous (1). If the analysis was stratified by menopausal status, the heterogeneity among studies remained, but a significant reduction in pain was observed in the two studies with a purely postmenopausal population (21, 24) (SMD –1.12, 95% CI –2.23 to –0.01).

In summary significant reduction in pain was observed when paracervical anesthetic injection was compared with placebo or no treatment although studies were heterogeneous **(LEVEL OF EVIDENCE I)**.

The other systematic review (2) assessed the efficacy of different types of pharmacological intervention for pain relief in office gynecological procedures. It included ten trials, which compared local anesthetic with placebo, or no treatment. All were already included in the other systematic reviews. The authors put all the studies together in the meta-analysis not distinguishing between the two way of administration (topical *vs* injectable). The review found overall beneficial effects of local anesthetic both during the procedure (SMD -0.45; 95% CI -0.73, -0.17) and within 30 minutes (SMD -0.51; 95% CI -0.81, -0.21). It should however be underlined that for both the results of meta-analysis there was very high statistical heterogeneity.

Recommendations

Topical anaesthesia

Routine instillation of local anesthetic into the uterine cavity and topical application of local anesthetic on ectocervix should be avoided as it does not reduce pain during diagnostic hysteroscopy **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION B).**

Injectable local anesthetic

Application of local anesthetic into and or around the cervix is associated with a reduction of the pain experienced during office diagnostic hysteroscopy. Since the clinical significance of such reduction in pain is unclear it should not be routinely administered **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION B).**

Paracervical injection of local anesthetic is associated with a reduction of the pain experienced during office hysteroscopy, mostly in postmenopausal women. Technical and technological improvements may diminish any advantage of paracervical anesthesia. Therefore its routine use should only be considered in selected cases (i.e. when outer diameter greater than 5mm hysteroscopes are being employed) **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION B).**

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4.6 Conscious sedation

Should conscious sedation be used to reduce pain associated with office *hysteroscopic procedures?*

P. Women undergoing diagnostic or operative hysteroscopy in the office setting i.e. without general anaesthesia.

I. Use of conscious sedation for pain relief during the procedure

C. No intervention or placebo.

O. Assessment of pain (primary outcome) and medication side effects (secondary outcome) associated with the procedure.

S. Randomised controlled trials (RCT's)

Bibliographic search

We searched: Medline (1950- Dec 2011) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscpopy. Ti,ab) AND (CONSCIOUS SEDATION/ OR "conscious sedation".ti,ab OR HYPNOTICS AND SEDATIVES/ OR Sedative.ti,ab). Embase (1980 - Sept2008) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR VAGINOSCOPY/ OR Vaginoscopy.ti,ab) AND (CONSCIOUS SEDATION/ OR "conscious sedation".ti,ab OR SEDATIVE AGENT/ OR Sedative.ti,ab) . CINAHL (1981 - Sept 2008) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy.ti,ab) AND (CONSCIOUS SEDATION/ OR "conscious sedation".ti,ab OR HYPNOTICS AND SEDATIVES/ OR SEDATIVES, BARBITURATE/ OR SEDATIVES, NONBARBITURATE/ OR Sedate*.ti,ab). The Cochrane Library (Cochrane Central Register of Controlled Trials) with the following key words: hysteroscopy AND sedation

Assessment and synthesis of the evidence

Conscious sedation is widely used in office endoscopic procedures of the gastrointestinal system. It is less commonly employed in office hysteroscopy. We didn't find any study comparing conscious sedations versus no sedation or placebo.

We found one systematic review of good methodological quality, which assessed the efficacy of different types of pharmacological intervention for pain relief in office gynaecological procedures (1). It included two trials which compared conscious sedation *vs* paracervical block (2,3)

and one which compared conscious sedation *vs* anti spasmodic/ NSAID (3). Guida 2003 (2) reported the use of conscious sedation using 0.25 mg fentanyl intravenous with 0.5 mg atropine and 2 mg midazolam immediately before operative office hysteroscopy – polypectomy, myomectomy, septoplasty and adhesiolysis using the Versapoint™ (Ethicon Inc.) bipolar electrode intrauterine system – compared with paracervical anaesthesia with 10 ml 1% mepivacaine hydrochloride without sedation. Sharma 2009 (3) compared the effect of intravenous sedation using diazepam with pentazocine with paracervical block using 1% lignocaine and with intravenous sedation using diazepam with pentazocine on pain perception during hysteroscopy and endometrial biopsy (3). The meta-analysis did not found significant differences in pain control during the procedure (SMD: 0.26 (95%CI -0.01- 0.54) but found an overall beneficial effect 30 minutes after the procedure (SMD: 0.34 (95%CI 0.06- 0.61) (**LEVEL OF EVIDENCE II).**

Also in the comparison with oral drotaverine with mefenamic acid Sharma 2009 (3) found results in favour of NSAIDS (SMS -0.86 (95%CI -1.51 - -0.21) (**LEVEL OF EVIDENCE II).**

Sedative drugs (anaesthetics, anxiolytics and opioids) are administered by oral, intravenous, transmucosal or inhalational routes. Any drug that depresses the central nervous system has the potential to impair respiration, circulation or both. Close monitoring of the woman must be undertaken by a designated staff member to ensure maintenance of continuous verbal contact and adequate oxygen saturation. Monitoring of blood pressure and electrocardiogram should be considered in high-risk cases and staff trained in acute airway management and anaesthetic support should be immediately available. **(LEVEL OF EVIDENCE VI).**

Recommendations

Conscious sedation should not be routinely used in office hysteroscopic procedures as it confers no advantage in terms of pain control and the woman's satisfaction over local anaesthesia. (**LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION A).**

Life-threatening complications can result from the use of conscious sedation. Appropriate monitoring and staff skills are mandatory if procedures are to be undertaken using conscious sedation (**LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

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4.7 Flexible vs rigid hysteroscopes

Should rigid or flexible hysteroscopes be used routinely in the office *setting?*

P. Women undergoing diagnostic or operative hysteroscopy in the office setting (i.e. without general anaesthesia).

I. Flexible hysteroscope

C. Rigid hysteroscope

O. Assessment of pain associated with the procedure.

S. Randomised controlled trials (RCTs).

Bibliographic search

We searched : Medline (1950- Dec 2011) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR vaginoscpopy. Ti,ab) AND (flexible.ti,ab OR flex*.ti,ab OR rigid.ti,ab OR rigid*.ti,ab). Embase (1980 - Febr 2009) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR VAGINOSCOPY/ OR Vaginoscopy.ti,ab) AND (Flex*.ti,ab OR Rigid.to,ab OR Rigid*.ti,ab OR Flexible.ti,ab). CINAHL (1981 - Febr 2009) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy.ti,ab) AND (Flexible.ti,ab OR Flex*.ti,ab OR Rigid.ti,ab OR Rigid*.ti,ab) . The Cochrane Library (Cochrane Central Register of Controlled Trials**)** with the following key words: hysteroscopy AND (flexible OR rigid)

Assessment and synthesis of the evidence

Two small randomised controlled trials compared the pain experienced during office hysteroscopy with the use of a flexible hysteroscope versus a rigid hysteroscope (1,2). Neither study presented data according to menopausal state or parity. Both studies found that use of the flexible

hysteroscope significantly reduced the woman's pain experience during the procedure ($P = 0.0001$ and $P < 0.001$, respectively). One of the studies reported no difference between the flexible and rigid groups in terms of procedure time and image view. There were no failed hysteroscopic procedures in either group.(1) The other study found that rigid scopes gave significantly better image quality ($P < 0.001$) and significantly shortened the time taken to perform the procedure ($P = 0.003$). There were two failed hysteroscopic procedures in the flexible group owing to cervical stenosis and these women were excluded from the analysis. Five more women in the flexible group had to be changed to a rigid hysteroscope because of inability to negotiate the cervical canal or inadequate visualisation. There were no failed hysteroscopies or change to flexible scopes in the rigid group. This study also reported that rigid hysteroscopes were cheaper to purchase and easier to sterilise and maintain than flexible hysteroscopes (2) **(LEVEL OF EVIDENCE II).**

Recommendations

Flexible hysteroscopes are associated with less pain during office hysteroscopy compared with rigid hysteroscopes. However, rigid hysteroscopes may provide better images, fewer failed procedures, quicker examination time and reduced cost. Thus, despite choice of hysteroscope should be left to the discretion of the operator, for the above mentioned qualities we would recommend rigid instruments mostly when operative procedures need to be performed **(LEVEL OF EVIDENCE II, STRENGHT OF THE RECOMMENDATION B).**

Rigid hysteroscope has to be equipped with single or double sheaths according to the chosen distension medium (i.e. single sheath with carbon dioxide and double sheaths with fluid distension medium) **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

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4.8 The effect of the vaginoscopic ('no touch') approach to office hysteroscopy on pain.

Does a vaginoscopic approach to office *hysteroscopy reduce pain and increase the feasibility of the procedure?*

P. Women undergoing diagnostic or operative hysteroscopy in the office setting. (i.e. without general anaesthesia).

I. Vaginoscopic technique

C. Traditional hysteroscopy using a vaginal speculum.

O. Assessment of the pain associated with the procedure (primary outcome) or the feasibility of vaginoscopic approach (secondary outcome).

S. Randomised controlled trials (RCTs).

Bibliographic search

We searched: Medline (1950- Dec 2011) with the following key words: (HYSTEROSCOPY/ae,mt OR Vaginoscopy.ti,ab OR "no touch".ti,ab OR Vaginoscop*.ti,ab) AND HYSTEROSCOPY/ OR hysteroscopy.ti,ab). Embase (1980 - Febr2009) with the following key words: (exp HYSTEROSCOPY/ OR hysteroscopy.ti,ab) AND (VAGINOSCOPY/ OR Vaginoscopy.ti,ab OR "no touch".ti,ab OR Vaginoscop*.ti,ab. CINAHL (1981 - Febr2009) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab) AND (HYSTEROSCOPY/AE,MT, OR Vaginoscopy.ti,ab OR "no touch".ti,ab OR Vaginoscop*.ti,ab) . The Cochrane Library (Cochrane Central Register of Controlled Trials) with the following key words: hysteroscopy AND (vaginoscopy OR vaginoscopic OR "no-touch")

Assessment and synthesis of the evidence

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. A systematic review (1) identified six small randomised controlled trials comparing the vaginoscopic versus traditional office hysteroscopy (2-7). There were no significant differences in feasibility (failed procedures) between the techniques (OR 1.28, 95% CI 0.74–2.24), but vaginoscopy was associated with significantly less procedural pain (SMD –0.44, 95% CI –0.65 to –0.22) in the four studies evaluating this outcome (1-3,5) **(LEVEL OF EVIDENCE I).**

Larger studies are indicated to better assess the feasibility of vaginoscopy in relation to the characteristics of the woman (e.g. body mass index, menopausal status, parity, caesarean section) and type of hysteroscope (size, angle, rigid/flexible endoscopes) and the risk of ascending pelvic

infection. Vaginoscopy allows increased external movement of the hysteroscope. Future studies should assess whether this manoeuvrability improves the feasibility and effectiveness of operative hysteroscopy.

Recommendations

Vaginoscopy reduces pain during office hysteroscopy, thus reducing the need of sedation and/or anesthesia during office procedures and, increasing the patient compliance.**.** On this basis, vaginoscopy should be the standard technique for office hysteroscopy with fluid distension medium **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION A).**

The use of a vaginal speculum is indicated when anatomical and technological issues overcome the advantages of absence of vaginal instrumentation. **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

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4.9 Cervical preparation

Does cervical preparation reduce uterine trauma, failure to access the uterine cavity or pain associated with office hysteroscopy?

P. Women undergoing diagnostic or operative hysteroscopy in the outpatient setting i.e. without general anaesthesia.

I. Use of cervical preparation prior to the procedure.

C. No intervention, or placebo

O. Assessment of pain

S. Randomised controlled trials (RCTs).

Bibliographic search

We searched: Medline (1950- Dec 2011) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscpopy. Ti,ab) AND (MISOPROSTOL/ OR DINOPROSTONE OR LAMINARIA/ OR PROSTAGLANDINS/ OR PROSTAGLANDINS, SYNTHETIC/ OR ESTROGENS/ OR (oestrogen OR estrogen).ti,ab OR PROGESTERONE/ OR PROGESTINS/ OR CERVICAL RIPENING/ OR "cervical preparation".ti,ab OR laminaria.ti,ab OR prostaglan*.ti,ab OR progest*.ti,ab OR "cervical ripening".ti,ab) .Embase (1980 -Febr 2010) with the following kety words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR VAGINOSCOPY/ OR Vaginoscopy.ti,ab) AND (MISOPROSTOL/ OR GEMEPROST/ OR PROSTAGLANDIN E2/ OR MIFEPRISTONE/ OR DILAPAN/ OR PROSTAGLANDIN/ OR UTERINE CERVIX DILATATION/ OR UTERINE CERVIX RIPENING/ OR "cervical ripening".ti,ab OR LAMINARIA/ OR laminaria.ti,ab). CINAHL (1981 - Febr2010) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy.ti,ab) AND (Misoprostol.ti,ab OR Laminaria.ti,ab OR prostaglandins.ti,ab OR (oestrogen OR estrogen).ti,ab OR progest*.ti,ab OR "cervical ripening".ti,ab OR "cervical prep*".ti,ab OR MISOPROSTOL/ OR PROSTAGLANDINS/ OR ESTROGENS/ OR PROGESTERONE/ OR CERVIX DILATATION

AND EFFACEMENT/). The Cochrane Library (Cochrane Central Register of Controlled Trials) with the following key words: hysteroscopy AND cervical preparation.

Assessment and synthesis of the evidence

Prostaglandin or misoprostol administration before diagnostic hysteroscopy performed under general anaesthesia is associated with a reduction in cervical resistance and need for cervical dilatation in premenopausal women (1-3) compared with placebo, although no such benefit was noted in postmenopausal women (4).

Prostaglandin: a systematic review of the use of cervical preparation before office hysteroscopy identified five randomised controlled trials (5-9) with administration of prostaglandin regimens varying from 4 hours to 30 hours before hysteroscopy (10). No reduction in the incidence of lacerations to the cervix with the use of vaginal prostaglandins was demonstrated in the three trials (5,6,9) assessing this outcome (OR 0.59, 95% CI 0.22–1.55) **(LEVEL OF EVIDENCE I).**

Prostaglandins are associated with gastrointestinal adverse effects and are contraindicated in severe uncontrolled asthma, chronic adrenal failure, acute porphyria, renal or hepatic impairment and breastfeeding (11). Four heterogeneous trials assessed the incidence of genital tract bleeding associated with vaginal prostaglandins before office hysteroscopy (5,7-9) and found no increased risk with the use of prostaglandins (OR 1.32, 95% CI 0.52–3.40) (10) **(LEVEL OF EVIDENCE I).** The main reason for failure to successfully perform an office hysteroscopy is inability to access the uterine cavity as a result of cervical stenosis; this is most commonly encountered in the postmenopausal population. Two randomised controlled trials (6,7) have assessed the feasibility of office hysteroscopy after vaginal prostaglandins and a meta-analysis showed no reduction in failure rates (OR 2.12, 95% CI 0.64–7.04) (10) **(LEVEL OF EVIDENCE II).**

Mifepristone One randomised controlled trial included in the systematic review examined the use of oral mifepristone in premenopausal women (12) . There were no failed hysteroscopies but the study did not found benefit in terms of reduction in pain experienced during office hysteroscopy (mean pain score 33.4 ± 23.5 versus 37.0 ± 30.0, $P = 0.60$) **(LEVEL OF EVIDENCE II).**

Misoprostol: Three studies examined the use of misoprostol 400 micrograms given vaginally before hysteroscopy to premenopausal women. The drugs were administered 4 hours before hysteroscopy in the first study (5) and 6 hours before hysteroscopy in the second (8). The low-quality study (5) found that pain during cervical dilatation was significantly reduced after the use of prostaglandin compared with placebo ($P < 0.05$); however, the other, high-quality study (8) found no significant reduction in pain during the hysteroscopy with the use of misoprostol ($P =$

0.72). The third study (13) assessed the effectiveness of 200 micrograms of sublingual misoprostol for cervical ripening before diagnostic hysteroscopy in 52 premenopausal women compared with placebo. The study did not found statistically significant difference in the number of women requiring cervical dilatation duration and easy of dilatation. Overall in premenopausal women misoprostol does not seem to have beneficial effects on pain or cervical dilatation (**LEVEL OF EVIDENCE II).**

Two studies (6,14) examined the effect of misoprostol on postmenopausal women. The first (6) assessed the efficacy of misoprostol 200 micrograms given vaginally 8 hours before hysteroscopy on pain. The median pain scores as the hysteroscope passed through the cervical os were five in the intervention group and seven in the placebo group ($P = 0.02$). When the pain severity was assessed by comparing the number of women scoring more than six on the visual analogue scale (i.e. considerable pain), there were significantly fewer in the intervention group ($P = 0.0132$). However, no significant difference between the groups was identified when assessing the presence of pain during clamping of the cervix ($P = 0.74$), during the examination ($P = 0.32$) or during the endometrial biopsy ($P = 0.19$).

The second study (14) compared the impact of 1000 lg of self-administered vaginal misoprostol versus self-administered vaginal placebo on preoperative cervical ripening after 2 weeks of pretreatment with estradiol vaginal tablets on 72 postmenopausal women. The degree of cervical dilatation immediately before the procedure was significantly higher in the misoprostol group (5.7mm vs 4.7mm). Overall misoprostol seems to have beneficial effect on pain and cervical dilatation on postmenopausal women, even though no firm conclusion can be drawn given the small number of studies and participants (**LEVEL OF EVIDENCE II).**

Two studies included both pre- and postmenopausal women in their study populations (7,9). One of the studies (7) gave misoprostol 400 micrograms vaginally 4–6 hours before the hysteroscopy and found that pain at the end of the procedure was significantly less in the intervention group compared with the group receiving no medication ($P = 0.03$). This was judged to be a low quality study owing to the lack of blinding. The second study (9) gave the same dose of misoprostol 12–24 hours before the procedure and assessed pain after the cervix was dilated to 6 mm. Pain was found to be significantly less in the misoprostol group ($P = 0.004$; when adjusted for baseline pain score $P = 0.01$). This study sub-grouped women according to menopausal status and found that there was a significant reduction in pain for postmenopausal women treated with misoprostol ($P = 0.004$;when adjusted for baseline scores $P = 0.006$) but not for premenopausal

women (P = 0.56;when adjusted for baseline scores P = 0.77). This was a high-quality study (**LEVEL OF EVIDENCE II).**

Recommendation

Routine cervical preparation before office hysteroscopy should not be used in the absence of any evidence of benefit in terms of reduction of pain, rates of failure or uterine trauma (**LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION A).**

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4.10 Distension medium

 a) *Which uterine distension medium should be used during office hysteroscopy?*

 b) *Does the type of distension medium affect pain experience during office hysteroscopy?*

 c) *Which distension medium causes the fewest vaso-vagal episodes during office hysteroscopy?*

 d) *Which distension medium produces the best image quality during office hysteroscopy?*

 e) *Which distension medium allows the quickest procedure?*

 f) *Which distension medium should be used for operative procedures?*

P. Women undergoing diagnostic or operative hysteroscopy in the office setting (i.e. without general anaesthesia).

I. Carbon dioxide for the office hysteroscopy.

C: Another distending medium

O. Assessment of pain associated with the procedure.

S. Randomised controlled trials (RCTs).

Bibliographic search

We searched: Medline (1950- Dec 2011) with the following key words: HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscpopy. Ti,ab) AND (DEXTRANS/ OR SODIUM CHLORIDE/ OR MANNITOL/ OR SORBITOL/ OR "distension media".ti,ab OR (uter* AND disten*).ti,ab OR CARBON DIOXIDE OR "carbon dioxide".ti,ab. Embase (1980 - Febr 2009) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR VAGINOSCOPY/ OR Vaginoscopy.ti,ab) ANDF ((uter* AND disten*).ti,ab OR "distension media".ti,ab OR SODIUM CHLORIDE/ OR CARBON DIOXIDE. CINAHL (1981 - Febr 2009) with the following key words: (HYSTEROSCOPY/ OR Hysteroscopy.ti,ab OR Vaginoscopy.ti,ab) AND ("distension media".ti,ab OR NORMAL SALINE/ OR SALINE SOLUTION, HYPERTONIC/ OR SODIUM CHLORIDE/ OR DEXTRANS/ OR Dextrans.ti,ab OR MANNITOL/ OR Mannitol.ti,ab OR CARBON DIOXIDE/ OR "carbon dioxide".ti,ab OR (uter* AND disten*).ti,ab) . The Cochrane Library (Cochrane Central Register of Controlled Trials) with the following key words: hysteroscopy AND distension media

Assessment and synthesis of the evidence

A systematic review was found which included seven studies (1-7) that looked at whether normal saline or carbon dioxide uterine distension media were associated with less ***pain*** during office hysteroscopy (8). One study was considered a duplication of data (6) from an earlier study by the same group (1). Therefore, six studies were included in the meta-analysis (1-5,7). The meta-analysis showed there to be no significant difference between the pain experienced with the use of carbon dioxide versus normal saline for office hysteroscopy (standard mean difference [SMD] 0.34, 95% CI –0.12 to 0.80) (8).

Two RCTs not included in the systematic review were also found. One (9) assessed the specific roles of the following selected factors that influence the perception of pain: instrument diameter (5.0- or 3.5-mm external sheath), uterine distension medium (CO_2 or saline solution), and hysteroscopist's experience in performing office vaginoscopic hysteroscopy on 184 women with primary infertility who were candidate to office hysteroscopy. Only 165 diagnostic hysteroscopies were successfully performed. Authors found that in the minihysteroscopy as well as in the normal hysteroscopy group, the VAS score was significantly lower when normal saline solution was used rather than CO_2 P< 0.05. But when hysteroscopist's experience was taken into account authors found that the distension medium on perceived pain is deeply influenced by gynaecologist experience and skill. Significant differences between experienced and inexperienced hysteroscopists were recorded when the procedure was performed using CO_2 as the distension medium. In contrast,

the difference in patient discomfort disappeared when normal saline solution was selected. The patients evaluated by either experienced or inexperienced hysteroscopists using normal saline solution provided similar results. More hysteroscopy training seems to abolish any differences in perceived pain stemming from the choice of different uterine distension media. The second trial (10) compared CO2 and saline solution on pain assessed by VAS on 264 women candidate to office hysteroscopy for the evaluation of abnormal uterine bleeding, suspected mullerian anomalies, the assessment of uncertain or abnormal findings on imaging studies, infertility, increased endometrial thickness, assessment of the endometrium in women taking tamoxifen, and cytological endometrial hyperplasia. No significant differences were found on perceived pain. Overall no significant difference were found on perceived pain with the use of carbon dioxide versus normal saline for office hysteroscopy (**LEVEL OF EVIDENCE I**).

Uterine distension pressures need to be sufficient to allow systematic inspection of the entire uterine cavity. However, care is needed to ensure that pressures are minimised to avoid overdistension of the uterus and consequent pain (**LEVEL OF EVIDENCE VI**).

The incidence of ***vasovagal episodes*** was reported in three of the randomised controlled trials included in the systematic review (2,4,5). A meta-analysis of these results showed significantly fewer vasovagal episodes with the use of normal saline compared with carbon dioxide (OR 3.24, 95% CI 1.23– 8.54) (8) (**LEVEL OF EVIDENCE I**).

Four randomised controlled trials included in the systematic review evaluated image quality for each of the distension media.(1,2,4,7) Three studies reported no significant difference in image quality between carbon dioxide and normal saline; (1,2,4) however, one of these studies reported changing the distension medium from carbon dioxide to normal saline in eight (10.1%) women. One study found a statistically significant increased risk of unsatisfactory view on hysteroscopy (RR 4.75, 95% CI 1.61–16.4) with the use of carbon dioxide. This was mainly attributed to bubbles and bleeding. Of the 19 women who had an unsatisfactory view at hysteroscopy using carbon dioxide, 17 were switched to normal saline and an improved view was reported in 11 (64.7%) (7). Normal saline produces lavage of the cavity and so washes away any blood or mucus which otherwise might obscure the view. A RCT (10) not included in the systematic review found that visual quality was better when hysteroscopy was performed with CO_2 distension. Overall no significant differences have been found on image quality between carbon dioxide and normal saline (**LEVEL OF EVIDENCE I**).

Four randomised controlled trials included in the systematic review compared ***procedure times*** between normal saline and carbon dioxide (1-4). All four found that hysteroscopies using normal saline were significantly quicker. This detail remained significant when the results were meta-analysed (SMD 1.32,95% CI 1.17–1.48) (8) (**LEVEL OF EVIDENCE I**).

Normal saline should be used as the distension medium when bipolar intrauterine equipment is used for hysteroscopic surgery. Thus, it is more practical to perform diagnostic procedures with normal saline in units offering simultaneous diagnosis and treatment as this avoids having to swap distension media should operative procedures need to be carried out. Hysteroscopic tubal sterilisation requires fluid distension medium; the choice of normal saline or glycine depends upon the specific technology adopted (**LEVEL OF EVIDENCE VI**).

Recommendation

Uterine distension with normal saline appears to reduce the incidence of vasovagal episodes and allows office diagnostic hysteroscopy to be completed more quickly**.** However, for routine office diagnostic hysteroscopy, the choice of distension medium between carbon dioxide and normal saline should be left to the discretion of the operator as neither is superior in reducing pain and in improving image quality **(LEVEL OF EVIDENCE I, STRENGHT OF THE RECOMMENDATION A).**

Operative office hysteroscopy, using electrosurgery, requires the use of fluid distension medium to act as both the distension and conducting medium (**LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMMENDATION A).**

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4.11 Antibiotic prophylaxis before hysteroscopy

Does antibiotic prophylaxis reducers the incidence of post procedural infections as defined as: leucorrhoea, cystitis, pelvic pain and fever during the first week after the intervention?

P: Patients undergoing office hysteroscopy

I: Antibiotic prophylaxis

C: No treatment

O: Post procedural infections as defined as: leucorrhoea, cystitis, pelvic pain, fever during the first week after the intervention

S: RCTs and their systematic reviews

Bibliographic search

We searched Medline (2007 to December 2011) with the following key words: (Hysteroscoy (Mesh) OR Office Hysteroscopy OR outpatient Hysteroscopy) AND (Anti-Bacterial Agents/ (Mesh) OR Antibiotic Prophylaxis/ (Mesh) OR antibiotic$.tw). We limited the search to articles published since 2007 to December 2011 because we found one systematic review which included studies published up to the end of 2006 (Thinkhamrop 2007).

Assessment and synthesis of the evidence

Only one study was found fulfilling the inclusion criteria (1). It is a Cochrane systematic review, which assesses the effectiveness and safety of antibiotic prophylaxis compared to placebo or no treatment in women undergoing any transcervical intrauterine procedures, including hysteroscopy. The authors performed a very comprehensive bibliographic search on five databases up to 2006 and included randomised controlled trials comparing antibiotic prophylaxis with placebo or no treatment. No studies were found and included in the review.

We included a quasi-experimental study (2) even though it did not strictly fulfill the inclusion criteria for study design because not other studies were retrieved. Depending on the hospital and according to local protocols, hysteroscopy was performed with (n. 266) or without (n. 365) antibiotic prophylaxis. Between the groups with and without antibiotic prophylaxis, significant differences were found for the variables female age, body mass index (BMI), and cause of infertility. Nevertheless, no significant differences were found for investigated possible risk factors for infectious complications, such as tubal pathology or hystologically diagnosed endometritis. No infections were recorded in the group not receiving prophylaxis and only one infection developed in the group receiving prophylaxis (**LEVEL OF EVIDENCE III).**

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Recommendations

Antibiotic prophylaxis should be avoided (unless otherwise requested) before performing office hysteroscopic procedures, since the risk of infectious complications is extremely low and is not affected by the pre-treatment with antibiotics (**LEVEL OF EVIDENCE III, STRENGH OF THE RECOMMENDATION B).**

5. USEFULNESS OF HYSTEROSCOPIC EVALUATION IN INFERTILITY WORK-UP

5.1.1 Background

Although the quality of the embryo and transportation to the uterine cavity are obvious requirements for successful implantation, attention has recently focused on the anatomical integrity of the uterine cavity, as a prerequisite for a receptive endometrium. Uterine factors, including abnormalities in the myometrium and in the endometrium, represent only 2 to 3 % of infertility, but they are much more common in infertile women (40-50%). and can be the cause of infertility and pregnancy loss, interfering with normal implantation and placentation.

Therefore, uterine cavity assessment has been suggested as a routine investigation in the evaluation of infertile women and, till today, most of the clinicians have used hysterosalpingography (HSG) and transvaginal sonography (TVS) to screen for uterine cavity abnormalities with saline infusion/gel instillation sonography (SIS/GIS) and hysteroscopy having a secondary role.

Offering simultaneously both the direct visualization of the uterine cavity and the opportunity to treat many intrauterine pathologies during the same diagnostic session, the role of hysteroscopy has been rapidly growing up in the last decades till it became to be considered by many authors as the gold standard procedure for the evaluation of uterine cavity. Nevertheless, its place as a routine procedure in the infertility work-up is under debate and there is no consensus on its effectiveness in improving the prognosis of infertile women.

Indeed, the National Institute for Health and Clinical Excellence (NICE) guideline on fertility assessment and treatment states: "*women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established*" (NICE 2004). The European Society of Human Reproduction and Embryology (ESHRE) has a similar perspective, indicating hysteroscopy to be unnecessary, unless it is "*for the confirmation and treatment of doubtful intrauterine pathology*". The Royal College of Obstetricians and Gynecologists gives the same recommendation: hysteroscopy should not be performed as a routine examination unless clinically indicated.

Starting from these considerations and moved on by clinical needs, we created the PICOS about the clinical usefulness of hysteroscopic evaluation of the endometrial cavity as a screening test in the diagnostic work up in infertile women, as well as its clinical usefulness in women candidate to IVF or affected by recurrent miscarriage. Whether or not operative hysteroscopy at any stage of the infertility work up may improve the pregnancy rate is analyzed too.

5.1.2 Hysteroscopy as a screening test in the diagnostic work up of infertile couple

5.1.2.1 Which is the diagnostic accuracy of hysteroscopy compared with other techniques (endovaginal ultrasonography, hysterosalpingography, saline infusion sonography) in detecting endouterine abnormalities?

P. Women of infertile couple

I. Hysteroscopy

C. Other techniques

O. Sensitivity and Specificity

S. Cross sectional diagnostic accuracy studies

Bibliographic search

We searched Medline (1966 to October 2011) with the following key words: ("Hysteroscopy"[Mesh] OR "office Hysteroscopy" OR "outpatient Hysteroscopy") AND "Infertility"[Mesh] AND "Sensitivity and Specificity"[Mesh]) without date and language restriction. Methodological quality of retrieved studies was assessed with the validated checklist reported in the method chapter of the guideline.

Assessment and synthesis of the evidence

Only four studies were finally included in the review because in the vast majority of the retrieved studies hysteroscopy was used as reference standard for the evaluation of the accuracy of other examinations (1-4).

With respect to the diagnostic accuracy of hysteroscopy for the detection of chronic endometritis, Cicinelli et al. (1) included 910 patients, of whom only 16.5% were evaluated because of infertility, whereas Polisseni & co-workers (2) did hysteroscopy in 50 infertile patients. The examination was performed during the follicular phase in both studies, with a chronic endometritis prevalence of 12%.

Studies reached very different results and conclusions; Polisseni found a sensitivity of 16.7% and a specificity of 93.2% in detecting endometritis (PPV: 25%; NPV: 89.1%), concluding that the hysteroscopy is not a useful exam for detecting chronic endometritis in infertile women. On the contrary, by using the same diagnostic criteria, Cicinelli found out a sensitivity of 91.8% and a specificity of 92.9% (PPV: 63.9%; NPV: 98.8%) in detecting chronic endometritis, values that allowed to conclude that hysteroscopy is a very useful and reliable examination and that it should be

performed in infertile women mainly when they are candidate to IVF. This discrepancy in results was attributed to the different distension media used (CO_2 in the case of lower accuracy and, saline solution when better accuracy was reached). However, the paper of Cicinelli did not report separate result for the subgroup of infertile women, that were only 6.5% of the sample.

The third study (3) compared the diagnostic accuracy of transvaginal ultrasound (TVS) versus hysteroscopy in the diagnosis of benign intrauterine lesions (prevalence in the population: 40.5%) in 126 infertile patients. TVS (Sensitivity: 95.4%; Specificity: 100%, PPV: 100%; NPV: 97.4%) had better performance than hysteroscopy (Sensitivity: 89.8%, Specificity: 93.3%, PPV: 89.8%, NPV: 93.3%) in detecting benign uterine lesion. Author concluded that when ultrasound does not show endometrial lesions, routine office hysteroscopy should not be considered mandatory in the investigation of the infertile woman.

The final fourth study (4) assessed the diagnostic accuracy in detecting endometrial lesions of a scoring system based on the findings by hysteroscopy evaluation. Established parameters were: endometrial thickness; surface; vascularisation; colour. For each of these a 0 to 2 points were given. Functional abnormalities and hyperplasia without atypia were considered as mild lesions, and hyperplasia with atypia and adenocarcinoma as severe lesions. The study is of poor methodological quality because of a serious risk of selection bias and verification bias. Moreover only 20% of patients included in the study wee infertile or had recurrent spontaneous abortion and the prevalence of different lesions is not reported. For mild lesions, sensitivity was 86.9%, specificity 87.4% (PPV 74.2%; NPV 45.7%), whilst sensitivity was of 96% a specificity 92.9% for severe lesions (PPV: 88.8%).

In summary, the diagnostic accuracy of hysteroscopy for the evaluation of abnormal uterine bleeding (AUB) has been clearly established and, compared with hystopathology or hysterectomy findings, endoscopic evaluation resulted very accurate for diagnosing intrauterine abnormalities.

However, limited evidence exists about the diagnostic accuracy of hysteroscopy for the detection of intrauterine causes in infertile patients, mainly because hysteroscopy is considered *a priori* the most accurate examination in these women and, therefore, used as the reference standard for the diagnostic accuracy studies.

Thus, with respect to the comparison between hysteroscopy and other techniques (TVS, HSG, saline infusion sonography) in detecting endouterine abnormalities, no definitive conclusion can be drawn, due to the poor methodological quality (4) and the conflicting evidences on the same pathology of the retrieved studies (1,2).

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5.1.2.2. *Does diagnostic and/or operative hysteroscopy performed at any stage of diagnostic work up improves pregnancy rate?*

P. Women of infertile couple

I. Hysteroscopy

C. No hysteroscopy

O. Pregnancy rate

S. RCTs and their SRs, prospective cohort studies, case control studies and their SRs

Bibliographic search

We searched Medline (2009 to October 2011) with the following key words: "Infertility, Female"[Mesh) AND ("Hysteroscopy"[Mesh] OR "office Hysteroscopy" OR "outpatient Hysteroscopy") AND "Pregnancy Rate"[Mesh]. We limited the search to articles published in : English, French, Italian, Spanish published since 2009 to December 2011 because we found one systematic review which included studies published up to the end of 2008 (Boostel 2010). Methodological quality of retrieved studies was assessed with the validated checklist reported in the method chapter of the guideline.

Assessment and synthesis of the evidence

Only 3 studies were included: two systematic reviews (1,2) and 1 retrospective controlled cohort study (3). Boostel 2010 (1) included two randomised controlled trials fulfilling our inclusion criteria, Lieng 2010 (2) included 1 RCT fulfilling our inclusion criteria and three observation controlled studies which did not meet our inclusion criteria.

Removal of endometrial polyps by hysteroscopy: one RCT was found (included in the SR of Boostel 2010 and in the SR of Lieng 2010) which compared operative hysteroscopy with diagnostic hysteroscopy alone on 215 patients with primary infertility (3). Results are in favour of the intervention, since pregnancy rate after four IUI had a RR 2.3 (95% CI: 1.6–3.2), and a spontaneous pregnancy rate with a RR 10 (95% CI: 3–30).

With respect to the role of *hysteroscopic myomectomy* one RCT was found (included in the SR of Boostel 2010) comparing intervention by hysteroscopy vs no intervention on 94 patients with primary infertility (4): the results were not statistically significant (RR: 1.6; 95% CI: 0.7–3.5).

In the case of *metroplasty for septate uterus,* no RCTs were found. One retrospective controlled cohort study (5) compared hysteroscopic metroplasty vs no intervention on 127 patients with primary infertility. Results are in favour of the intervention, since pregnancy rate was of 43.1% vs 20% (P: 0.03); live birth rate of 35.3% vs 8% (P: 0.008). It should be considered however that there was a big imbalance between treated and control group (102 vs 25) which could bias the results.

Regarding s*ynechiolysis* no RCTs or non randomised controlled studies were found comparing hysteroscopic intervention *vs* no intervention, not allowing us to drive conclusions

In summary, few methodologically sounding studies evaluated the role of diagnostic and operative hysteroscopy in improving pregnancy rate after treatment of intrauterine abnormalities. The lack of well-conducted RCTs is the main limiting factor; this is due to ethical concerns in randomizing women, as intrauterine abnormalities are likely to negatively affect reproductive outcome. Thus definitive conclusions cannot be drawn. Despite no definite conclusions can be made because of limited number of RCT, the retrieved studies suggest a positive role of the hysteroscopic polypectomy (**LEVEL OF EVIDENCE II**) and metroplasty (**LEVEL OF EVIDENCE III**) in improving pregnancy rate, but not of myomectomy (**LEVEL OF EVIDENCE II**).

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Recommendation

Given the low invasiveness and the safety of office hysteroscopy and the desire for the infertile couple to shorten as much as possible the diagnostic period which is often reason of anxiety and uncertainty, it is reasonable to recommend evaluation of uterine cavity by hysteroscopy in the diagnostic work up of infertile couples **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMMENDATION B).**

Wherever intrauterine diseases are detected, their removal should be performed in order to improve pregnancy outcome **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMMENDATION B)**.

5.1.3 Hysteroscopy in women candidate to IVF

A. Does diagnostic or operative hysteroscopy performed before the first IVF improves pregnancy rates?

P. Women of infertile couple candidate to first IVF

I. Hysteroscopy

C. No hysteroscopy

O. Pregnancy rate

S. RCTs and their SRs, prospective cohort studies, case control studies and their SRs

B. Does diagnostic or operative hysteroscopy performed after one failed IVF before the further IVF attempt improves pregnancy rates?

P. Women of infertile couple candidate to second IVF (after one failed)

I. Hysteroscopy

C. No hysteroscopy

O. Pregnancy rate

S. RCTs and their SRs, prospective cohort studies, case control studies and their SRs

C. Does diagnostic or operative hysteroscopy performed after two or more failed IVF before the further IVF attempt improves pregnancy rates?

P. Women of infertile couple with two or more previous IVF failed attempts candidate to further IVF

I. Hysteroscopy

C. No hysteroscopy

O. Pregnancy rate

S. RCTs and their SRs, prospective cohort studies, case control studies and their SRs

Bibliographic search

We searched Medline (2009 to October 2011) with the following key words: ("Hysteroscopy"[Mesh] OR "office Hysteroscopy" OR "outpatient Hysteroscopy") AND (IVF pregnancy OR "In vitro fertilization" OR intracytoplasmatic sperm injection"OR "Fertilization in Vitro"[Mesh]) . We limited the search to articles published in : English, French, Italian, Spanish, and published between 2009 and September 2011 because we already had two systematic reviews which included studies published up to the end of 2008 (Boostel 2010, El Toukhy 2008)

Assessment and synthesis of the evidence

Six potentially relevant studies (1-6) were identified; however we were unable to retrieve the full text of one of those studies (4) . Thus five studies were finally included. All were relevant to question C (1-3,5,6) and two also for questions A (2,6). The methodological quality of all the included studies was good.

Efficacy of diagnostic or operative hysteroscopy performed before the first IVF on improving pregnancy rates. The SR of El Toukhy 2008 (2) included two non randomised studies where patients were having their first or subsequent IVF attempt as well as the RCT of Shawki 2012 (6), In Shawki 2012 and one of the two non randomised study included in the SR separate data for women with two or more previous attempt and women at their first attempt are not reported.

The other non randomised included in the SR (7) included 600 patients. Three hundred patients with normal transvaginal ultrasound and hysterosalpingogram had hysteroscopy just before starting their first IVF cycle and were compared with 300 patients with similar characteristics who did not have a hysteroscopy before their IVF cycle. The authors reported no significant differences between the two groups with regards to ovarian stimulation or number and quality of oocytes and embryos replaced. The pregnancy rate was significantly higher in the hysteroscopy group (38% versus 18%, $P = 0.02$). The authors noted no difference within the hysteroscopy group in the pregnancy rate between those who had normal or abnormal hysteroscopic findings.

Efficacy of diagnostic or operative hysteroscopy performed after the first failed IVF and before the further IVF attempt on improving pregnancy rates. No studies were retrieved which assessed the efficacy of hysteroscopy performed after the first failed IVF on pregnancy rate.

Efficacy of diagnostic or operative hysteroscopy performed after two or three failed IVF and before the further IVF attempt on improving pregnancy rates. One study (3) is a protocol of a randomised controlled trial, which has the aim to assess if hysteroscopy performed prior to IVF improves the live birth rate in women who had two, or more failed IVF cycles versus no hysteroscopy.

Two studies are systematic reviews (1,2). Both include two randomised controlled trials (8,9: 941 participants) Meta-analysis of the two studies gave an RR of 1.57 (95%CI 1.29-1.92) in favour of hysteroscopy . In the intervention group there was no significant difference in treatment effect between women with normal findings and women with uterine pathology: RR 1.0 (95%CI 0.7-1.2).

The fourth study (5) is a prospective observational study with 1475 patients who performed office hysteroscopy (OH) and 414 historical controls matched for infertility, female age (±6 months), normal uterine cavity on HSG performed within 12 months before the first IVF attempt, history of 2 consecutive implantation failures, no obvious pathology of the uterine cavity on USS, and new fresh IVF cycle in the same IVF unit with same type of ovarian stimulation protocol, same type of IVF method (conventional IVF or ICSI), and embryo transfer on the same day post retrieval

with the same number and similar quality of transferred embryos. The study found that performing OH significantly increases pregnancy rate : (35% vs 25.1%, p:0.002) In the OH group clinical pregnancies were significant more frequent in women with found and treated abnormalities compared with those with no abnormalities (37.2% vs 32.2% p :0.04)

The last study is a randomised controlled trial (6) with 240 participants; 20.2% in the control group and 27.4% in the experimental group had 2 or more failed IVF trials. Pregnancy rate was significantly increased in the overall experimental group versus control: 38% vs 27.2%, p< 0.05) as well as in the normal OH subgroup (35.7% vs 27.2% p<0.05) and in the subgroup with abnormalities found and corrected during OH (42.8% vs 27.2% p vs control < 0.05). The results of the study did not report disaggregated data for women with at least two failed IVF trails and women with one or none failed IVF trials.

In summary, hysteroscopy is beneficial for women experiencing implantation failures after IVF. Uterine cavity abnormalities, mostly unsuspected on previous ultrasound scan and HSG, are identified in a remarkable proportion (25–50%) of such women. The correction of these abnormalities improves pregnancy rates, at least when compared to controls while not having a hysteroscopy. There is also evidence that subsequent pregnancy rates are improved even in reference women with normal hysteroscopy compared to controls, and that just the application of the procedure has a positive prognostic value for achieving a subsequent pregnancy.

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Recommendations

Hysteroscopy should be recommended for women with repeated implantation failure **(LEVEL OF EVIDENCE I, STRENGH OF THE RECOMMENDATION A).** Whether a similar beneficial effect applies to women who are going for the first or second IVF needs to be further investigated **(LEVEL OF EVIDENCE III)**. However, a "screening" hysteroscopy should be performed before including patients in an IVF program in order to minimize any negative intrauterine influence on IVF outcome **(LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMENDATION B).**

5.1.4 Hysteroscopy in women with recurrent miscarriages

Does office hysteroscopy performed in women with recurrent pregnancy loss (at least three consecutive spontaneous miscarriage) improve live birth rate?

P. Women with at least three consecutive spontaneous miscarriages

I. Hysteroscopy

C. No hysteroscopy

O. Live birth rate

S. RCTs and their SRs, prospective cohort studies, case control studies and their SRs

Bibliographic search

We searched Medline (2009 to October 2011) with the following key words: ("Abortion, Habitual"[Mesh] OR miscarriage, recurrent OR recurrent pregnancy loss) AND ("Hysteroscopy"[Mesh] OR "office Hysteroscopy" OR "outpatient Hysteroscopy"). We limited the search to articles published in : English, French, Italian, Spanish published up to December 2011.

Assessment and synthesis of the evidence

We were unable to retrieve the full text of 9 of the potentially relevant study. We tried to retrieve some useful information from the abstract or from narrative reviews or other primary studies where they were cited. Fourteen studies were finally included after inspection of the full text, and other 6 using only the information available of the abstract (1,7,10,12,15,17). All but one of the included studies (18) were prospective or retrospective uncontrolled case series. We decided to include these studies even though they didn't fulfil the inclusion criteria for study design because they were the only source of available evidence.

The methodological quality of the studies was very low: there was not an untreated control group, the characteristics of participant was poorly described with regard to other possible causes of recurrent miscarriage and the length of follow up was not reported in 44% of the studies.

Valli 2004 (18) in a controlled prospective cohort study compared live birth rate in women who underwent hysteroscopic metroplasty for septate uterus and in women who did not because they refused surgery. During a 36 months follow up live birth rate was 71.6% in the treated group and 33.2% in the control group. The results of the uncontrolled case series are reported in Table 1.

Table I: results of the uncontrolled case series regarding the role of hysteroscopy in women with recurrent miscarriages. **SUA**: structural uterine anomalies; **n.r.**: not reported

Author	Participants	Follow up (months)	Live birth rate
Ayhan 1992	102 with bicornuate and septate uterus	n.r.	75%
Choe 1992	19 with uterine septum	42	66.6%
Colacurci 1996	48 with septate uterus	n.r.	64.6%
De Cherney 1986	72 with septate uterus	46	87.4%
Dendrinos 2008	25 with normal hysteroscopy. 23 with SUA: 9 intrauterine adhesions, 4 submucous myomas, 2 polyps and 5 septate uterus 3 bicornuate uterus	n.r.	successful ongoing pregnancy: SUA patients: (78%). normal hysteroscopy group, (32%).
Doridot 2003	33 with septate uterus	36	36.4%
Giacomucci 2011	170 with T-shaped uterus, septum/partial septum and arcuate uterus	n.r.	T-shaped uterus: 66.7%, septum/partial septum: 62.8% arcuate uterus: 55.6%
Goldemberg 1995	11 with septate uterus 12 with intrauterine adhesions	21.1 ± 10.3	intrauterine septum 45% intrauterine adhesions: 58.3%
Grimbizis 1998	9 with septate uterus	35.5 ± 19.7	88.9%
Guarino 1989	19 with septate uterus	n.r.	68%
Hollet Caines 2006	19 with septate uterus	58	72%
March 1987	79 with septate uterus	n.r.	87%
Nouri 2010	22 with septate uterus	68.6 ± 25.2	50%
Pabuccu 1997	24 with intrauterine adhesions	16	71%
Preutthipan 2001	28 with septate uterus	42	75%
Saygilli 2003	59 with septate uterus	18	89.7%
Valle 1996	124 with septate uterus	n.r.	73%
Ventolini 2004	14 with normal hysteroscopy. 9 with SUA: 5 intrauterine adhesions, 2 septated uterus, 1 submucosal leiomyoma, and 1 with the association of submucosal leiomyoma and septated uterus.	n.r.	SUA patients: 77.8%. normal hysteroscopy group :28.6%.
Venturoli 2002	72 with septate uterus	36±19.5	61.6%

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Recommendations

Diagnosis and treatment by hysteroscopy of uterine malformations and intrauterine adhesions in such patients may improve live birth rate and, therefore, their treatment could be recommended **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMENDATION B).**

It is recommended to evaluate uterine cavity by hysteroscopy in women with recurrent miscarriage **(LEVEL OF EVIDENCE VI, STRENGHT OF THE RECOMENDATION B)**.

5.2 USEFULNESS OF HYSTEROSCOPIC EVALUATION IN WOMEN UNDER TAMOXIFEN TREATMENT

5.2.1. Background

Breast cancer is the commonest cause of cancer death in women worldwide. Its incidence is increasing worldwide: most affected women have primary operable disease, which has an 80% 5-year survival rate overall (1). After breast-conserving surgery for pre- and post-menopausal patients with estrogen receptor-positive early and advanced breast cancer, administration of tamoxifen for 5 years constitutes the main adjuvant endocrine therapy (2). Indeed, many of the established risk factors for breast cancer are linked to estrogens, and the clinical rationale of using tamoxifen is based on the fact that it functions as an anti-estrogenic compound that competitively blocks the local estrogenic receptors preventing estrogen from binding to its receptor, and, therefore, blocking cancer cell growth (3).

The clinical interest regarding the use of tamoxifen relies on the fact that despite its reported antagonist effect, in other tissues such as the endometrium it behaves as an agonist, and thus may be characterized as a mixed agonist/antagonist activity (3,4), with the potential of causing endometrial cancer in some women. A great number of researchers reported a possible relation between tamoxifen and the development of malign neoplasies of the endometrium (5-8), and this is a reason why tamoxifen is typically only used for 5 years (2). Studies examining the relationship between risk for endometrial cancer and tamoxifen use have conflicting results. However, since the potential number of tamoxifen users is great as well as the risk of developing an endometrial cancer, based on the hypothesis that tamoxifen use slightly increases risk for endometrial cancer, some researchers advocate routine ultrasonography and endometrial biopsy for screening all women receiving tamoxifen (9).

After more than thirty years since its introduction - tamoxifen was approved by the FDA in 1978 for the treatment of breast cancer - several epidemiological, clinical and research studies have demonstrated that:

i) the endometrium of patients with breast cancer do present a greater frequency of proliferative wounds, before tamoxifen treatment (10);

ii) in the majority of patients taking tamoxifen the most frequent endometrial disease detected by hysteroscopy and histological evaluation refers to cystic atrophy, due to the imprisonment of glandulary secretions caused by the atrophy of glandular cells under the effect of the drug (11, 12);

iii) the activity of tamoxifen over the endometrium and its occasional carcinogenesis is not clearly determined yet (13);

iv) due to the large use of tamoxifen and its supposed carcinogenic effect on the endometrium, one would expect that the incidence of endometrial cancer in patients taking the drug to be greater than in the normal population (14).

Therefore, in creating the PICOS about the clinical usefulness of hysteroscopic evaluation of the endometrial cavity in tamoxifen users, we evaluated RCTs to test the hypotheses that the use of hysteroscopy at different times may reduce the incidence of endometrial lesions or of advanced endometrial cancer.

Bibliographic search

For all the PICOS questions we searched Medline without date restriction with the following key words: ("*Hysteroscopy*"[Mesh] OR "*Office Hysteroscopy*" OR ""*Outpatient Hysteroscopy*") AND "*Endometrial Neoplasms*"[Mesh] AND "*Tamoxifen*"[Mesh]. We limited the search to articles published in : English, French, Italian, Spanish. We also performed a broader search with the free text key words: *Hysteroscopy* AND *tamoxifen*. Finally we inspected the references of the retrieved studies by the search to retrieve further potentially useful articles.
Methodological quality of retrieved studies was assessed with the validated checklist reported in the method chapter of the guideline

5.2.2 Baseline endometrial evaluation by hysteroscopy

Does hysteroscopy performed before tamoxifen treatment reduce the incidence of endometrial lesions in women with breast cancer and candidate to therapy?

P: Patients with breast cancer candidate to tamoxifen therapy

I: Hysteroscopy before the start of tamoxifen therapy

C: No hysteroscopy (only endovaginal UV)

O: Incidence of endometrial lesions at follow up during therapy; Prevalence at baseline of endometrial lesions

S: RCTs e their systematic reviews, prospective controlled cohort studies, case control studies

Assessment and synthesis of the evidence

None of the retrieved studies strictly fulfilled the inclusion criteria because none of them was a comparative study with a control group of women not exposed to hysteroscopic baseline evaluation. We identified 10 uncontrolled case series (15-24) of women candidate to tamoxifen

therapy and assessed for baseline and incidence lesions, but were unable to retrieve 2 full text articles potentially relevant (23, 24).

One thousand and thirty patients were evaluated by hysteroscopy before starting tamoxifen treatment, and the median prevalence of baseline benign endometrial pathology - mainly endometrial polyps - was of 13.25%, ranging from 0% to 21.2%. With respect to the incidence of precancerous lesions – mainly atypical lesions - in these patients it ranged from 0 to 5.7%. On the contrary, at three years follow-up, incidence of atypical lesions in patients in whom endometrial pathology was found at baseline evaluation, ranged from 0 to 25%, median 2.4%.

Evaluation of the uterine cavity by hysteroscopy before tamoxifen treatment may help in identifying a group of high risk patients more sensitive to the carcinogenic effect of tamoxifen. On the other hand, the very low rate of atypical emerging lesions associated with tamoxifen intake would suggest the hypothesis that tamoxifen act as a promoter of already existing lesions.

Recommendations

Since the prevalence of precancerous lesions is high in estrogen receptor-positive breast cancer patients before tamoxifen administration, we would suggest screening at baseline by hysteroscopy and, if it is necessary for a better diagnosis, endometrial biopsy **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION B).**

5.2.3 Routine endometrial evaluation by hysteroscopy

Does hysteroscopy at regular interval (i.e. annually) reduce the incidence of endometrial lesions in women with breast cancer who receive tamoxifen therapy?

P: Patients with breast cancer who receive tamoxifen therapy

I: Hysteroscopy at regular interval (i.e. annually)

C: No hysteroscopy (only endovaginal UV)

O: Incidence of endometrial lesions at follow up during therapy;

S: RCTs and their systematic reviews, prospective controlled cohort studies, case control studies

Assessment and synthesis of the evidence

No articles were retrieved which fulfilled the inclusion criteria defined by PICOS because none of them was a comparative study with a control group of women not exposed to hysteroscopy

during tamoxifen therapy. Thus, only 2 cross sectional studies were identified (25, 26).

In one (25) of these studies hysteroscopy was performed only on women already in tamoxifen therapy with endometrial thickness > 5 mm., as assessed by ultrasounds, to ascertain prevalence of endometrial pathology during treatment: endometrial lesions were found in 54% of women with endometrial thickness above the ultrasonography threshold. None was atypical lesions or cancer.

In the second cross sectional article (26), the use of hysteroscopy in patients who receive tamoxifen therapy was able to reveal the presence of polyps in 36% and atypical lesions in 4% of patients.

The diagnostic accuracy of hysteroscopy in detecting endometrial pathology in women taking tamoxifen for at least six months was also evaluated (27-29). The sensitivity and specificity of two cut-offs of endometrial thickness (at 6 mm: 87% and 27%; at 10 mm: 36% and 57%) by the means of transvaginal ultrasounds (TVS) were compared to those of diagnostic hysteroscopy and endometrial sampling for histological examination (50% and 98%). At hysteroscopy and histological examination non atypical hyperplasia was found in 4.8%, atypical changes in 1.3% and carcinoma in 1% of patients (27).

In another study (28) the diagnostic accuracy of TVS and hysteroscopy was found to be comparable (sensitivity and specificity were 85% and 100% for TVS and 77% and 92% for hysteroscopy). Finally, Garuti and co-workers (29) found that sensitivity and specificity of hysteroscopy in detecting endometrial lesions were 100% and 94.1%, respectively.

Data suggest that TVS is a poor screening tool because of the high false-positive rate, and the fact that TVS does not seem accurate in identifying hyperplasia and polyps because both endometrial thickness (whatever cut-off is chosen) and ultrasonographic feature (echotexture, borders) missed hyperplastic changes and polyps in a significant number of women (30).

Recommendation

It seems reasonable to perform a single hysteroscopy annually in such women in order to reduce the incidence of endometrial lesions. However the lack of significant data on the cost-effectiveness of such innovative approach cannot allow to draw any definitive conclusion (**LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION C).**

5.2.4 Endometrial evaluation by hysteroscopy in abnormal uterine bleeding

Does hysteroscopy at the first appearance of abnormal endometrial bleeding reduce the incidence of advanced endometrial cancer in women with breast cancer who receive tamoxifen therapy?

P: Patients with breast cancer who receive tamoxifen therapy with abnormal endometrial bleeding

I: Hysteroscopy

C: No hysteroscopy

O: Incidence of endometrial cancer

S: RCTs and their systematic reviews, prospective controlled cohort studies, case control studies

Assessment and synthesis of the evidence

No articles were retrieved who fulfilled the inclusion criteria defined by PICOS question because none of them was a comparative study with a control group of women not exposed to hysteroscopy We found four cross sectional studies assessing the prevalence of endometrial pathology in women with and without vaginal bleeding taking tamoxifen for at least six months (31-34).

All the studies found a significant higher prevalence of endometrial pathology – both benign and malignant lesions - in women with vaginal bleeding [64.5% vs 22,3% (31); 56.5% vs 16.2% (32); 78% vs 47.4% (33); 67.6% vs 15.5% (34)]. A total of 15 endometrial adenocarcinoma was found, of whom only 2 in women without uterine bleeding.

Recommendations

Endometrial evaluation and sampling for histological evaluation are recommended in women receiving tamoxifen therapy with vaginal bleeding to early recognize and, therefore, reduce the incidence of endometrial cancer (**LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION B**).

5.2.5 Endometrial evaluation by hysteroscopy and increased endometrial thickness

Does hysteroscopy in case endometrial thickness ≥ 8mm reduce the incidence of advanced endometrial cancer in women with breast cancer who receive tamoxifen therapy?

P: Patients with breast cancer who receive tamoxifen therapy with endometrial thickness ≥ 8 mm

I: Hysteroscopy

C: Endovaginal UV

O: Incidence of endometrial cancer

S: RCTs e their systematic reviews, prospective controlled cohort studies, case control studies

Assessment and synthesis of the evidence

No articles were retrieved who fulfilled the inclusion criteria defined by PICOS question because none of them was a comparative study with a control group of women not exposed to hysteroscopy. We found one study (33) which assessed prevalence and incidence of endometrial pathology in women submitted to hysteroscopy in the case of endometrial thickness ≥ 8 mm. revealed that prevalence of endometrial diseases was significantly higher (60%) in women who had the thickness above the cut-off than those (6.2%) who had not.

Similar findings were retrieved by a prospective uncontrolled observational study (35): a significantly higher prevalence (18%) both of benign and malignant endometrial lesions were found by hysteroscopy followed by biopsy in women with an endometrium thickened above 8mm, than those with normal endometrial thickness (3.3%). Moreover, a significant association between endometrial pathology and both cumulated dose and total duration of tamoxifen was found, since prevalence of any endometrial lesion increased with years of therapy (8.1% after 1; 15.5% after 1-2; 25.6% after 2-5; 37.5 after more than 5 years) (35).

Contrasting findings were retrieved by the study of Seoud et al. (36), however due to the limited sample size the study did not reach the sufficient statistical power to drive detect differences.

Recommendations

Since increasing endometrial thickness is likely to be associated with precancerous endometrial lesions, in asymptomatic women receiving tamoxifen with endometrial thickness ≥ 8 mm hysteroscopy should be performed in order to detect endometrial polyp and/or cancer. **(LEVEL OF EVIDENCE V, STRENGH OF THE RECOMMENDATION B).**

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5.3 ROLE OF HYSTEROSCOPY FOR DIAGNOSING ENDOUTERINE ABNORMALITIES IN WOMEN WITH ABNORMAL UTERINE BLEEDING

5.3.1 Background

Abnormal uterine bleeding (AUB) – i.e. bleeding that occurs between menstrual periods or excessive menstrual bleeding in fertile patients or any uterine bleeding in a menopausal woman (other than the expected cyclic bleeding that occurs in women taking sequential post-menopausal hormone therapy) - is responsible for as many as one-third of all office gynecologic visits, with the majority of cases occurring in the perimenopausal period (1,2). It can be caused by a wide variety of local and systemic disease or related to drugs. However a significant number of women who complain of abnormal uterine bleeding have uterine abnormalities (eg, fibroids, polyps, adenomyosis), or neoplasia (3).

While the diagnosis of AUB is based on a woman's personal assessment of her blood loss and its impact upon her quality of life (4), uterine abnormalities can only be diagnosed by imaging studies, and excision is sometimes required for confirmation of the diagnosis and treatment. Thus, woman's medical history and physical examination to evaluate overall health is mandatory. Pelvic examination with inspection of the cervix is important to confirm that the bleeding originates from the uterus and not from another site (eg, the external genitalia, urinary tract or rectum). A Pap smear may be obtained to exclude cytological anomalies of the cervix. After excluding hormonal irregularities leading to chronic anovulation, coagulopathies and other relevant medical conditions and pregnancy in premenopausal women, an assessment of the uterus and of the endometrium has to be performed to exclude endometrial cancer or hyperplasia and inrtrauterine abnormalities.

In the PICOS we ideated on AUB, we weighted the clinical relevance and the diagnostic accuracy of hysteroscopy compared to other techniques (US, sonohysterograpgy, D&C, Pipelle, Vabra, Novack) in leading the physician to a final diagnosis on endouterine pathologies.

Bibliographic search

For all the PICOS questions we performed the following search strategies: In first instance the following bibliographic search was done on Medline without date restriction to search only systematic reviews: Hysteroscopy" [Mesh] AND ("Uterine Hemorrhage/diagnosis" [Mesh] OR "Polyps/diagnosis"[Mesh] OR "Endometrial Neoplasms/diagnosis" [Mesh] OR "Endometrium/pathology" [Mesh]) AND "Sensitivity and Specificity" [Mesh] LIMIT TO "Systematic reviews" on clinical queries. Then a bibliographic search with the same search strategy but without the limit for systematic reviews was performed since January 2006 to November 2012

to search for diagnostic accuracy primary studies published after the date of the most updated systematic review retrieved with the first search. Finally a broader search without date restriction and without the key word "Sensitivity and Specificity"[Mesh] was done to retrieve RCTs or comparative observation studies for question 3.2.2. Only studies published in English, Italian, French and Spanish were considered for all the searches. Methodological quality of retrieved studies was assessed with the validated checklist reported in the method chapter of the guideline.

5.3.2 Hysteroscopy in fertile women

*Is hysteroscopy more accurate than other techniques (endovaginal UV, sonohysterography) in diagnosing endouterine pathologies (myoma, polyps, hyperplasia, caesarian scar, isthmocel, cancer) in **premenopausal women** with AUB?*

P: Fertile women with abnormal uterine bleeding

I: Hysteroscopy

C: Other techniques (US, sonohysterograpgy)

O: Sensitivity and Specificity for detecting endouterine pathologies (myoma, polyps, hyperplasia, caesarian scar, isthmocel, cancer)

S: Cross sectional diagnostic accuracy studies

Assessment and synthesis of the evidence

Seven studies were judged relevant for this question. The review of Farquhar et al. (5) was really pertinent to the above PICOS, since it compared the diagnostic accuracy of TVUS, hysteroscopy and, sonohysterography for premenopausal women with AUB, by evaluating 19 studies involving 2,917 women. The studies did not provide direct comparison of the different tests on the same women, but they assessed the accuracy of a single test in the respect of a reference standard. In the detection of any intrauterine pathology TVUS sensitivity ranged from 46% to 100% and specificity from 12% to 100%, Likelihood ratio (LR) for a positive test ranged from1.05 to 51.56 and for a negative test from 0.07 to 0.79. Sonohysterography sensitivity ranged from 85% to 100% and specificity from 81% to 100%, with LR for a positive test ranging from 1.96 to 80.0 and for a negative test the pooled LR being 0.12 (95% CI: 0.08, 0.18). With respect to hysteroscopy, sensitivity ranged from 90% to 97% and specificity from 62% to 93%; LR for a positive test ranged from 2.55 to 14.56 and for a negative test the pooled LR was 0.07 (95% CI: 0.04, 0.15).

In the detection of any endometrial hyperplasia or carcinoma TVUS sensitivity ranged from 33% to 100% and specificity from 79% to 99%; LR for a positive test ranged from 2.59 to 679 and

for a negative test from 0.04 to 1.00. Sonohysterography sensitivity ranged from 29% to 80% and specificity from 82% to 100%; LR for a positive test ranged from 1.55 to 70.40 and for a negative test from 0.14 to 0.88. Hysteroscopy sensitivity ranged from 90% to 100% and specificity from 97% to 100%. Pooled LR for a positive test was 92.84 (95% CI: 47.0, 111.7) and for a negative test was 0.05 (95% CI: 0.02, 0.12). When the results were not pooled it was because of statically significant heterogeneity. Authors concluded that all the tests are moderately accurate in detecting intrauterine pathology but the high heterogeneity found between the results should be carefully considered.

The paper of Van Dongen et al. (6) assessed the accuracy of hysteroscopy in diagnosis any intracavitary abnormalities including all intrauterine polyps, myomas, synechiae, septae, and (pre-) malignancies, including 8 studies with premenopausal women. However, no comparisons were done regarding diagnostic accuracy between hysteroscopy and other tests. Pooled LR for a positive test was 8.3 (95% CI 2.9–23.9) and for a negative test was 0.11 (95% CI 0.08–0.15), allowing Authors to conclude that diagnostic hysteroscopy is both accurate and feasible in the diagnosis of intrauterine abnormalities.

We also selected the review of Clark et al (7), as well as the primary studies published after January 2006 (8-11) tùhat, however, did not show separate data for premenopausal women but for both pre and post- menopausal women considered altogether. Some studies (7-9) only assessed the diagnostic accuracy of hysteroscopy without comparison of diagnostic accuracy between hysteroscopy and other tests, whereas the study of Khan et al. (11) and Makirs et al (9) compared the diagnostic accuracy of hysteroscopy with saline infusion sonohysterography (3D SIS or 3-DHS, respectively). The results of these studies are shown in Table 1.

5.3.3 Hysteroscopy in post-menopausal women

*Is hysteroscopy more accurate than other techniques (endovaginal UV, sonohysterography) in diagnosing endouterine pathology in **postmenopausal women** with abnormal uterine bleeding?*

P: Post-menopausal women with abnormal uterine bleeding

I: Hysteroscopy

C: Other techniques (US, sonohysterograpgy)

O: Sensitivity and Specificity for detecting endouterine pathology (mioma, polyps, hyperplasia, cesarean scar, istmocele, cancer)

S: Cross sectional diagnostic accuracy studies

Assessment and synthesis of the evidence

Nine studies were considered relevant for these questions. The study of Van Hanegen et al. (12) included 9 systematic reviews (SRs) assessing the diagnostic accuracy of transvaginal sonography (TVS), outpatient endometrial sampling, saline infusion sonography (SIS) and hysteroscopy. Four SRs assessed the use of TVS (13-16), one described the use of SIS (17), 2 study evaluated the use of outpatient endometrial sampling (18,19). Authors concluded that all four types of test (hysteroscopy; TVS; outpatient endometrial sampling; SIS) are accurate and feasible in excluding or diagnosing endometrial cancer, by their high sensitivities and specificities. However, they also concluded that in neither systematic reviews nor international guidelines can consensus be found regarding the sequence in which the different procedures should be implemented.

With respect the accuracy of hysteroscopy in diagnosing any endouterine pathology in post-menopausal women, Clark (7) evaluated the diagnostic accuracy for endometrial cancer, hyperplasia or both and for endometrial cancer alone. Positive and negative LR was 38.3 (95%CI: 26.1 – 56.1) and 0.13 (95%CI 0.09 – 0.18), respectively, for endometrial cancer; 20.4 (95%CI 15.7 – 56.6) and 0.14 (95%CI 0.11 – 0.19) respectively for any endometrial disease. Authors concluded that hysteroscopy is highly accurate in diagnosing endometrial cancer, but is only moderately accurate in diagnosing endometrial disease.

The study of Van Dongen (6) evaluated the diagnostic accuracy for intrauterine polyps, myomas, synechiae, septae, and (pre-)malignancies. Pooled sensitivity was 0.96 (95% CI 0.93–0.99), specificity: 0.90 (95% CI 0.83–0.95), LR + 7.9 (95% CI 4.79–13.10), LR - : 0.04 (95% CI 0.02–0.09). Authors concluded that diagnostic hysteroscopy is both accurate and feasible in the diagnosis of intrauterine abnormalities. Out of the seven primary studies included four (9-11) did not show separate data for postmenopausal women but for both pre and post- menopausal women considered altogether, and were listed in Table 2 reported above.

Table 2 refers on the diagnostic accuracy between hysteroscopy and other tests [in detecting benign lesions, endometrial hyperplasia, carcinoma (20); endometrial atrophy, hyperplasia, polypoid lesions, myoma and cancer using histology as reference standard (21); uterine abnormalities (22)]. In more details, Bingol et al. (21) concluded that TVUS, sonohysterography and hysteroscopy (HS) were similar in the detection of endometrial atrophy and endometrial cancer. On the other hand, although inferior to biopsy as a gold standard, the accuracy of SIS and HS in the detection of submucosal myoma was identical and better than TVS. The accuracy of HS and SIS in the detection of endometrial hyperplasia and polypoid lesions was comparable and significantly better than TVS.

On the contrary, Tinelli (22) concluded that hysteroscopy is significantly more accurate as

diagnostic method for the detection of endometrial pathology than TVS, has better specificity, and should be considered for all women with AUB with an endometrial thickness of more than 4 mm. Indeed, in the opinion of the Authors, an endometrial thickness less than 4 mm in women with AUB is of no absolute safety in excluding relevant endometrial pathology. They suggest that hysteroscopy should be indicated in cases of AUB with an endometrial thickness of less than 4 mm on ultrasonography because of the possibility of missing infrequent (0.8%) but relevant endometrial pathologies. Hysteroscopy with eye directed biopsy should be performed in selected women with AUB when the endometrial thickness is less than 4 mm and risk factors for endometrial carcinoma are present.

Finally, Elfayomy et al. (20) concluded that hysteroscopy can be used as the first line diagnostic tool for evaluating the benign endometrial lesions, such as endometrial polyp and submucosal myoma, nonetheless hysteroscopy has poor validity for excluding endometrial hyperplasia and cancer in women presenting with the postmenopausal bleeding and thick endometrium.

Table 1: Diagnostic accuracy of hysteroscopy for pre and postmenopausal women with AUB considered altogether. HA: Hysteroscopy

Authors	Participants	Any endometrial disease	Endometrial cancer	Endometrial hyperplasia
Clark et al., 2002	26346 patients	Sens 78 % (76.3 – 79.6) Spec 95.8 % (95.6 – 96.1) LR + 10.4 (9.7 – 11.1) LR – 0.24 (0.22 – 0.25)	Sens 86.4 % (84 – 88.6) Spec 99.2 % (99.1 – 99.3) LR + 60.9 (51.2 – 61.5) LR - 0.15 (0.13 – 0.18)	
Lasmar et al., 2006	4054 patients		Sens 80.0 (70.8–86.9) Spec 99.5 (99.2–99.7) PPV 81.6 (72.4–88.3) NPV 99.5 (99.2–99.7)	Sens 56.3 (52.2–60.2) Spec 89.1 (88.0–90.1) PPV 48.0 (44.3–51.7) NPV 92.0 (91.0–92.9)
Makris et al., 2007	242 patients	**- HA** Sens 98.7% Spec 99.4% PPV 98.7% NPV 99.4% **- 3-DHS** Sens 93.5% Spec 99.4% PPV 98.6% NPV 97%		
Zlatkov et al., 2007	635 patients		Cancer and precancer lesions Sens 74.1% Spec 90.6% PPV 53.6% NPV 95.9%	
Khan et al., 2011	55 patients	**- HA** Sens 98% Spec 67% PPV 98% NPV 67% **- 3D SIS** Sens 100% Spec 67% PPV 98% NPV 100%		

Table 2: Diagnostic accuracy of hysteroscopy for postmenopausal women with AUB.

Authors	Partici pants	Any endometrial disease	Endometrial cancer	Endometrial hyperplasia	Polypoid lesions	Myoma
Bingol 2011	137 patients	**- TVS** Sens 0.700 (0.600–0.785) Spec 0.500 (0.324–0.675) PPV 0.809 (0.711–0.884) NPV 0.354 (0.221–0.505) **- SIS** Sens 0.896 (0.822–0.944) Spec 0.773 (0.545–0.923) PPV 0.953 (0.895–0.985) NPV 0.583 (0.385–0.766) **- HS** Sens 0.923 (0.858–0.964) Spec 0.807 (0.581–0.944) PPV 0.962 (0.910–0.989) NPV 0.653 (0.443–0.828)	**- TVS** Sens 0.375 (0.085–0.755) Spec 0.976 (0.932–0.995) PPV 0.500 (0.118–0.882) NPV 0.961 (0.912–0.984) **- SIS** Sens 0.375 (0.085–0.755) Spec 0.992 (0.957–0.999) PPV 0.750 (0.194–0.993) NPV 0.962 (0.913–0.987) **- HS** Sens 0.375 (0.085–0.755) Spec 0.962 (0.913–0.987) PPV 0.600 (0.146–0.947) NPV 0.961 (0.913–0.987)	**- TVS** Sens 0.692 (0.524–0.829) Spec 0.806 (0.714–0.878) PPV 0.587 (0.432–0.729) NPV 0.686 (0.780–0.929) **- SIS** Sens 0.923 (0.791–0.938) Spec 0.979 (0.928–0.997) PPV 0.947 (0.822–0.993) NPV 0.969 (0.913–0.993) **- HS** Sens 0.948 (0.826–0.993) Spec 0.989 (0.944–0.999) PPV 0.973 (0.861–0.999) NPV 0.979 (0.929–0.997)	**- TVS** Sens 0.557 (0.413–0.694) Spec 0.847 (0.752–0.916) PPV 0.690 (0.529–0.823) NPV 0.757 (0.659–0.839) **- SIS** Sens 0.961 (0.868–0.995) Spec 0.953 (0.883–0.978) PPV 0.953 (0.821–0.975) NPV 0.957 (0.915–0.997) **- HS** Sens 0.980 (0.897–0.999) Spec 0.965 (0.900–9.992) PPV 0.944 (0.846–0.988) NPV 0.988 (0.935–0.999)	**- TVS** Sens 0.650 (0.407–0.846) Spec 0.850 (0.621–0.968) PPV 0.812 (0.543–0.959) NPV 0.708 (0.488–0.873) **- SIS** Sens 0.700 (0.457–0.881) Spec 0.944 (0.727–0.998) PPV 0.933 (0.680–0.998) NPV 0.7391 (0.516–0.897) **- HS** Sens 0.700 (0.457–0.881) Spec 0.944 (0.727–0.998) PPV 0.933 (0.680–0.998) NPV 0.7391 (0.516–0.897)
Elfayomy 2011		Only any benign abnormality Sens 0.947 Spec 0.978 PPV 0.973 NPV 0.957	Sens: 0.50 Spec 0.942 PPV: 0.636 NPV 0.902	Sens 0.565 Spec 0.916 PPV 0.722 NPV 0.846		
Tinelli 2008		**- TVS** Sens 0.89 Spec 0.86 PPV 0.82 NPV 0.92 **- HS** Sens 0.98 Spec 0.91 PPV 0.88 NPV 0.98				

Recommendations

Sonohysterography, hysteroscopy and transvaginal ultrasound are accurate and feasible in diagnosing or excluding endouterine diseases both in pre and postmenopausla women. Hysteroscopy should always bep erformed in women presenting with AUB, in whom other tests (sonohysterography and/or transvaginal ultrasound) already reported or could non exclude endouterine pathologies **(LEVEL OF EVIDENCE III, STRENGH OF THE RECOMMENDATION B)**.

5.3.4 *Should hysteroscopy be performed in postmenopausal women with abnormal uterine bleeding and negative ultrasound?*

P: Post-menopausal women with abnormal uterine bleeding and negative ultrasound (endometrial thickness < 5mm)

I: Hysteroscopy

C: No intervention

O: Incidence of endometrial cancer

S: RCTs and their systematic reviews, prospective controlled cohort studies, case control studies

Assessment and synthesis of the evidence

No studies were found which were directly aimed to answer to this question. However, we report the paper of Timmermans et al. (23), that was aimed at assessing the efficacy of removal of polyps by hysteroscopy vs. expectant management on the incidence of endometrial cancer. Unfortunately, the trial failed because of lack of recruitment related both to doctors seeking for informed consent as well as to patients' unwillingness to participate in this trial.

Recommendations

Despite no studies are available on this topic, it is reasonable to recommend evaluation of endometrial cavity by hysteroscopy when repeated episodes of AUB are reported by such women (**LEVEL OF EVIDENCE VI, STRENGH OF THE RECOMMENDATION B**).

5.3.5 *Does eye (target) directed biopsy during hysteroscopic examination improve diagnostic accuracy of atypical lesions (atypical hyperplasia, endometrial carcinoma ?)*

P: Post- menopausal women with abnormal uterine bleeding and negative ultrasound (endometrial thickness < 5mm)

I: Directed biopsy during hysteroscopic examination

C1: Blind biopsy (D&C, Pipelle, Vabra, Novak)

C2: Oriented biopsy (i.e. hysteroscopy performed before the blind biopsy)

O: Sensitivity and specificity in detecting atypical lesions

S: Cross sectional diagnostic accuracy studies

Assessment and synthesis of the evidence

Only the RCT of Zhu et al, (24) was considered relevant for this question, since it evaluated the accuracy in detecting endometrial carcinoma by using hysteroscopy and guided biopsy compared to D&C in 287 pre and post- menopausal patients with endometrial carcinoma who were randomised to receive hysteroscopy and guided biopsy or D&C. It also computed the overall 3 and 5 year survival for patients and, the risk of endometrial cancer cell abdominal spreading in the peritoneal cavity. Authors found that hysteroscopy and directed biopsy were superior to D&C in diagnosing endometrial carcinoma, with an overall accuracy of 97.8% for hysteroscopy and directed biopsy and of 88.8% for D&C *(P* <0.05). The study also failed to retrieve statistically significant differences in positive peritoneal cytology (5.6% vs 6.1% for hysteroscopy with directed biopsy and D&C respectively) as well as in 3 (hysteroscopy and directed biopsy : 91.4% D&C: 95.6%) and 5 year survival (hysteroscopy and directed biopsy: 82.4% D&C: 86.7%). Authors concluded that *i)* hysteroscopy with an infusion pressure below 80 mmHg did not increase the risk of positive peritoneal washings; ii) it did not influence the long-term survival rate or the prognosis and , that iii) hysteroscopy and directed biopsy were safe to perform on patients with endometrial cancer with careful manipulation and controlled intrauterine pressure.

With respect to the risk of the putative abdominal spreading of endometrial tumoral cells after hysteroscopy, we also found that SR of Polyzos et al. (25) that estimated the risk for disease upstaging associated with the hysteroscopic procedure before surgery in women with endometrial cancer. The outcomes considered were the incidence of malignant cells in peritoneal washings before hysterectomy, incidence of tumour upstaging due solely to the presence of a positive peritoneal cytological feature in patients with apparent clinical early-stage disease limited to the uterus; overall survival, disease-free survival, and disease recurrence. The results showed that hysteroscopy in patients with endometrial cancer resulted in statistically significant higher endometrial cancer cell seeding within the peritoneal cavity [OR: 1.78; (95% CI, 1.13-2.79)]. Sensitivity analysis including only trials in which hysteroscopy with isotonic sodium chloride was used showed a further increased risk [OR, 2.89; (95% CI, 1.48-5.64)], as well as sensitivity analysis including only trials in which inflated distension medium pressure reached or exerted 100 mm Hg [OR 3.23; (95% CI, 0.94-11.09)]. Also a statistically significant higher tumour upstaging was found when hysteroscopy was performed in patients with disease limited to the uterus compared with no hysteroscopy [OR, 2.61; (95% CI, 1.47-4.63)]. Data regarding overall survival and disease recurrence supported the notion that no significant difference for the prognostic outcomes tested was observed. Nonetheless, the number of events (deaths or recurrences) was too small and the

patients' follow-ups were inconsistent among eligible trials. Results of this meta-analysis should be considered with caution because only one RCT and one prospective study were included and all the others were retrospectives studies. Moreover only two observational studies adjusted for potential confounding and no information are given about the comparability of the groups at baseline for the non-randomised trials. Finally Authors combined in the meta-analysis the results of randomised and non-randomised studies, that is a questionable method. Looking at the results of the studies taken individually, the only RCT included in the SR had a sample size of only 50 patients and reported a non significant difference between groups for both the outcomes.

Recommendations

Eye directed biopsy is more accurate than blind biopsy, and therefore hysteroscopy with multiple target biopsies should be used in place of blind techniques in the diagnostic work-up for atypical lesions **(LEVEL OF EVIDENCE II, STRENGH OF THE RECOMMENDATION B).**

The possible risk of the spreading into the abdominal cavity of neoplastic cells should not limit the use of hysteroscopy in favour of blind techniques **(LEVEL OF EVIDENCE II, STRENGH OF THE RECOMMENDATION A).**

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