The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynecological symptoms: a systematic review

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Introduction

- The position of hysteroscopy in current fertility practice is under debate.
  - The procedure is well tolerated.
- No consensus on effectiveness of HSC in improving prognosis of subfertile women.
- systematic review on HSC in management of subfertile women is lacking

- Royal College of Obstetricians and Gynecologists (RCOG) *does not* recommend HSC as an initial investigation unless clinically indicated.
- European Society for Human Reproduction and Embryology has similar viewpoint.

Aims

systematic review (SR)

- operative hysteroscopy and **pregnancy rates** in subfertile patients with polyps, fibroids, septate uterus and intrauterine adhesions, with no other gynecological symptoms.
- diagnostic or operative hysteroscopy and **pregnancy rates** in subfertile patients treated by IVF or IUI.

Methods

- Literature search *(by 2 researchers)*
  - **Key words**: hysteroscopy, polyps, fibroids, congenital anomalies, Asherman's syndrome, adhesions and assisted reproductive techniques
  - **Database**: MEDLINE (1966 to 2008.11), EMBASE (1974 to 2008.11), CINAHL (1981 to 2008.11), the Cochrane Library (1970 to 2008.11)

Study selection

- RCTs and controlled studies
  - Study intervention → diagnostic / operative HSC
  - Main outcome → pregnancy rate
- Study group:
  - Subfertile women without symptoms with polyps, fibroids, septate uterus and intrauterine adhesions
  - Women treated by IVF / IUI

- Aim: the effectiveness of HSC in **restoring reproductive potential**
  - Exclude pregnancy complications as recurrent miscarriage, preterm labor or increased C/S rate due to malpresentation
  - Trials on diagnostic accuracy, pt compliance, cost-effectiveness not included
  - No language restriction

- The selected studies were assessed for methodological quality.
  - QUOROM guidelines for RCTs
  - MOOSE guidelines for non-randomized studies
- Statistical analysis
  - ∵ limited # of RCTs, additional meta-analysis or assessment for publication bias was not carried out.

Results

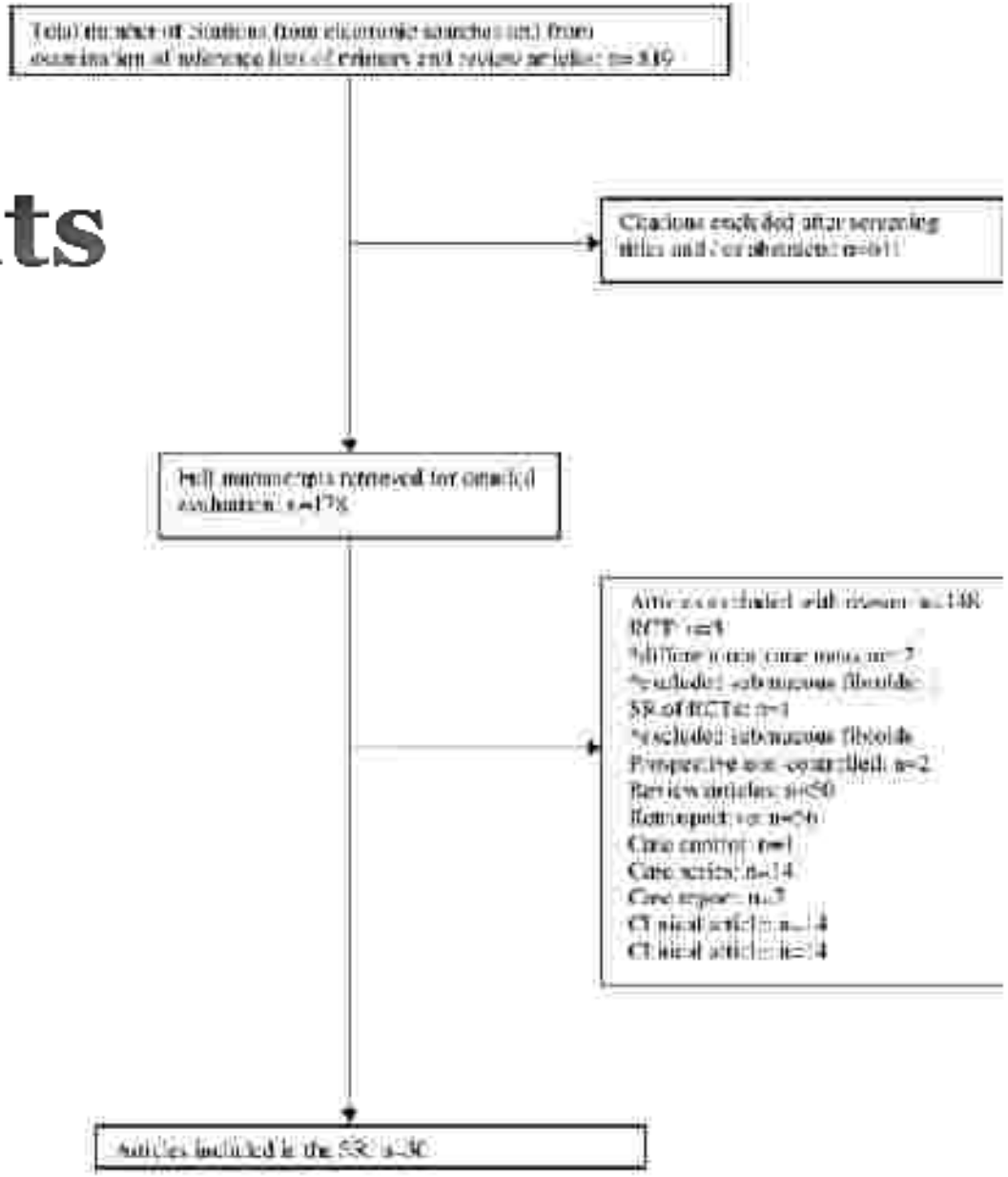


Figure 1 Flowchart for systematic review (SR) of benefit of hysteroscopy in current fertility practice.

Table 1 Effectiveness of operative hysteroscopy for polyps, fibroids and septate uterus on outcome (pregnancy); study characteristics

Pathology	Polyps	Fibroids	Septate uterus
Reference	Pérez-Medina et al., 2005	Casini et al., 2006	Corfman et al., 2007
Randomization method	Computer generated list	Randomization code	Computer generated list
Allocation concealment	Yes	No	No
Blinding	No	No	No
Groups comparable	Unclear	Yes	Yes
Intention-to-treat analysis	No	Yes	No
Follow-up rate analysis	>95%	>95%	<85%
Power calculation	Yes	No	No
Number of included patients	215	64	160
Intervention group	Hysteroscopic polypectomy (n = 107)	Hysteroscopy and/or laparotomy (n = 32)	5 mm hysteroscopy with Versapoint (n = 80)
Control group	Diagnostic hysteroscopy (n = 108)	No surgery (n = 32)	8 mm resectoscopy (n = 80)
Outcome measure	Total pregnancy rate and time for success after four cycles	Clinical pregnancy rate after 12 months	Clinical pregnancy rate

SR (1): 22 controlled studies

Table II Outpatient hysteroscopy in recurrent IVF failure

Reference	Demirol and Gurgan, 2004	Rama Raju et al., 2008
Method of randomization	Computer-generated list	Computer-generated list
Concealment	Yes	Not clear
Blinding	No	Yes
Groups comparable	Yes	Yes
Intention to treat analysis	Yes	Yes
Follow-up rate analysis	>95%	>95%
Number of included patients	421	320
Type of infertility	Primary	Primary
Previous investigations	HSG	HSG
IVF history	≥2 failed cycles	≥2 failed cycles
Timing of hysteroscopy	Follicular phase	Follicular phase
Dilatation medium	Saline	Glycine
% Abnormal findings	36%	37%
Intervention	5 mm hysteroscopy (*n* = 210)	5 mm hysteroscopy (*n* = 165)
Control	No hysteroscopy (*n* = 211)	No hysteroscopy (*n* = 155)
Outcome measure	Clinical pregnancy rate, miscarriage rate	Clinical pregnancy rate, miscarriage rate, live birth rate

Part I:

Does operative HSC increase the pregnancy rate in subfertile pt with specified intrauterine pathology?

- Polyps
- Fibroids
- Septate uterus
- Intrauterine adhesion

Hysteroscopic polypectomy

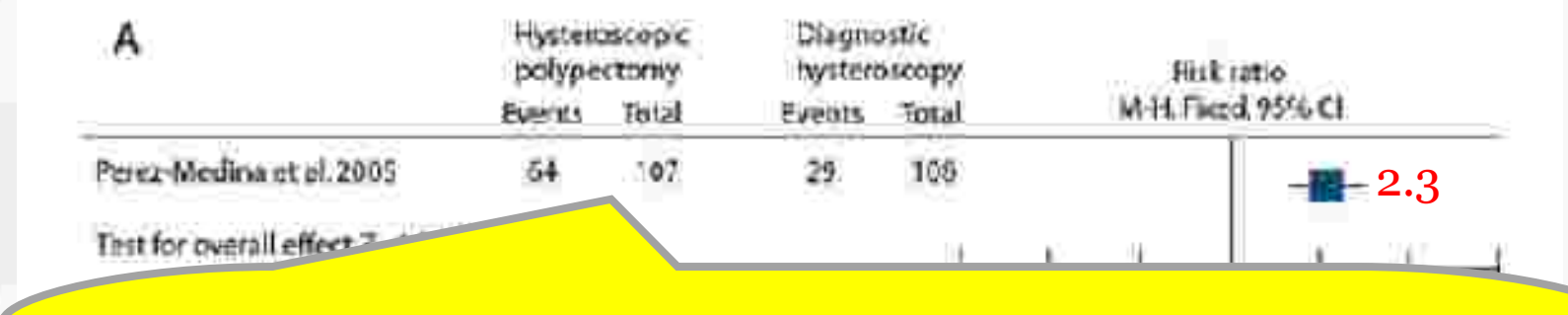
- Reference: Pe'rez-Medina et al., 2005, Muzii et al., 2007
- Settings: infertility clinic of university hospital for 50 months
- Study population:
  - subfertile pts without conceiving for >24 months and planned for IUI (n=2800)
  - TVS: hyperechoic mass with regular contour r/o EM polyp, presence of a vascular stalk on Doppler (n=452)
  - # of included pts: 215

Randomization

- Intervention group (n=107): 5.5 mm HSC polypectomy
- Control group (n=108): diagnostic HSC with biopsy

➔3 months later ➔ IUI for 4 cycles with hyperstimulation with rFSH

Clinical pregnancy rate: ↑hCG + sac(+) by TVS



- 65% of all pregnancies occurred before 1st IUI
- spontaneous pregnancy rate: 29% (polypectomy) vs. 3% (control group) ➔ RR=10

- Effect of size of polyp: 3-24 (16) mm

  pregnancy rate:

  - <5 mm: 19/25 (76%)
  - 5-10 mm: 18/32 (56%)
  - 11-20 mm: 16/26 (61%)
  - >20 mm: 11/18 (61%)

  $P>0.05$

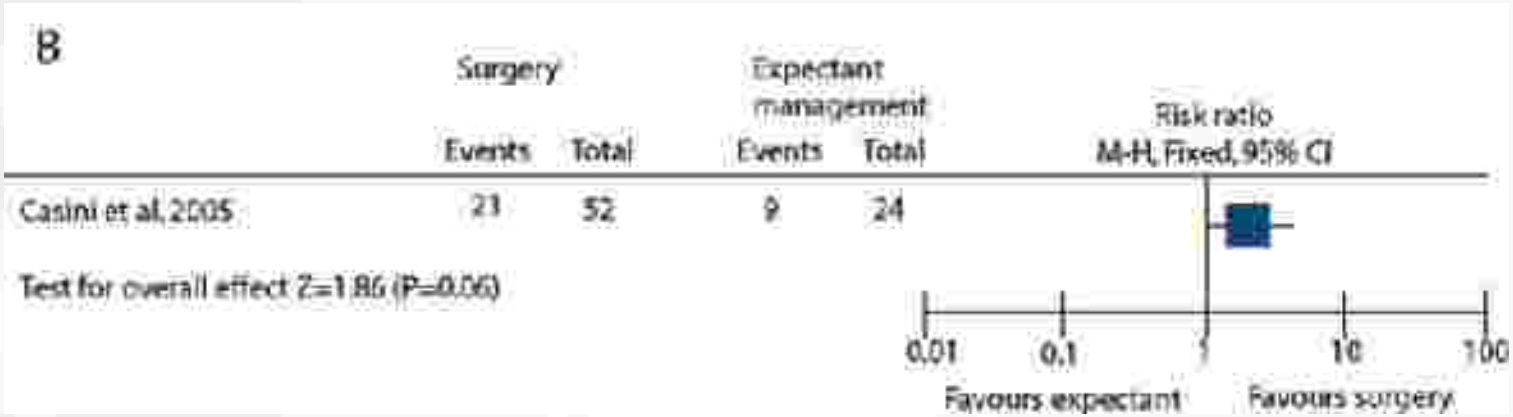
- No data on # and location of polyps

Hysteroscopic myomectomy

- Reference: Casini et al., 2006
- Settings: university fertility center, 01. 1998 ~ 04, 2005
- Study population: (n=193)
  - < 35 y/o, unexplained subfertile pts > 1 year, except for one knot(?)
  - ± TVS: fibroid <4 cm (symptoms not reported)
- Randomization: (n=181)
  - Laparotomy or operative HSC – abstinence for 3 months – timed intercourse
  - Expectant – timed intercourse immediately

- Data included only pts with submucosal myoma (n=94) ± intramural myoma
  - Surgical group: n=52
  - Expectant group: n=42
- Unclear about …
  - If all pts were systemically examined by HSC to confirm or exclude submucosal myoma?
  - Only intramural myoma with uterine cavity deformation included or not?

- Pregnancy: FHB(+) at 6-7 wks'



- author's report: pregnancy rate doubled after myomectomy in pts with submucosal ± intramural myoma (RR=1.9; CI 1.0-3.7)→ marginally significant
- No significant difference if only submucosal myoma

Hysteroscopic metroplasty

- Reference: Colacurci et al., 2007
- Study population: (n=160)
  - Subfertility and recurrent pregnancy loss
- Randomization:
  - 5 mm HSC with Versapoint (n=80)
  - 8 mm RSC (n=80)

- Clinical pregnancy: ↑hCG + sac(+) by TVS
  - significantly fewer pregnancies after hysteroscopic metroplasty in the subfertile subgroup (RR =0.7; 95% CI: 0.5–0.9) than in recurrent pregnancy loss group
- interaction between subfertility and recurrent pregnancy loss was not studies

Hysteroscopic synechiolysis

- **No** RCT or controlled studies available

Part II:

Does diagnostic or operative HSC increase pregnancy rate in subsequent IVF cycles in subfertile patients undergoing IVF ?

Table II Outpatient hysteroscopy in recurrent IVF failure

Reference	Demirol and Gurgan, 2004	Rama Raju et al., 2008
Method of randomization	Computer-generated list	Computer-generated list
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Blinding	No	Yes
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Number of included patients	421	320
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Outcome measure	Clinical pregnancy rate, miscarriage rate	Clinical pregnancy rate, miscarriage rate, live birth rate

All pts had primary infertility and normal uterine cavity on HSG

a: normal (n=314)
b: pathology (n=151) → treated

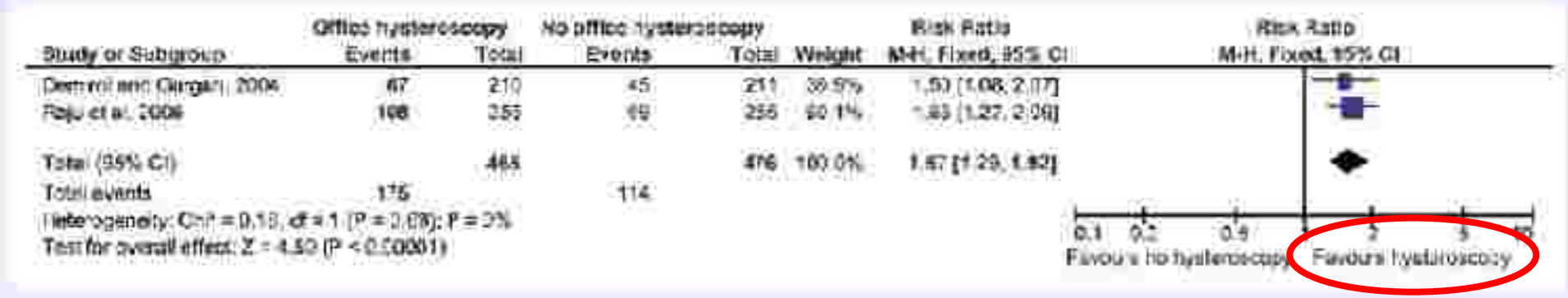

Figure 3 Hysteroscopy versus no hysteroscopy in patients with at least two failed IVF attempts.

- Clinical pregnancy: FHB(+) at 6 wks
- in the intervention group: no significant difference in treatment effect between women with normal findings and uterine pathology
- it was unknown which patients in the control group had intrauterine pathology → interaction was not studied

Summary (1)

- Hysteroscopic polypectomy doubles the pregnancy rate when compared with diagnostic HSC in patients undergoing IUI. (RR=2.3)
- In patients with fibroid < 4 cm, there was a marginally significant benefit from myomectomy when compared with expectant management (RR=1.9).

Summary (2)

- Hysteroscopic metroplasty for septate uterus resulted in fewer pregnancies in patients with subfertility compared with recurrent pregnancy loss (RR =0.7).
- RCTs on hysteroscopic treatment of intrauterine adhesions are lacking.
- HSC prior to subsequent IVF nearly doubles the pregnancy rate in patients with > 2 failed IVF attempts compared with starting IVF immediately (RR =1.7).

Discussion

- Polyps
- Fibroids
- Septate uterus
- Intrauterine adhesion
- IVF

Polyps

- absence of blinding
- difference in undetected and untreated *pelvic pathology (ex, endometriosis)* could introduce bias
- Other non-controlled studies failed to present consistent results.
  - Pregnancy rate higher after removal of tubocornual polyps than other locations → tubocornual polyps may have different effect on reproductive function
  - possible association between endometrial polyps and endometriosis

- Hypothesis 1 → tubocornual polyps
  - especially when bilaterally present and large, may interfere with oocyte/embryo transport
  - protect against retrograde menstruation (through a valve mechanism) and possibly pelvic endometriosis
- Hypothesis 2 → isthmocervical polyps
  - may interfere with sperm transport and facilitate retrograde menstruation through valve mechanism, obstructing the outflow tract
- explain the differences in conception rates after polypectomy in different locations

Fibroids

- The impact of fibroids on fertility remains *controversial*
- underpowered and not blinded
- HSC in all pts? “knot”?
- Observational studies → inconclusive
  - Small sample size and lack of correlation for confounding factors

- *mechanism between fertility vs. fibroids?*
  - altered contours of uterine cavity → altered pressure or abnormal uterine contractility
  - local inflammation caused by submucosal myoma → endometrial vascular disturbance, chronic endometritis or secretion of vasoactive substances
  - localized at cervix → interfere with sperm transport; localized at tubocornual → impair ooccyte/embryo transport

- Size effect relationship can hardly be demonstrated.
  - Non-controlled trials: #, size and distortion effect of fibroids on the uterine cavity may be important
- gynecological problems (pain, menorrhagia, recurrent pregnancy loss)
- Pregnancy complications (preterm labor, malpresentation)

Septate uterus

- Hysteroscopic metroplasty is frequently performed in recurrent miscarriage because a uterine septum is associated with an adverse pregnancy outcome.
  - Effectiveness is at present NOT demonstrated by RCTs
- This review are biased → women with recurrent pregnancy loss as controls (consideration of ethical issue)
- a randomized trial currently underway (http://www.studies-obsgyn.nl/trust NTR 1676)

- *mechanism between uterine septum vs. subfertility?*
  - Endometrium of the septum may be unsuitable for blastocyst implantation.
  - Morphological development of endometrial septal specimen is suboptimal.
  - Septate uterus and endometriosis?
- pregnancy complications: malpresentation, IUGR

Intrauterine adhesion

- RCTs or controlled studies on reproductive outcome after hysteroscopic synechiolysis are absent.
- The overall quality of the available non-controlled studies is very poor.
- Subfertility may be caused by complete or partial occlusion of the tubal ostia, uterine cavity or the cervical canal, preventing sperm migration or embryo implantation.
- Severe destruction of the endometrium → defective or absent implantation

IVF

- The higher pregnancy rates after HSC even in the absence of intrauterine pathology is a somewhat unexpected but biologically plausible observation.
  - cervical dilatation
  - direct visualization of the uterine cavity facilitates ET
  - immunological mechanism triggered by HSC manipulation or by the effect of distension medium on the endometrium
- A new randomized trial is ongoing.

Conclusions and future agenda

- In patients with at least two failed IVF or ICSI, HSC before a subsequent IVF or ICSI is thought to improve reproductive outcome.
  - role of HSC before 1 IVF attempt ?
- Scarce evidence on the effectiveness of hysteroscopic surgery in subfertile women with polyps, fibroids, septate uterus or intrauterine adhesions suggests a potential benefit.

- Should hysteroscopy be offered as a first-line investigation in all subfertile women ??
- The effectiveness of anti-adhesive barrier agents as adjunctive therapy to hysteroscopic synechiolysis in patients with severe intrauterine adhesions should be addressed by a randomized trial.

THE END