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Does Laparoscopy and Hysteroscopy Have a Place in the Diagnosis of Unexplained Infertility?

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Abstract

The standard fertility workup includes assessment of ovulation, semen analysis, and evaluation of tubal patency. If the fertility workup is found to be normal, a diagnosis of unexplained infertility is made. The role of laparoscopy in fertility workup has been a matter of debate. The current review presents the evidence for and against laparoscopy and hysteroscopy during fertility workup and subsequently prior to fertility treatment. After appraising the literature, we found the role of diagnostic laparoscopy in fertility workup is limited and is dependent on factors like prevalence of pelvic infection, setting, and availability of expertise. Moreover, whenever a laparoscopy is planned as a part of the fertility workup, the preparation should include ability to carry out simultaneous therapeutic intervention to maximize the benefit. Similarly, the routine use of hysteroscopy in women with unexplained infertility cannot be recommended. There is a need to investigate the impact of choice of tubal test on chances of spontaneous conception and treatment outcomes in women with unexplained infertility. Our future research agenda should also include high-quality multicenter randomized trials assessing the cost-effectiveness of screening and operative hysteroscopy prior to intrauterine insemination or in vitro fertilization.

Keywords

- unexplained infertility
- laparoscopy
- hysteroscopy

In everyday clinical practice, once the standard fertility workup is completed and all the tests are found to be normal, the diagnosis of unexplained infertility is made. This condition refers to a lack of a specific diagnosis that negatively impacts the spontaneous conception rates. The prevalence of unexplained infertility among infertile couples varies between 22 and 30% of subfertile couples.^{1,2}

The basic fertility workup is not very comprehensive and the possibility of missing subtle etiologies remains. A key consideration is that these subtle pelvic pathologies should have a cause–effect relationship with infertility. In many cases,

causality has been suggested but has not yet been established by high-quality evidence. There are two different schools of thought about diagnosis of unexplained infertility. While one group believes that use of “unexplained infertility” is not valid since it is dependent on which test has been chosen to complete the fertility workup,³ the other group believes that^{Q5} there are a limited number of management options and reducing invasive, costly, or unnecessary testing is the way forward.^{4,5}

It is important to explore the role of laparoscopy and hysteroscopy in the fertility workup. In this review, we plan

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Issue Theme Unexplained Infertility;
Guest Editors, Roger Hart, MD and
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to explore the place of laparoscopy and hysteroscopy in the diagnosis of unexplained infertility in contemporary practice.

Laparoscopy

Current Recommendations for Tubal Test during Infertility Workup

For the diagnosis of unexplained infertility, the following tests are essential: semen analysis, assessment of ovulation, and evaluation of tubal patency by techniques such as hysterosalpingography (HSG) or laparoscopy.⁶ The role of HSG versus laparoscopy for establishing tubal patency continues to be debated.

To evaluate tubal patency, HSG, saline infusion sonography (SIS), HyCoSy, and laparoscopy with chromotubation are the available techniques in clinical practice. According to the American Society of Reproductive Medicine (ASRM) Practice Committee guidelines, HSG is the standard method for evaluating tubal patency and the role of routine laparoscopy for female infertility workup is limited.⁷ However, laparoscopy is the only method for directly visualizing pelvic anatomy and diagnosing peritoneal factors such as minimal or mild endometriosis. Laparoscopy is recommended in infertile women with symptoms related to pelvic pathology, those with risk factors for peritoneal disease, those with abnormal HSG, and those with prolonged duration of infertility without any obvious abnormalities.⁷ The NICE guidelines also recommend HSG as first option for tubal patency over laparoscopy in women without comorbidities such as pelvic inflammatory disease, previous ectopic, or endometriosis.⁸ Laparoscopy is recommended for women with pelvic comorbidities.⁸

Overall, the diagnosis of unexplained infertility can be made by documenting tubal patency either by HSG or laparoscopy. It is important to know if the choice of tubal test during female infertility workup has an impact on the prognosis and management of unexplained infertility.

HSG as a Tubal Test and Undiagnosed Pelvic Pathologies

During an infertility workup, after ruling out male factor and documenting ovulation in the female partner with no obvious signs and symptoms of pelvic pathology, the clinicians need to document normal patent tubes for a diagnosis of unexplained infertility. HSG has sensitivity and specificity of 65 and 83% for diagnosing tubal blockage, respectively.⁹ Even though the specificity is relatively high, negative HSG test (i.e., patent tubes) will not rule out tubal disease.⁹ While the high specificity of HSG has been consistently documented across several studies, the sensitivity appears to vary according to risk factors such as history of pelvic inflammatory disease.¹⁰ The sensitivity for unilateral tubal pathology was 38 and 61% in women with low-risk and high-risk history, respectively. The possible explanation of reduced sensitivity of HSG in women with low-risk history is technical issues that may be encountered while performing a laparoscopy due to which it may be an “imperfect gold standard.”¹⁰ The positive predictive value (PPV) and negative predictive value (NPV) of HSG is 38 and 94%, respectively.⁷ In a diagnostic

accuracy study, out of 194 documented bilateral occlusion on HSG, subsequent laparoscopy confirmed the same finding in 69 (PPV, 35%), while in the remaining women, 44 had one-sided occlusion and another 81 had no occlusion.¹¹ In clinical practice, the low PPV would translate into high numbers of laparoscopy to confirm or refute the HSG findings.

In a study by Tanahat et al, accuracy of diagnostic laparoscopy was evaluated prior to intrauterine insemination (IUI) and included 495 women with normal HSG.¹² In 124 women (25%), the laparoscopy changed the initial treatment plan of IUI. While eight women (1.6%) were referred for direct in vitro fertilization (IVF) due to bilateral tubal abnormalities, remaining 116 (23.4%) had fertility-enhancing surgical interventions. However, it was unclear if treating the abnormalities such as minimal and mild endometriosis increases success of subsequent IUI. In an earlier study, among 486 women with documented bilateral patency on HSG, 12 (2.5%) had bilateral and 24 (5%) had unilateral tubal obstruction on laparoscopy.¹¹ While the 3-year treatment-independent ongoing pregnancy rate was 11% among those women with bilateral patency on HSG and laparoscopy, none of the women with bilateral patency on HSG but one or two sided obstruction on laparoscopy conceived.

The HSG has limited role in diagnosing distal tubal disease and has no value in identifying peritubal adhesions.^{9,13} Furthermore, HSG has no role in investigating physiological function of tubes. An earlier study reported inability of HSG to detect abnormality in tubal function in almost 85% of the cases.¹⁴ Finding of elevated tubal perfusion pressure has been linked to pelvic endometriosis.^{3,14}

The prevalence of endometriosis varies between 30 and 50% among the infertile women.¹⁵ The impact of minimal and mild endometriosis on chances of natural conception and treatments such as IUI has been a matter of debate. However, the studies have suggested the presence of endometriosis affects tubal function as well as other reproductive functions such as embryo development and implantation.^{3,16}

In an observational study, different screening strategies for tubal infertility were evaluated and tests such as *Chlamydia trachomatis* antibody testing (CT) and HSG were compared with laparoscopy which was the reference standard.¹⁵ In women who did not conceive in 6 months of normal HSG, or those with positive CT results, a laparoscopy was advised. Overall, laparoscopy revealed endometriosis in 50% of women (176/355), out of which 88% had minimal endometriosis with peritoneal adhesions and 5% had minimal endometriosis with peritoneal adhesions.^{Q6} The remaining 7% had ovarian endometriosis with or without adhesions. In the study by Tanahat et al, out of 495 women with normal HSG, 99 (20%) had minimal to mild endometriosis, while another 12 (2.4%) had moderate to severe endometriosis.¹²

Option of Concurrent Therapeutic Treatment during Laparoscopy

Minimal/Mild Endometriosis

A large randomized controlled trial (RCT) from Canada evaluated the effectiveness of laparoscopic resection of

endometrial lesion versus only diagnostic laparoscopy in women with minimal or mild endometriosis ($n = 341$) and follow-up period was 3 years.¹⁷ The cumulative probability of pregnancy lasting more than 20 weeks of gestation was significantly higher in the women treated with ablation of endometriotic lesions compared with no ablation (50/172, 30.7% vs. 29/169, 17.7%; $p = 0.006$). Minor complications were reported in both the groups (three in ablation and one in control group). The authors reported increase in fecundity following laparoscopic ablation of endometriotic lesion. A RCT from Italy evaluated the role of laparoscopic ablation of minimal/mild endometriosis in women aged < 36 years ($n = 101$) with unexplained infertility of more than 2 years of duration.¹⁸ The live birth rate after 1 year follow-up was not significantly different between women who had ablation of endometriotic lesion during laparoscopy (10/51, 19.6%) and those who did not have ablation during diagnostic laparoscopy (10/45, 22.2%). However, some women received gonadotropin-releasing hormone therapy for 3 months in the postoperative period.

In a Cochrane systematic review which evaluated role of laparoscopic surgery versus diagnostic laparoscopy, results from two RCTs were pooled.¹⁹ There was an improvement in the live birth or ongoing pregnancy rate (odds ratio [OR]: 1.94, 95% confidence interval [CI]: 1.20–3.16, $p = 0.007$, two RCTs, 382 participants, $I^2 = 0\%$) and clinical pregnancy rate (OR: 1.89, 95% CI: 1.25–2.86, $p = 0.003$, three RCTs, 528 participants, $I^2 = 0\%$). The quality of evidence was moderate for both the outcomes. However, there was insufficient data on safety of the intervention. The number needed to treat for a benefit (NNTB) was 24; that is, for each of 24 women with minimal and mild endometriosis treated by ablation, one additional clinical pregnancy was obtained.¹⁵

There are no RCTs which have studied the effectiveness of operative laparoscopy for improving spontaneous conceptions in moderate to severe endometriosis, as many authors are convinced that designing and conducting RCTs in women suffering from pain due to moderate and severe endometriosis would be unethical. A large prospective cohort study followed up infertile women with endometriosis who underwent operative laparoscopy for 3 years.²⁰ The cumulative probability rates of pregnancy after 3 years were 46 and 44%, respectively, for stage III ($n = 197$) and stage IV ($n = 204$) endometriosis. Earlier study reported the spontaneous pregnancy rates in moderate and severe endometriosis as 25 and 0%, respectively, after follow-up period of 1 to 25 months.²¹ Clinician should offer operative laparoscopy in subfertile women with moderate to severe endometriosis to increase spontaneous conception rate.^{8,22}

Tubal Adhesions

A Cochrane review evaluating the role of conservative surgery for tubal infertility in subfertile women did not identify any RCT.²³ In a large retrospective study which followed up women who underwent tubal reconstructive surgery by open method for tubal disease reported 75 and 55% pregnancy rates for fimbrioplasty and neosalpingostomy, respectively.²⁴ The ectopic pregnancy rate was 4% for fimbrioplasty

and 6.7% for neosalpingostomy. However, for severe tubal disease with poor prognosis, the success rate was low (i.e., between 10 and 20%) and ectopic pregnancy rate was high (22%). The authors considered laparoscopic approach more traumatic for distal tubal disease. A systematic review of observational studies investigated the effectiveness of conservative surgery for tubal hydrosalpinx.²⁵ A total of 22 studies were pooled ($n = 2,810$) and cumulative pregnancy rate of 25% was reported after follow-up period of 2 years. The pooled ectopic pregnancy rate was 10%.

Proximal Tubal Block and Hysteroscopic Cannulation under Laparoscopy Guidance

For proximal tubal blockage with no other evidence of pelvic pathology, hysteroscopic cannulation under laparoscopic guidance can be offered. There were no RCTs comparing hysteroscopic cannulation versus no intervention for women with proximal tubal block. A systematic review reported ongoing pregnancy rate of 49% following hysteroscopic cannulation and ectopic rate of 4.4% after pooling results from four studies.²⁶ In comparison, the selective salpingography and tubal catheterization results in lower ongoing pregnancy rate (23%). The risk of tubal perforation has been reported in 2 to 5% of women.⁸

Cost-Effectiveness of Laparoscopy versus HSG

A study by Mol et al evaluated the cost-effectiveness of CT, HSG, and laparoscopy in subfertile women.²⁶ Data from more than 2,000 infertile couples were used.²⁷ The authors reported that the strategy of using initial CT or HSG test for deciding whether laparoscopy should be performed immediately or postponed by a year was the most cost-effective one. Another cost-effectiveness analysis study compared different tubal test strategies which included no testing and treating, immediate and delayed treatment (IVF), HSG followed by tailored treatment, HSG and laparoscopy in case tubal patency is not proven, and laparoscopy followed by tailored treatment.²⁸ The most cost-effective strategy was to perform no tubal test and delay IVF by 1 year in women younger than 38 years and immediate IVF in 39 years and older. If an invasive test was chosen, then HSG followed by tailored treatment was most cost-effective. HSG and laparoscopy, if no tubal patency is shown, were more cost-effective than direct laparoscopy and tailored treatment.

Ovarian Stimulation with IUI in Unexplained Infertility

In a couple with unexplained infertility and patent tubes documented on HSG, option of proceeding with ovarian stimulation (OS) and IUI has been advocated to avoid invasive laparoscopy.^{15,29} Proceeding with stimulated IUI seems a more reasonable treatment option than expectant management in women with unfavorable prognosis for natural conception. In an open label RCT, effectiveness of OS with IUI was compared with expectant management in women with unexplained infertility and unfavorable prognosis for natural conception.³⁰ Cumulative live birth rate after three cycles of either clomiphene citrate or letrozole stimulated IUI cycle ($n = 101$) was compared with that of three cycles of expectant management ($n = 100$). The cumulative live birth was significantly higher

(31 vs. 9%; risk ratio [RR]: 3.41, 95% CI: 1.71–6.79) following OS with IUI compared with expectant management. In a large RCT, OS with letrozole ($n = 299$) was compared with clomiphene ($n = 300$) and gonadotropin ($n = 301$) in women with unexplained infertility.³¹ Up to four cycles of OS and IUI were performed and live birth was recorded. The live birth after letrozole was significantly lower compared with live birth after gonadotropin (18.7 vs. 32.2%; $p = 0.001$). However, multiple birth following gonadotropin stimulation was much higher than letrozole stimulation (32 vs. 13%; $p = 0.006$). Due to concerns about multiple births, currently, three to four cycles of OS with either clomiphene citrate or letrozole and IUI has been recommended instead of second-line OS with gonadotropin.⁶

Hysteroscopy

In women with unexplained infertility, hysteroscopy may reveal the presence of endometrial polyps, fibroids, septa, or intrauterine adhesions that may have been missed by transvaginal ultrasound. Treatment of intracavitary pathology is feasible by doing operative hysteroscopy. Many hypotheses on how uterine lesions may negatively affect reproductive outcomes have been published in the literature. However, our current knowledge on the complex mechanisms that regulate the implantation of the human embryo remains limited.³² A discussion of these mechanisms is outside the scope of this contribution. Our goal is to focus on the (cost) effectiveness of screening hysteroscopy and/or operative hysteroscopy for improving reproductive outcomes in women with unexplained infertility in the clinical scenarios of expectant management prior to OS combined with IUI or prior to IVF/ICSI (intracytoplasmic sperm injection).

Role of Screening Hysteroscopy in the Fertility Workup

In daily clinical practice, diagnostic hysteroscopy is very often offered as a screening test in the fertility workup because it is considered as being the gold standard.³³ A key consideration should be the (cost) effectiveness of screening hysteroscopy for improving reproductive outcomes either by restoring the normal implantation capability after removing uterine abnormalities or by a major change in the intended fertility treatment schedule when no abnormalities with a causal relationship to infertility are detected.

A Cochrane review summarized and graded the evidence on the effectiveness and safety of screening hysteroscopy in the fertility workup and in women bound to undergo treatment with IUI or IVF/ICSI.³⁴ The primary outcomes were live birth rate and adverse events (complications following hysteroscopy). Eleven RCTs were included and critically appraised. We present the results (summary effect estimates) using RR with 95% CIs and a fixed-effect model. The quality of the evidence was graded by using GRADE criteria. The evidence is current up to April 17, 2019.

Expectant Management

Only one study including 200 women was retrieved.³⁵ Ongoing pregnancy was reported in the primary study report and was

used as a surrogate outcome for live birth. In women with unexplained infertility of 2 years of duration, offering a screening hysteroscopy would increase the chance for an ongoing pregnancy between 23 and 81% on the assumption of a 10% ongoing pregnancy rate in an average fertility clinic when no hysteroscopy is done. This means an RR of 4.30 (95% CI: 2.29–8.07; one RCT; $n = 200$). The evidence was graded as very low quality (very serious risk of bias arising from the randomization process, serious risk of indirectness). No adverse events were reported in both comparison arms of this single-center study. There were no statistically significant differences between the intervention (screening hysteroscopy) and the comparator (no hysteroscopy) for the following secondary outcomes: clinical pregnancy rate (RR: 3.80, 95% CI: 2.31–6.24; one RCT; $n = 200$) and miscarriage rate (RR: 2.80, 95% CI: 1.05–7.48; one RCT; $n = 200$). The evidence was graded as very low quality (very serious risk of bias arising from the randomization process, serious risk of indirectness, serious risk of imprecision). In summary, at present there is no high-quality evidence from this single RCT to support offering a screening hysteroscopy in women with at least 2 years of unexplained subfertility who are trying to conceive spontaneously. There is no evidence in favor of hysteroscopy as a tool in the basic fertility workup for screening the general population of infertile women with a normal ultrasound or HSG for improving reproductive success rates.

Women Bound to Be Treated with IUI or IVF/ICSI

Ten studies were retrieved including 1,836 women in the intervention group (screening hysteroscopy) and 1,914 women in the comparator (no hysteroscopy) bound to undergo IVF/ICSI.^{36–45} No RCTs were found in women bound to be treated with IUI. In 8 of the 10 studies, there were some concerns about risk of bias arising from the randomization process (unclear allocation concealment). Other limitations in the quality of the evidence were inadequate reporting of study methods and substantial statistical heterogeneity. Moreover, women were bound to undergo treatment with IVF/ICSI for a variety of reasons, including but not restricted to unexplained infertility. Doing a screening hysteroscopy would increase the chance for live birth between 25 and 32% on the assumption of a 22% live birth rate (RR: 1.26, 95% CI: 1.11–1.43; six RCTs; $n = 2,745$; $I^2 = 69\%$). The evidence was graded as low quality (serious risk of bias arising from the randomization process, serious risk of inconsistency). A sensitivity analysis done by pooling only studies at low risk of bias showed no statistically significant differences between both comparison arms (RR: 0.99, 95% CI: 0.82–1.18; two RCTs; $n = 1,452$; $I^2 = 0\%$). The data of this analysis are therefore not robust. Four studies measured adverse events^{40–42,45}; three RCTs reported no complications.^{40–42} There were no statistically significant differences between both comparison arms (Peto OR: 7.47, 95% CI: 0.15–376.42; four RCTs; $n = 1,872$; $I^2 =$ not applicable; very low-quality evidence). Performing a screening hysteroscopy would increase the chance for a clinical pregnancy between 33 and 40% assuming a 28% clinical pregnancy rate. The RR was 1.32 (95% CI: 1.20–1.45; 10 RCTs; $n = 3,750$; $I^2 = 49\%$). The evidence was graded as low quality (serious risk of bias arising from the

randomization process, serious risk of inconsistency). For the outcome of miscarriage, there were no statistically significant differences (RR: 1.01, 95% CI: 0.67–1.50; three RCTs; participants = 1,669; $I^2 = 0\%$; low-quality evidence).

In summary, there is no robust, high-quality evidence from 10 RCTs in 3,750 women that screening hysteroscopy before IVF/ICSI for various medical indications may offer a benefit for the outcomes of live birth or clinical pregnancy rate.

(Cost) Effectiveness of Operative Hysteroscopy in Women with Otherwise Unexplained Infertility

Uterine abnormalities including endometrial polyps, submucous fibroids, uterine septa, or intrauterine adhesions are detected by hysteroscopy in 10 to 15% of women seeking medical treatment for infertility.⁴⁶ The hysteroscopic treatment of these lesions is feasible by operative hysteroscopy, most often as a day-care procedure, often without the need for general anesthesia.⁴⁷ There is no doubt that a surgical treatment by hysteroscopy cannot be offered (feasibility). The main question is should operative hysteroscopy be done because it improves the occurrence of a successful reproductive outcome by restoring the normal anatomy, hence facilitating the implantation of the human embryo with minimal adverse events and at an acceptable cost for the individual and society (cost-effectiveness).

A second Cochrane review by our group summarized and graded the evidence on the effectiveness and safety of operative hysteroscopy for treating infertility associated with uterine cavity abnormalities detected by ultrasound, SIS, gel instillation sonography, or HSG in women with otherwise unexplained infertility prior to expectant management or prior to IUI or IVF/ICSI.⁴⁸ The uterine cavity abnormalities included endometrial polyps, submucous fibroids, uterine septa, or intrauterine adhesions. The primary outcomes were live birth rate and adverse events (complications following hysteroscopy). We included and critically appraised two trials. We present the results (summary effect estimates) using RR with 95% CI and a fixed-effect model. The quality of the evidence was graded by using GRADE criteria. The evidence is current up to June 20, 2018.

Expectant Management

We retrieved one study including 94 women.⁴⁹ In women with otherwise unexplained subfertility and submucous fibroids, we were uncertain whether hysteroscopic myomectomy may increase the chance for clinical pregnancy compared with expectant management only: the RR was 1.85 (95% CI: 0.96–3.58; $p = 0.07$, $n = 94$). There were no statistically significant differences between both comparison arms for the outcome miscarriage rate (RR: 1.45, 95% CI: 0.53–3.98; $p = 0.47$, $n = 94$). For both outcomes, we graded the evidence from this single study as very low quality (very serious risk of bias arising from the randomization process, serious risk of imprecision). We found no data on live birth or hysteroscopy complication rates.

Regarding women with a septate uterus, an international multicenter cohort study on 257 women has recently been published.⁵⁰ In this study, live birth occurred in 80 of 151

women following a septum resection (53%) compared with 76 of 106 women following expectant management (71.7%; hazard ratio [HR]: 0.71, 95% CI: 0.49–1.02) and ongoing pregnancy occurred in 89 women who underwent septum resection (58.9%) compared with 80 women who had expectant management (75.5%; HR: 0.74, 95% CI: 0.52–1.06). Despite correcting for the most relevant patient characteristics, the results might not be free of residual confounding and need to be confirmed in RCTs.

We found no studies in women with endometrial polyps or intrauterine adhesions for this randomized comparison.

In summary, there is only one RCT in 94 women studying the effectiveness of hysteroscopic myomectomy and we are uncertain about its value for improving reproductive outcomes in women wishing to conceive by regular sexual intercourse. There have been two RCTs on the hysteroscopic resection of the uterine septum: the TRUST study (NTR 1676), whose results will be shortly published, and the “Pilot randomized controlled trial of hysteroscopic septal resection” (ISRCTN2896), which was stopped due to poor recruitment after including six patients, and is now waiting for follow-up to be completed.

Women Bound to Be Treated with IUI or IVF/ICSI

We retrieved one RCT in this category, including 204 women.⁵¹ In women bound to undergo IUI for various reasons including but not restricted to unexplained infertility, the evidence suggests that the hysteroscopic removal of endometrial polyps detected by ultrasound would increase the cumulative chance for a clinical pregnancy after four IUI cycles between 45 and 89% on the assumption of a 28% cumulative clinical pregnancy rate after four IUI cycles in an average fertility clinic when polyps are left untreated. This means an RR of 2.25 (95% CI: 1.60–3.17; $p < 0.00001$, $n = 204$). The evidence was graded as low quality (serious risk of bias arising from selective outcome reporting, serious imprecision). We found no data on live birth, hysteroscopy complication, or miscarriage rates in women with endometrial polyps prior to IUI. Interestingly a post hoc subgroup analysis studied the effect of the timing of the IUI treatment after hysteroscopic removal of polyps on the outcome clinical pregnancy. About 29% of women in the polypectomy group, compared with only 3% in the diagnostic hysteroscopy group, became pregnant in the 3-month period after operative or diagnostic hysteroscopy, respectively, before therapy with gonadotropin and IUI was initiated. These data were obtained from a Kaplan–Meier survival analysis in the published report of the primary study.⁵¹ The NNTB in women waiting expectantly for 3 months before being treated with gonadotropin and IUI was 4 (95% CI: 3–6). In women who started gonadotropin and IUI treatment, the cumulative clinical pregnancy rates per woman were 49% in the women who had a polyp removal versus 26% in women after simple diagnostic hysteroscopy only. The NNTB was 4 (95% CI: 3–12). The authors of the primary study had reported that this observation had induced them to delay the first IUI attempt to three menstrual cycles after the surgical removal of polyps in these women.⁵¹ Data from their observation and our sensible post hoc subgroup analysis could be used in the

future for an economic evaluation of the possible cost-effectiveness of hysteroscopic polypectomy in women prior to IUI treatment. We found no studies in women with submucous fibroids, intrauterine adhesions, or uterine septum prior to OS with gonadotropin and IUI or in women with all types of suspected uterine cavity abnormalities prior to IVF/ICSI.

In summary, a single low-quality RCT in 204 women studying the effectiveness of hysteroscopic removal of endometrial polyps suspected on ultrasound in women prior to IUI suggests an increase in the cumulative clinical pregnancy rate after four IUI cycles compared with simple diagnostic hysteroscopy without polyp removal.

Conclusion

With increasing reliance on IVF/ICSI as a treatment option, the role of invasive techniques, especially laparoscopy is being questioned during fertility workup and management. There is consistent evidence which suggest underdiagnosis of various pelvic pathologies such as endometriosis or peritubal adhesions when HSG is performed to reach a diagnosis of unexplained infertility. While treating some of these pelvic pathologies such as minimal/mild endometriosis and proximal tubal blockage during laparoscopy may improve the chances of spontaneous conception, it remains to be established whether the positive therapeutic effect also helps in increasing success of subsequent treatments such as IUI and IVF/ICSI in women who do not conceive spontaneously. Furthermore, there is some evidence to suggest laparoscopy as a first-line tubal test is less cost-effective approach than HSG or CT.

Currently, the role of diagnostic laparoscopy in fertility workup is limited. However, several factors including the prevalence of PID due to *Chlamydia trachomatis* or pelvic tuberculosis, the local setting, and individual expertise should be taken into consideration before deciding which tubal test should be offered. Moreover, whenever a laparoscopy is planned as a part of the fertility workup, the preparation should include ability to carry out simultaneous therapeutic intervention to maximize the benefit.

Concerning the implications for daily clinical practice, the use of hysteroscopy in all women with unexplained infertility, let alone the general infertile population, cannot be routinely recommended. Currently, the validity of the NICE guideline still holds: "*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.*"⁸ Women should be counseled using the shared-decision model approach that the balance of benefits and adverse events for improving reproductive outcomes still needs to be established. More high-quality research is needed before current practice can be changed.

There is a need to investigate the impact of choice of tubal test on chances of spontaneous conception and treatment outcomes in women with unexplained infertility. Research should focus on comparing effectiveness of different strategies to diagnose and manage unexplained infertility. Our future

research agenda should also include high-quality multicenter pragmatic RCTs assessing the cost-effectiveness of screening and operative hysteroscopy prior to IUI or IVF/ICSI, especially in women prior to a first IVF/ICSI treatment cycle for unexplained infertility and in women with recurrent implantation failure. There is an urgent need for concerted, close partnership cooperation with basic research teams who are dedicated to unraveling the complex mechanisms that regulate human embryo implantation and reproductive processes in women suffering from endometriosis.

Conflict of Interest

J.F.W.R. reports grants and nonfinancial support from Amsterdam University Medical Center, Amsterdam, the Netherlands, during the conduct of the study.

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THIEME