Tubal subfertility and ectopic pregnancy. Evaluating the effectiveness of diagnostic tests
Mol, B.W.J.

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6. Comparison of hysterosalpingography and laparoscopy in predicting fertility outcome

Ben W.J. Mol, John A. Collins, Elizabeth A. Burrows, Fulco Van der Veen, and Patrick M.M. Bossuyt

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Abstract

Objective: To compare the prognostic significance of hysterosalpingography (HSG) and laparoscopy for fertility outcome.

Methods: In a prospective cohort study in eleven clinics participating in the Canadian Infertility Treatment Evaluation Study (CITES), consecutive couples who registered for the evaluation of subfertility and who underwent HSG and laparoscopy were included. Unilateral and bilateral tubal occlusion at HSG and laparoscopy were related to treatment-independent pregnancy. Cox regression was used to calculate fecundity rate ratios (FRR) for the occurrence of ongoing pregnancy.

Results: Of the 794 patients that were included, 114 (14%) showed one-sided tubal occlusion and 194 (24%) showed two-sided tubal occlusion on HSG. At laparoscopy, 94 (12%) showed one-sided tubal occlusion and 96 (12%) showed two-sided tubal occlusion. Occlusion detected on HSG and laparoscopy showed a moderate agreement beyond chance (weighted kappa-value 0.42). Multivariate analysis showed FRRs of 0.80 and 0.49 for one-sided and two-sided tubal occlusion, respectively. For laparoscopy, these FRRs were 0.51 and 0.15. After a normal HSG or a HSG with one-sided tubal occlusion, laparoscopy showed two-sided occlusion in 5% of the patients, and fertility prospects in these patients were virtually zero. If two-sided tubal occlusion was detected on HSG but not during laparoscopy, fertility prospects were slightly impaired. Fertility prospects after a two-sided occluded HSG were strongly impaired in case laparoscopy showed one-sided and two-sided occlusion, with FRRs of 0.38 and 0.19, respectively.

Conclusion: Although laparoscopy performed better than HSG as a predictor of future fertility, it should not be considered as the perfect test in the diagnosis of tubal pathology. For clinical practice, laparoscopy can be delayed after normal HSG for at least 10 months, since the probability that laparoscopy will show tubal occlusion after a normal HSG is very low.

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6.1 Introduction

Laparoscopy is currently regarded as the most reliable tool in the diagnosis of tubal causes of subfertility. Since laparoscopy visualizes morphologic abnormalities of the fallopian tubes directly, it is generally accepted as the reference standard for assessment of the performance of other diagnostic tools for tubal pathology, such as hysterosalpingography (HSG) or Chlamydia Antibody Testing (CAT). In the pre-IVF era, surgical correction of tubal abnormalities was the only available treatment for tubal subfertility. Since then, in vitro fertilization and embryo-transfer (IVF-ET) has gradually replaced tubal surgery as the treatment of choice for tubal subfertility in many countries. It has become the treatment of last resort for persistent subfertility due to any cause. In contrast to tubal surgery, the choice for IVF-ET does not depend on the detection of morphologic abnormalities, but on fertility prognosis. Therefore, the central issue in the work-up of subfertility has changed from a diagnostic question into a prognostic question.

Previous studies have shown that bilateral tubal pathology diagnosed at HSG or laparoscopy did affect fertility prospects strongly, whereas unilateral pathology affected future fertility less severely, as was shown in chapter 5. Although a substantial part of the population in these studies underwent HSG and laparoscopy, a direct comparison on the prognostic capacity between HSG and laparoscopy has never been made. In a previous study in 11 Canadian infertility clinics addressing the prognosis of live birth among untreated subfertile couples, presence of tubal pathology was shown to reduce prospects for treatment-independent pregnancy with 50%. In that particular study, tubal pathology was detected with HSG and/or laparoscopy. Comparison of HSG and laparoscopy was beyond the scope of that study. In the present study, the data of the Canadian study are reanalyzed for this purpose.

6.2 Materials and Methods

Patients

We used data prospectively collected in the Canadian Infertility Treatment Evaluation Study (CITES). All couples who registered for the first time in 11 Canadian academic infertility clinics between April 1, 1984 through March 31, 1987, and who had both HSG and laparoscopy done were included. Patients with an abnormal HSG usually underwent laparoscopy without delay, whereas in patients with a normal HSG, laparoscopy was only performed in cases where subfertility persisted for a longer period of time.

Findings at HSG were classified as no tubal occlusion, one-sided tubal occlusion or two-sided tubal occlusion (partial or total occlusion). Findings at laparoscopy were classified as normal, one-sided tubal occlusion or two-sided tubal occlusion. Additional tubal pathology observed at laparoscopy, i.e., phimosis or adhesions, was scored separately. Furthermore, endometriosis detected at laparoscopy was classified according to the classification of the American Fertility Society.
The following potential prognostic factors were also used in the analysis: female age (per year older than 30 years), duration of subfertility at the time of laparoscopy, type of subfertility (primary or secondary), ovulation factor, and sperm factor.

Follow up

Follow-up ended when treatment-independent pregnancy occurred, or at the day at which fertility treatment started. Pregnancy was defined as an ongoing pregnancy at a gestational age of 12 weeks. When ectopic pregnancy or spontaneous abortion occurred, follow-up ended on the estimated day of conception. If a woman did not become pregnant and was not treated, follow-up ended on the day of last contact. A woman was presumed to be 'at risk' for treatment-independent conception for as long as the couple was in the study.

Analysis

Tubal occlusion detected at HSG was compared with occlusion detected at laparoscopy in a three-by-three table. Sensitivity and specificity (with 95% confidence intervals [CI]) of HSG in the diagnosis of tubal occlusion were calculated, considering laparoscopy as the reference standard. Sensitivity and specificity were calculated twice, once when tubal occlusion was defined as one-sided or two-sided occlusion, and once when the definition of tubal pathology was limited to two-sided occlusion. Agreement beyond chance between HSG and laparoscopy was expressed as a weighted kappa-statistic. Whereas an unweighted kappa-statistic weights disagreement on one tube equally worse as disagreement on two tubes in one patient, a weighted kappa-statistic values cases in which HSG and laparoscopy disagree on the status of one tube, but agree on the status of the other tube less severe than cases in which HSG and laparoscopy disagree on both tubes.

Three-year cumulative pregnancy rates were calculated for each category of HSG and laparoscopy findings, using Kaplan-Meier analysis. Subsequently, fecundity rate ratios (FRR) and 95% confidence intervals (CI) for the occurrence of treatment-independent ongoing pregnancy were calculated for HSG findings as well as for findings at laparoscopy through Cox regression modeling. Furthermore, the tubal status as assessed by a combination of HSG and laparoscopy was related to treatment-independent pregnancy. In addition, we determined FRRs for other potential prognostic factors. A FRR expresses the probability of spontaneous intra-uterine pregnancy per time unit for patients with a particular feature, relative to the probability in those without that feature. To adjust the

Table 1: Tubal status detected at HSG as compared to the tubal status detected at laparoscopy

<table>
<thead>
<tr>
<th>HSG</th>
<th>Laparoscopy</th>
<th>Two-sided occlusion</th>
<th>One-sided occlusion</th>
<th>No occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-sided occlusion</td>
<td>69</td>
<td>44</td>
<td>81</td>
<td>194</td>
</tr>
<tr>
<td>One-sided occlusion</td>
<td>15</td>
<td>26</td>
<td>73</td>
<td>114</td>
</tr>
<tr>
<td>No occlusion</td>
<td>12</td>
<td>24</td>
<td>450</td>
<td>486</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>94</td>
<td>604</td>
<td>794</td>
</tr>
</tbody>
</table>

Weighted kappa-value 0.42 (95% CI 0.37 to 0.48)

Disease defined as any abnormality:

Sensitivity 0.81 (95% CI 0.76 to 0.87) Specificity 0.75 (95% CI 0.71 to 0.78)

Disease defined as two-sided abnormality:

Sensitivity 0.72 (95% CI 0.62 to 0.81) Specificity 0.82 (95% CI 0.79 to 0.85)
FRRs of HSG and laparoscopy findings for these prognostic factors, multivariable analysis was performed.

Since the aim of the study was to compare the prognostic significance of HSG and laparoscopy, we performed three separate multivariable analyses: one in which the FRRs of HSG were corrected for all other prognostic factors but findings at laparoscopy, one in which the FRRs of laparoscopy were corrected for all other prognostic factors but HSG findings, and one in which the FRRs of combined results of HSG and laparoscopy were corrected for all other prognostic factors.

6.3 Results

Of the 2198 couples that were included in CITES, 1357 had a HSG done. Among the 563 patients who had a HSG but no laparoscopy, 107 had a treatment-independent pregnancy. The 794 who had a HSG and a laparoscopy done were included in the present study. Mean maternal age was 29.6 years (min 20 years - max 42 years) and mean duration of subfertility was 41 months (min 12 months - max 153 months). The median time between HSG and laparoscopy was 10 months when HSG was normal, 8.5 months when HSG was one-sided abnormal and 4.5 months when HSG was two-sided abnormal. Among the 794 included women, 86 had a treatment independent pregnancy. Of these 86 couples, 4 had an ectopic pregnancy, whereas 12 pregnancies resulted in miscarriage. Thus, 70 women had a treatment-independent ongoing pregnancy, of which 50 resulted in a live birth and three in a perinatal death. In 17 couples pregnancy outcome was unknown.

Table 1 shows tubal status detected at HSG as compared to tubal status detected at laparoscopy. At HSG, 114 patients (14%) showed one-sided tubal occlusion and 194 patients (24%) showed two-sided tubal occlusion. At laparoscopy, 94 patients (12%) showed one-sided tubal occlusion and 96 (12%) showed two-sided tubal occlusion. Sensitivity of HSG was 0.81 (95% CI 0.76 to 0.81) and specificity of HSG was 0.75 (95% CI 0.71 to 0.78) when disease was defined as any form of tubal occlusion detected at laparoscopy, be it one sided or two-sided. Sensitivity and specificity of HSG were 0.72 (95% CI 0.62 to 0.81) and 0.82 (95% CI 0.79 to 0.85), respectively, when the definition of disease

<table>
<thead>
<tr>
<th>Tubal status at HSG and laparoscopy</th>
<th>Number of patients</th>
<th>Number of IUPs*</th>
<th>Three-year cumulative ongoing intra-uterine pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSG patent, laparoscopy patent</td>
<td>450</td>
<td>50</td>
<td>11%</td>
</tr>
<tr>
<td>HSG one-sided occluded, laparoscopy patent</td>
<td>73</td>
<td>6</td>
<td>8%</td>
</tr>
<tr>
<td>HSG two-sided occluded, laparoscopy patent</td>
<td>81</td>
<td>7</td>
<td>9%</td>
</tr>
<tr>
<td>HSG patent, laparoscopy one-sided occluded</td>
<td>24</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>HSG one-sided occluded, laparoscopy one-sided occluded</td>
<td>26</td>
<td>3</td>
<td>12%</td>
</tr>
<tr>
<td>HSG two-sided occluded, laparoscopy one-sided occluded</td>
<td>44</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>HSG patent, laparoscopy two-sided occluded</td>
<td>12</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>HSG one-sided occluded, laparoscopy two-sided occluded</td>
<td>15</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>HSG two-sided occluded, laparoscopy two-sided occluded</td>
<td>69</td>
<td>2</td>
<td>3%</td>
</tr>
</tbody>
</table>

*IUP = intra-uterine pregnancy

62
Table 3: Comparison of HSG and laparoscopy

<table>
<thead>
<tr>
<th>Tubal status at HSG</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=794 (%)</td>
<td></td>
</tr>
<tr>
<td>Tubal status at HSG</td>
<td>FRR* on IUPT (95%CI)</td>
<td>FRR* on IUPT (95%CI)</td>
</tr>
<tr>
<td>No occlusion†</td>
<td>486 (62)</td>
<td>1</td>
</tr>
<tr>
<td>One sided occlusion</td>
<td>114 (14)</td>
<td>0.82 0.40 to 1.7</td>
</tr>
<tr>
<td>Two sided occlusion</td>
<td>194 (24)</td>
<td>0.53 0.27 to 1.0</td>
</tr>
<tr>
<td>Tubal status at laparoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No occlusion†</td>
<td>604 (76)</td>
<td>1</td>
</tr>
<tr>
<td>One sided occlusion</td>
<td>94 (12)</td>
<td>0.56 0.28 to 1.1</td>
</tr>
<tr>
<td>Two sided occlusion</td>
<td>96 (12)</td>
<td>0.18 0.04 to 0.73</td>
</tr>
<tr>
<td>Other tubal pathology at laparoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>130 (16)</td>
<td>0.73 0.37 to 1.5</td>
<td></td>
</tr>
<tr>
<td>Tubal status at combined HSG &amp; laparoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS G patent, laparoscopy patent‡</td>
<td>450 (57)</td>
<td>1</td>
</tr>
<tr>
<td>HSG one-sided occluded, laparoscopy patent</td>
<td></td>
<td>0.81 0.34 to 1.9</td>
</tr>
<tr>
<td>HSG normal/one-sided occluded, laparoscopy one-sided occluded</td>
<td></td>
<td>0.58 0.18 to 1.9</td>
</tr>
<tr>
<td>HSG normal/one-sided occluded, laparoscopy two-sided occluded</td>
<td></td>
<td>0.70 0.31 to 1.6</td>
</tr>
<tr>
<td>HSG two-sided occluded, laparoscopy patent</td>
<td></td>
<td>0.38 0.09 to 1.6</td>
</tr>
<tr>
<td>HSG two-sided occluded, laparoscopy one-sided occluded</td>
<td></td>
<td>0.19 0.05 to 0.80</td>
</tr>
<tr>
<td>HSG two-sided occluded, laparoscopy two-sided occluded</td>
<td></td>
<td>0.52 0.26 to 1.1</td>
</tr>
<tr>
<td>No endometriosis§</td>
<td>621 (78)</td>
<td>1</td>
</tr>
<tr>
<td>Endometriosis grade I/II</td>
<td>160 (20)</td>
<td>0.40 0.16 to 1.0</td>
</tr>
<tr>
<td>Endometriosis grade III/IV</td>
<td>13 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of subfertility (per month)</td>
<td></td>
<td>0.99 0.98 to 1.0</td>
</tr>
<tr>
<td>Age (per year older than 30)</td>
<td></td>
<td>1.0 0.94 to 1.1</td>
</tr>
<tr>
<td>Secondary subfertility</td>
<td></td>
<td>0.89 0.50 to 1.6</td>
</tr>
<tr>
<td>Ovulation factor</td>
<td></td>
<td>0.71 0.35 to 1.4</td>
</tr>
<tr>
<td>Sperm factor</td>
<td></td>
<td>0.76 0.40 to 1.5</td>
</tr>
</tbody>
</table>

*FRR = Fecundity Rate Ratio; IUPT = intra-uterine pregnancy; CI = Confidence Interval; Reference category.

References:
1. American Society for Reproductive Medicine (ASRM) Fertility and Sterility Board.
2. World Health Organization (WHO) Fertility and Sterility Board.
3. Society for Assisted Reproductive Technology (SART) Fertility and Sterility Board.
4. Society for Reproductive Medicine (SRM) Fertility and Sterility Board.
5. Society for Menopausal Medicine (SMM) Fertility and Sterility Board.
was limited to double-sided tubal occlusion detected at laparoscopy. The weighted kappa-value expressing the agreement between HSG findings and laparoscopy beyond chance was 0.42 (95% CI 0.37 to 0.48).

Table 2 shows the distribution of HSG findings and laparoscopy in relation to the number of subsequent pregnancies and the 3-year cumulative ongoing pregnancy rate. Three-year cumulative ongoing pregnancy rates varied between 11% in case HSG and laparoscopy were both two-sided patent or one-sided occluded and 0% in several categories.

Table 3 shows the results of the univariable and multivariable Cox regression analysis. In the multivariable analysis, one-sided occlusion detected at HSG was found to decrease fertility prospects slightly (FRR 0.80), whereas a two-sided occlusion had a stronger impact on fertility prospects (FRR 0.49). Occlusion detected at laparoscopy had a stronger impact on fertility prospects, with a FRR of 0.51 for a one-sided occlusion and 0.15 for a two-sided occlusion. Other tubal pathology at laparoscopy, i.e., phimosis and/or adhesions, was associated with a FRR of 0.60. Endometriosis grade I/II had a FRR of 0.52, whereas there were no pregnancies among couples with endometriosis grade III/IV.

If one-sided occlusion at HSG was followed by normal laparoscopy, fertility prospects were slightly impaired (FRR 0.81). If a normal HSG or a one-sided occluded HSG was followed by a laparoscopy that showed one-sided occlusion, which occurred in 8% of the patients (50/600) with such HSGs, fertility prospects were moderately decreased (FRR 0.58). When a normal HSG or a one-sided occluded HSG was followed by a laparoscopy that showed two-sided abnormalities, which occurred in 5% of the patients (27/600) with such HSGs, no spontaneous pregnancies occurred (FRR 0). When a two-sided occluded HSG was followed by a normal laparoscopy, which occurred in 42% of the patients (81/194) with such HSGs, fertility prospects were slightly impaired (FRR 0.70). When a two-sided abnormal HSG was followed by a laparoscopy that showed one-sided or two-sided abnormalities, which occurred in 23% (44/194) and 36% (69/194) of patients with such HSGs, respectively, fertility prospects were strongly impaired, with FRRs of 0.38 and 0.19, respectively.

6.4 Discussion
Laparoscopy is currently regarded as the best available method to assess tubal occlusion. In this study, tubal occlusion was detected at 24% of the laparoscopies. Two-sided occlusion appeared to affect fertility prospects considerably, whereas one-sided occlusion affected fertility prospects less strongly. In the same sample of patients, HSG indicated tubal occlusion in 39%. The weighted kappa-value was 0.42 (95% CI 0.37 to 0.48), indicating moderate agreement beyond chance between HSG and laparoscopy. Findings at laparoscopy had a stronger impact on spontaneous fertility course than results at HSG. After a completely normal HSG or a HSG with a one-sided abnormality, a one-sided occluded laparoscopy affected fertility prospects slightly, whereas no spontaneous pregnancies occurred after double-sided occlusion detected at laparoscopy. After a HSG with two-sided abnormalities fertility prospects were only slightly decreased in cases where
Comparison of HSG and laparoscopy for fertility outcome

Laparoscopy showed patent tubes. However, in cases where laparoscopy had one-sided or two-sided abnormalities in these patients, fertility prospects were strongly decreased, with FRRs of 0.38 and 0.19 respectively.

Laparoscopy was performed at the end of the work-up for subfertility, after the performance of HSG. Patients with an abnormal HSG usually underwent laparoscopy with a short delay, whereas in patients with a normal HSG laparoscopy was withheld for a longer time. This selection bias possibly hampers the interpretation of the findings in two ways. Firstly, unexplained subfertility, that might be associated with an unknown fertility reducing factor, could be overrepresented in patients with a normal HSG. If such a selection bias were to play a role in the present study, this bias might cause an underestimation of the prognostic capacity of HSG as detected in this study. Secondly, the delay of laparoscopy among patients with normal HSG results in an overestimation of patients with abnormal laparoscopy among all patients undergoing HSG.

Many studies have associated morphologic abnormalities with fertility outcome in patients who underwent microsurgical correction for tubal occlusion. So far only one study has assessed the significance of findings at laparoscopy in patients evaluated for subfertility. Norderskjöld et al. reported on 433 subfertile women who had laparoscopy. Presence of adhesions reduced fertility prospects in the same order as unilateral tubal occlusion, with relative risks of 0.74 (95% CI 0.57 to 0.98) and 0.73 (95% CI 0.39 to 1.4), respectively. None of 10 patients with a double sided occlusion of the tube became pregnant. The fact that 101 (23%) of the patients had microsurgery some time after laparoscopy was not addressed in that study, thereby hampering interpretation of the results. Furthermore, dichotomizing subfertile couples into couples who conceived and couples who did not conceive does not address the true nature of (sub)fertility. Instead, analysis of time to pregnancy, as was done in the present study, is more appropriate.

In the meta-analysis comparing results of HSG and laparoscopy for the diagnosis of tubal pathology that was discussed in chapter 3, HSG had a sensitivity of 65% for the diagnosis of tubal occlusion, in case laparoscopy was presumed to be the 'gold' standard. This finding implicates that 35% of the tubes that were found to be occluded at laparoscopy showed patency at HSG. That particular finding made the choice of laparoscopy as the 'gold' standard questionable, since patency at HSG in our opinion proves that laparoscopy was incorrect in diagnosing tubal occlusion in these patients. The results of the present study, however, seem to indicate that laparoscopy is a better predictor for infertility than HSG, be it not a perfect one. This conclusion is hampered by the fact that the median interval to laparoscopy after normal HSG was 10 months, compared to 4.5 months in cases where HSG was two-sided abnormal. Thus, the difference in prognostic capacity between HSG and laparoscopy is likely to be overestimated, only prognostic studies in which HSG and laparoscopy are performed at the same moment can overcome this issue.

Despite the fact that laparoscopy seems to be a better predictor for subfertility than HSG, we think that HSG should keep its place in the diagnostic work-up for subfertility. Normal HSG reduces the probability that a tubal factor plays a role in future fertility.
prospects. Only in 5% of the patients with normal HSG double-sided tubal occlusion was
detected at laparoscopy. Although fertility prospects in these couples were virtually zero,
we think that a probability of 1 in 20 to detect severe abnormalities at laparoscopy - that
was observed after a median time between HSG and laparoscopy of 10 months - is so low,
that earlier laparoscopy is not justified. It should be kept in mind that the median delay of
laparoscopy of 10 months implicates that the fraction of abnormal laparoscopy among all
patients with a normal HSG is even lower than 5%. When deciding about a delay of
laparoscopy, one should also take into account other aspects of the prognostic profile of
the couple, female age being the most important. In case female age is exceeds 36 years, the
success rates of IVF-ET are expected to decline strongly if this treatment is delayed.
Expectant management is in that case not justified.\textsuperscript{13,14}

In contrast, laparoscopy performed after a two-sided abnormal HSG showed no
abnormalities in 42% of the patients. Since fertility prospects in these patients were only
slightly impaired, whereas patients with two-sided occluded HSG and a laparoscopy
showing unilateral or bilateral tubal occlusion had strongly impaired fertility prospects, a
laparoscopy performed after a two-sided abnormal HSG could be very useful, since it
divides patients with such HSGs in a large group in whom fertility prospects are slightly
impaired and a large group in which fertility prospects are strongly impaired.

When comparing HSG and laparoscopy, we should keep in mind that both procedures
provide more information than the condition of the fallopian tubes alone. Whereas HSG
provides information on the status of the intra-uterine cavity, laparoscopy allows inspection
of the intra-abdominal cavity, for instance to see if endometriosis is present. The latter has
become especially important, since it was recently shown that laparoscopic treatment of
endometriosis improves fertility prospects with 13%, corresponding with a Numbers
Needed to Treat of eight.\textsuperscript{15} Thus, in the final decision on the clinical value of HSG and
laparoscopy, one should consider other issues than solely tubal pathology. Such an analysis
is beyond the scope of this study. When focusing on tubal pathology, it is concluded that
laparoscopy should not be considered as the perfect test in the diagnosis of tubal pathology.
In the next chapter several strategies containing HSG, laparoscopy and/or CAT will be
compared with respect to number of live births, time to pregnancy and costs.

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2. Mol BWJ, Dijkman AB, Wertheim P, Lijmer JG, Van der Veen F, Bossuyt PMM. Chlamydial antibody
3. Land JA, Evers JLH, Goossens VJ. How to use Chlamydia antibody testing in subfertility patients?
Comparison of HSG and laparoscopy for fertility outcome


