Tubal subfertility and ectopic pregnancy. Evaluating the effectiveness of diagnostic tests
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8. Summary and clinical implications

The aim of this part of the thesis was to assess the performance of hysterosalpingography (HSG), Chlamydia antibody testing (CAT) and laparoscopy in the assessment of tubal pathology in subfertile women in terms of accuracy and fertility prognosis, and to provide guidelines for the diagnosis of tubal pathology in such women.

In chapter 2 the reproducibility of the interpretation of HSG was assessed with respect to proximal and distal occlusion, hydrosalpinx and peritubal adhesions. The reproducibility of the diagnosis proximal tubal occlusion was almost perfect. In contrast, the reproducibility of the diagnosis of distal tubal occlusion and hydrosalpinx was substantial, but the reproducibility of the diagnosis adhesions was only moderate to substantial. Hysterosalpingography is therefore of no value for the diagnosis of peritubal adhesions, whereas it might be of use in the diagnosis of proximal tubal occlusion, distal tubal occlusion and hydrosalpinx.

Comparison of the diagnosis 'proximal tubal occlusion' on HSG and on laparoscopy in the 143 patients studied revealed a specificity of 92% for a sensitivity of only 44%. The almost perfect reproducibility of the diagnosis proximal tubal occlusion on HSG both between and within observers indicated that this low sensitivity could not be due to differences in interpretation between or within observers. It was hypothesized that laparoscopy is unlikely to be a perfect reference test, since more than 50% of the tubes that were occluded at laparoscopy were patent at HSG.

In chapter 3, the low sensitivity of HSG as compared to laparoscopy in the diagnosis of tubal occlusion was confirmed in a meta-analysis. A sensitivity of 65% for a specificity of 83% was calculated from three studies in which HSG and laparoscopy had been judged independently. Unfortunately, in the other 17 studies incorporated in the meta-analysis comparing HSG and laparoscopy, both tests had not been evaluated independently. Another methodological problem in the studies comparing HSG and laparoscopy was that in the majority of studies, the time between HSG and laparoscopy was considerable. Thus, women who conceived after HSG and women who refused further investigations following HSG were not included in these studies. Although the impact of this verification bias could not be quantified, it is likely to have caused an underestimation of the specificity of HSG.

In chapter 4, the performance of CAT in the diagnosis of tubal pathology was evaluated in a meta-analysis that incorporated studies using laparoscopy as the reference standard. The diagnostic performance of CAT turned out to be dependent on the type of assay that was used. Summary Receiver Operating Characteristic (ROC)-curves estimated for enzyme immunoassay (ELISA) or (micro)-immunofluorescence (MIF/IF) revealed a better discriminative capacity than the summary ROC-curve estimated for immunoperoxidase assay (IPA). The diagnostic performance of CAT by means of ELISA, MIF or IF in the diagnosis of any tubal pathology was comparable to that of HSG in the diagnosis of tubal occlusion.

Whether the work-up for tubal pathology should focus on a morphologic diagnosis of tubal abnormalities is questionable if one bears in mind the massive changes in the treatment...
of subfertility over the last 20 years. In vitro fertilization and embryo-transfer (IVF-ET) has gradually replaced tubal surgery as the treatment of choice in subfertile couples with severe tubal pathology. Although the success rates of IVF-ET vary strongly between couples with different characteristics, the effectiveness of IVF-ET is beyond doubt. In contrast, the effectiveness of surgical correction of tubal abnormalities is still a matter of debate, since this treatment has never been evaluated in large prospective cohort studies, let alone randomized clinical trials.

Taking this into account, the subfertility work-up should produce a valid fertility prognosis to identify those patients who will benefit from therapy, rather than focusing on the detection of clinically relevant morphologic abnormalities of the fallopian tubes. Chapter 5 and chapter 6 dealt with the capacity of HSG and laparoscopy to predict fertility outcome.

In chapter 5, HSG findings were related to fertility outcome. One-sided tubal pathology on HSG was found to affect fertility prospects only slightly as compared to a normal HSG, with a fecundity rate ratio (FRR) of 0.81. Two-sided tubal pathology, however, reduced fertility prospects considerably (FRR 0.30), but was present in only 17% of the patients.

A problem in the interpretation of the results of chapter 5 is the fact that a considerable part of the patients either underwent tubal surgery or conceived as a result of other treatments. As a consequence, time to spontaneous pregnancy had to be considered as censored in case of tubal surgery or conception after treatment. This censoring process has to be taken into account when estimating the prognostic capacity of HSG. However, the sensitivity analysis that was performed to assess the impact of informative censoring, did not alter the conclusions of the initial analysis.

Chapter 6 compared the prognostic capacity of HSG and laparoscopy for fertility outcome in 794 patients that were included in the Canadian Infertility Treatment Evaluation Study (CITES) and underwent both tests. Multivariable analysis showed FRRs of 0.80 and 0.49 for one-sided and two-sided occlusion at HSG, respectively. For laparoscopy, these FRRs were 0.51 and 0.15, respectively. After a normal or one-sided occluded HSG, 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 confirmed 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. 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, since some treatment-independent pregnancies occurred in patients in whom laparoscopy had demonstrated two-sided tubal occlusion.

In chapter 7, thirteen strategies that can be used for the work-up for tubal pathology were evaluated. The most cost-effective strategies were those that started with HSG or CAT, and in which laparoscopy was performed immediately in patients in which the probability of tubal pathology was increased, while laparoscopy was delayed within one year in other patients. For couples in which the 3-year cumulative probability for pregnancy resulting in live birth was > 14%, a strategy starting with CAT was slightly more cost-effective than a
strategy starting with HSG. For couples in which this probability was \leq 14\%, a strategy starting with HSG was slightly more cost-effective. Performance of serum CA-125 measurement was only cost-effective in patient in whom the probability for 3-year spontaneous conception was \lt 5\%. The diagnostic work-up to detect tubal pathology in subfertile couples should start with CAT in couples with relatively good fertility prospects (expected 3-year conception rate > 15\%), whereas couples with relatively poor fertility prospects benefit from immediate HSG (expected 3-year conception rate \lt 15\%).

Apart from HSG, CAT and laparoscopy, there are also other tests that can be used for the assessment of tubal pathology. Falloposcopy allows direct visualization of the lumen of the fallopian tubes. Its prognostic capacity is reported to be better than that of HSG, although reports on large series of patients are lacking. Hysterosalpingo-contrast-sonography (HyCoSy) is a new method for assessing tubal patency using a contrast and transvaginal ultrasound investigation of the fallopian tubes, and is thought to have several advantages over hysterosalpingography (HSG). HyCoSy can be performed as an outpatient procedure and does not expose the patient to irradiation. Studies on the diagnostic performance of HyCoSy compared to HSG show conflicting results. Some found the discriminative capacity to be comparable, whereas others found HyCoSy to be less reliable than HSG.

Transvaginal hydrolaparoscopy is performed as a needle puncture technique of the pouch of Douglas using an adjusted Veres-needle trocar system. It allows direct visualization of peritubal and periovarian adhesions and endometriotic implants, and can be performed as an outpatient procedure.

These new techniques could have better diagnostic and prognostic performance than CAT, HSG or laparoscopy. Unfortunately, studies evaluating such techniques have often been limited to relatively small groups of patients, and the design of these studies was not as sound as it should be. These techniques should only be implemented in clinical practice if there is evidence that their use improves the take-home baby rate of subfertile couples in a cost-effective way. Thus, a final judgement on their use can only be made if their performance is evaluated in a decision analytic framework or in a correctly performed randomized clinical trial.

With respect to therapy, it is worrisome that randomized clinical trials evaluating the effectiveness of tubal surgery are still lacking. As a consequence, it remains questionable whether surgical treatment of tubal pathology in subfertile women is useful. If future randomized clinical trials would show that tubal surgery is effective, diagnostic laparoscopy will be important identify patients that can profit from tubal surgery. This would also affect the diagnostic management of subfertile couples.

Another issue of importance is the therapeutic impact of HSG. Watson et al. performed a meta-analysis of studies comparing pregnancy rates after HSG with either oil or water soluble contrast media. This meta-analysis incorporated four studies of which only one study was truly randomised. This study, that did not use life-table analysis, reported a beneficial relative risk of 1.3 after the use of oil-soluble contrast media, but the effect was not statistically significant. Only one study reported on the therapeutic effect of
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HSG, using patients without a HSG as controls.\(^\text{11}\) This study indicated that pregnancy rates after HSG were significantly higher than without a HSG, with a relative risk of almost 3. However, the 95\% confidence interval of this relative risk was between 1.3 and 6. If the relative risk was really to be near 6, this would affect the results of the analysis performed in chapter 7. Thus, the effectiveness of HSG with respect to fertility outcome should be subject of new randomized clinical trials.

8.1 References