Diagnostic and prognostic aspects of tubal patency testing
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General discussion
It is estimated that tubal pathology accounts for subfertility in around 10 to 30 percent of couples (Evers 2002). The subfertility work-up is therefore usually ended with invasive tubal patency testing, such as hysterosalpingography (HSG) or laparoscopy with tubal testing, of which the latter is still regarded as the gold standard for diagnosing tubal pathology. In the late nineties, 89% of all fertility specialists in the USA routinely performed diagnostic laparoscopy in the fertility work-up (Glatstein 1997). The majority of diagnostic laparoscopies will not reveal any abnormality (Forman et al., 1993), as a result of which its role in current fertility practice is heavily debated (Tanahatoe et al., 2003; Lavy et al., 2004; Tanahatoe et al., 2005; Bosteels et al., 2008).

As laparoscopy is an expensive investigation, and not without risk of complications (Jansen et al., 1997; Chapron et al., 1998; Härkki-Siren et al., 1999), some authors have searched for less invasive alternatives like hysterosalpingo-contrast-sonography (Schlief and Deichert, 1991) or transvaginal hydrolaparoscopy (Gordts et al., 1998). However, these newer test have not gained widespread use in daily clinical practice, as a result of which most clinicians still use hysterosalpingography and/or diagnostic laparoscopy to conclude the fertility work-up. The reasons for this conservatism are unclear, but it might be due to uncertainty about the validity of published reports on such test alternatives (Chapter 2).

Other groups have searched for better screening strategies to only subject those women with a high probability of finding tubal abnormalities to invasive tubal testing. The majority of this work has focused on the value of Chlamydia trachomatis antibody (CAT) testing (Mol et al., 1997; den Hartog et al., 2006; Broeze et al., 2011). CAT testing is not routinely performed worldwide, and is not a recommended investigation in international guidelines on the fertility work-up. Some authors have explored the predictive value of medical history taking, and concluded that medical history is of limited use for a policy of restricted use of laparoscopy (Johnson et al., 2000; Hubacher et al., 2004). This conclusion has been disputed by others (Thomas et al., 2001; Donnez and Jadoul, 2004; McComb, 2004; Tulandi and Platt, 2004).
Diagnostic aspects of tubal testing

For the work presented in this thesis, we decided to go back to the basis and explore the grounds on which guidelines advocate medical history taking for selecting women for invasive tubal testing (Luttjeboer et al., 2009). We found that a history of complicated appendicitis, pelvic surgery, ectopic pregnancy and endometriosis are strong risk indicators for tubal pathology in subfertile women. Due to limitations related to conventional meta-analytic techniques (Broeze et al., 2009), we were unable to estimate exact probabilities of tubal pathology, and to correct for dependency.

Therefore, we developed two prediction models for (severe) tubal pathology that express the probability of tubal pathology, and correct for mutual dependence (Chapters 4 and 5). While the first model was derived in a relatively small data set, and used as a pilot study for the development of the large-scale model, all factors from this model were also present in the larger model. We showed for any tubal pathology, that a prolonged duration of subfertility, a pregnancy of both partners or of only the male partner in a previous relationship, male smoking habits, a history of PID, history of Chlamydia infection, history of ectopic pregnancy, a history of legally induced abortion and previous pelvic surgery are all factors that increase the likelihood of tubal pathology. Clinically more relevant is the model for bilateral tubal pathology, for which it was shown that referral by a gynaecologist, female age above 32 years, dysmenorrhoea and smoking of the woman increase the likelihood of disease, as does a longer duration of subfertility, a pregnancy of both partners in a previous relationship, male smoking habits, history of PID, history of Chlamydia infection, ectopic pregnancy and previous pelvic surgery. In contrast, a previous pregnancy in the current relationship and a higher male age lower the probability of bilateral tubal pathology.

The association of male characteristics with female tubal disease was remarkable, as male age, male smoking habits, as well as having fathered a pregnancy in a previous relationship cannot causally be related to tubal damage in a woman. Possibly these male characteristics act as indicators for some unrecorded variables, such as number of sexual partners or socio-economic status, or they reflect lifestyle and selection mechanisms.
Although both models are able to make an almost perfect distinction between women with a low and high probability of tubal pathology, our models have not been externally validated yet, so caution has to be taken to apply them already in daily clinical practice. Reassuringly though, a recent study from Israel confirmed several of the risk factors identified in our study, including increasing age, secondary subfertility, and male smoking habits (Farhi et al., 2011). Our findings were also confirmed in an individual patient data-meta analysis (Broeze et al., 2012), which showed a similar predictive performance for medical history taking as did our models. Interestingly, this study also showed that both CAT and HSG independently improve the performance of the model when compared with the results of diagnostic laparoscopy.

Prognostic aspects of tubal testing

It is our opinion that medical history taking is certainly of value in selecting those women that might benefit from early tubal testing. The next question is which tubal test should then be applied. As the purpose of the fertility work-up has shifted from a purely diagnostic question to a prognostic orientation, it is not so much the question which tubal test is the most accurate, but to what extent an abnormal test result interferes with chances of natural conception. To answer this question we related findings at HSG and laparoscopy to spontaneous pregnancy (Chapter 6). We found that women with unilateral tubal pathology at HSG or laparoscopy have a moderate, non-significant reduction in spontaneous pregnancy chances, whereas those with bilateral tubal pathology at HSG or laparoscopy have a severe reduction in the ability to achieve natural conception. This reduction in fertility prospects was similar for HSG and laparoscopy, suggesting that HSG and laparoscopy have a comparable predictive capacity for natural conception.

It is noteworthy that unilateral pathology is of only minor prognostic relevance, confirming that the goal of tubal testing should be to detect women with bilateral tubal pathology, so that they can be treated with IVF. Studies on the prediction of pregnancy after intra-uterine insemination also failed to show a statistically significant impact of unilateral tubal pathology on pregnancy rates (Steures et al., 2004). In addition, no evidence-based treatment policies are known for women affected by unilateral tubal pathology. In case of unilateral abnormalities on HSG, one could consider several options, e.g. one could perform a diagnostic
laparoscopy. In 95% of cases though, laparoscopic findings will not change the HSG-based treatment plan (Lavy et al., 2004). Alternatively, one could aim to increase pregnancy chances with IUI with mild ovarian stimulation or bypass the Fallopian tube with IVF. We found only one case-control study in the literature, which evaluated IUI/COH in women with unilateral tubal pathology on HSG as compared to IUI/COH in women with unexplained subfertility. Similar pregnancy rates were found in both groups (Farhi et al., 2007). One of the studies that still needs to be performed therefore is a randomized controlled trial comparing expectant management, IUI/COH and IVF in women with unilateral tubal pathology, evaluating pregnancy rates and costs.

Currently, after invasive tubal testing has shown bilateral patent tubes, the result of CAT testing is generally ignored (Chapter 7). We questioned whether evidence of a past Chlamydia infection affects the probability of spontaneous pregnancy in women without visible tubal pathology, and found that subfertile women with a positive CAT test but without visible tubal pathology on HSG or laparoscopy have a 33% lower probability of pregnancy as compared to CAT negative women. Results from previous studies on this topic are conflicting, which urges the need for external validation of our findings. If confirmed, it would imply a new prognostic factor that could be incorporated when developing updated prognostic models for treatment independent pregnancy.

**Ultimate value of tubal testing**

Although much effort is being put in evaluating accuracy of different screening strategies, the main question is whether ultimately tubal testing will increase the likelihood of conception. For laparoscopy, there is no evidence that the procedure itself increases this likelihood (Al-Fadhli et al., 2006; Luttjeboer et al., 2007). For hysterosalpingography, there is some evidence that performing the procedure with oil-soluble contrast medium increases the probability of natural conception when compared with water-soluble contrast medium. However, the evidence is based on aggregated data of two trials, where statistical heterogeneity was present and the higher quality trial failed to show a significant difference. Currently, the H2Oil study is recruiting women to answer the question whether we should use oil-based contrast medium during a diagnostic HSG (H2Oil trial number: NTR3270).
One randomized controlled trial examined the value of a standard laparoscopy after normal hysterosalpingography before start of intrauterine insemination and found that a standard laparoscopy with therapeutic interventions does not increase the likelihood of conception (Tanahatoe et al., 2005). Another randomized study showed that early tubal testing did not increase spontaneous pregnancy rates if compared with delayed tubal testing (Lindborg et al., 2009). Whether a tubal test strategy should start with hysterosalpingography or whether this test can be abandoned was evaluated in a randomised trial (Perquin et al., 2006). In this study the fertility workup was completed with either HSG with water-based contrast or immediate laparoscopy. In case of no abnormalities at HSG, women were managed expectantly for 6 months. In case of no pregnancy after this time period, women underwent a laparoscopy. In case of an abnormal HSG, women underwent laparoscopy within one to two months. At 18 months of follow-up, no differences in pregnancy rates between both strategies were noted. The authors concluded that HSG has no role in the fertility work-up, but we criticized this study due to an inadequate methodological design (as no specific treatment strategies followed a specific test result) and showed that a strategy starting with HSG results in a 30% reduction in the number of laparoscopies (Coppus et al., 2006). Although more and more authors advocate that HSG is a useless test in modern fertility practice (den Hartog et al., 2008; Lim et al., 2011), we feel that given the current evidence HSG still deserves a prominent role in the fertility workup.

In conclusion, a difference in outcome between different tubal testing strategies can currently only be made by referring women with bilateral tubal pathology for IVF early. To end the debate on whether we should perform tubal testing, and if so, with which tests, a large scale multilevel randomized trial is needed, comparing different screening strategies with explicit treatment rules in case of abnormal test results. Only by performing such a study, the true value and cost-effectiveness of tubal testing can be revealed.
References


H2Oil study: www.studies-obsgyn.nl/h2olie


