Diagnostic tests for tubal pathology from a clinical and economic perspective
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Epilogue
With an estimated prevalence between 11 and 30% in subfertile populations, tubal pathology is an important cause for subfertility (Hull et al., 1985, Collins et al., 1995, Snick et al., 1997). The American Society of Reproductive Medicine (ASRM) recommends a careful medical history and physical examination to identify symptoms and signs suggesting a specific cause for subfertility, which can be the focus of subsequent diagnostic evaluation. The National Institute for Clinical Excellence (NICE) guideline advises the use of patient characteristics to decide whether tubal testing should be performed and women without comorbidities should be offered HSG. The guideline of the Dutch Society for Obstetrics and Gynaecology (NVOG) mentions the use of patient characteristics as a first step in the diagnostic strategy (ASRM, 2006; NICE, 2004; NVOG, 2004).

Although all these guidelines recommend medical history and physical examination as a primary evaluation in the fertility work-up, a clear evidence based recommendation in whom, when and which tubal patency tests should be performed is not provided. As a consequence there is wide variation in clinical practice concerning the use of tubal patency tests. A diagnostic strategy in which all available information from the medical history and physical examination is integrated with the results of tubal patency tests could potentially lead to more cost-effective testing of tubal pathology. We have performed and published several studies on patient characteristics and these diagnostic tubal tests since the publication of these guidelines. In one study we developed decision rules to express the probability of tubal pathology at the first consultation based on patient characteristics only (Coppus et al., 2007). In another study we showed that the addition of Chlamydia trachomatis Antibody Test (CAT) to a diagnostic model based on patient characteristics increased the AUC for the diagnosis of any tubal pathology from 0.65 to 0.70, although not significantly (Coppus et al., 2007). In a separate IPD-analysis, it was shown that from three commonly used Chlamydia Antibody Tests, the Micro Immuno Fluorescence (MIF) test, showed a moderate ability to discriminate between women with and without tubal pathology, but performed best of the three CAT tests (Broeze et al., 2011). Additional testing for a high-sensitive CRP (hs-CRP), a possible marker for persistence of a Chlamydia Trachomatis infection, to the CAT, increased the diagnostic accuracy of CAT, but the result of that study requires confirmation before it is implemented in clinical practice (Den Hartog et al., 2008). In another study we provided decision rules in which information from medical history and physical examination were combined with the results of tubal testing in order to calculate the predicted probability of tubal pathology (Broeze et al., 2012). The combination of patient characteristics with CAT and HSG results provided the best diagnostic performance for the diagnosis of bilateral tubal pathology. We also showed that the diagnostic performance of HSG is invariant over several subgroups of patients, suggesting that HSG is able to diagnose both any and bilateral tubal pathology equally in all subfertile women and is a useful screening test for all subfertile women. Of note is that in women at low risk for tubal pathology (i.e. no risk indicators in the history and a negative CAT result), the sensitivity of HSG was low, but the speci-
ficity remained stable (Broeze et al., 2011). This is most likely due to false positive results at laparoscopy, which is the standard reference test in diagnostic studies on tubal patency. In women at low-risk for tubal pathology and a normal HSG, laparoscopy can show abnormalities which, we think, are often caused by technical problems at laparoscopy. These technical problems can consist of vaginal leakage of dye, low pressure at chromopertubation, premature ending of the procedure, difference in flow when one tube is patent or invisibility of the fimbrial ends. In another study we found that HSG and Laparoscopy show comparable performance in predicting natural conception, indicating that from that perspective there is no preference for one of these tests (Verhoeve et al., 2011). One randomised trial showed no additional advantage of diagnostic laparoscopy if this was performed following a normal HSG, on treatment decision and pregnancy outcome (Tanahatoe et al., 2005) and, in another randomised trial, the number of diagnostic laparoscopies was substantially reduced if diagnostic laparoscopy was preceded by HSG (Perquin et al., 2006). Combining the results of these studies, it can be concluded that medical history and physical examination can differentiate between women at low and at high risk for tubal pathology. Identification of those women at highest risk for bilateral tubal pathology, who have the lowest chances for natural conception, is best obtained by combining patient characteristics with CAT and HSG. In a cost-effective analysis, different diagnostic strategies for presence of tubal pathology were assessed. In this study, patient characteristics were taken into account and obtained from IPD-analyses (Broeze et al. 2012), the prognostic model of Hunault for unexplained subfertility was used (Hunault et al., 2004) as well as a prognostic model for pregnancy outcome after IVF treatment in a Dutch cohort (Lintsen et al., 2007). This study showed that no diagnostic test and expectant management is the most cost-effective strategy until the age of 38 years, and no diagnostic test but direct treatment from the age of 39 years. If, however, a diagnostic tubal test is planned, a strategy of first HSG followed by diagnostic laparoscopy, where HSG shows bilateral occlusion, followed by management depending on the test result, is the most cost-effective strategy (Verhoeve et al., 2013).

We suggest the following for tubal patency tests in the fertility work-up; in women until 38 years and at low risk for tubal pathology based on medical history, physical examination and CAT result, expectant management and no diagnostic test for at least 12 months is justified and will reduce the number of unnecessary invasive diagnostic tests, complications and costs. An HSG followed by laparoscopy, if HSG shows bilateral occlusion, should be considered, if conception does not occur after expectant management and if a couple prefers fertility treatment other than IVF. In women with bilateral distal occlusion, HSG can be helpful to decide whether laparoscopic salpingostomy is preferable above or before IVF, although randomised evidence for this is lacking. In women 39 and older, direct treatment is the most cost-effective scenario, irrespective of the medical history, physical examination and CAT result. It is not to be expected that every couple is prepared to start directly with IVF treatment. The second best strategy is then to prove tubal patency by HSG and if the tubes are found to be open, couples
can be counselled to choose between expectant management, intra uterine insemination or IVF, obviously taking the prognosis for natural conception into account. (Hunault et al., 2004; Steures et al., 2006). In some women sonographically visible bilateral hydrosalpinges may be detected before tubal testing. In these women direct laparoscopy is advised and can be combined at the same time with salpingectomy or laparoscopic tubal occlusion, since it has been shown that this improves IVF-outcome (Johnson et al., 2010).

Our recommendation and findings can serve as a framework for a new evidence based guideline for the diagnosis of tubal pathology in subfertile couples. Several aspects still need to be addressed and considered. Although our decision rules showed good calibration (the correspondence between model-based probabilities and observed tubal pathology rates) and can be easily applied in clinical practice, external validation is still required (Leushuis et al., 2009).

Also further research is needed concerning the finding of unilateral tubal pathology. Although our findings did not show a significant reduction in pregnancy rates in this group of women (Mol et al., 1999; Verhoeve et al., 2011), the pregnancy rate may be overestimated due to use of conventional methods of analysis (van Geloven et al., 2012). It is thus possible that in case of unilateral tubal pathology, active management such as surgery, IUI or IVF may result in significantly higher pregnancy rates. To answer this question requires a randomised controlled trial in this group of women.

Finally, we recommend expectant management and deference of tubal testing in a substantial number of couples. A recent survey amongst patients and professionals in the Netherlands showed that not only patients’ appreciation of expectant management was moderate, but also the professionals’ adherence to expectant management. Improvement of adherence may be obtained by providing more information material to patients about prognostic models and providing protocols and training to professionals and by improving their communication skills (van den Boogaard et al., 2012). Tubal tests may have additional effects on patients’ health apart from the consequences of subsequent management decisions (Bossuyt and McCaffery, 2009; Lenhard et al., 2005). These additional effects, such as knowing the cause of the subfertility, being reassured that tubes are patent or anxiety provoked when the tests reveal bad news, have not been studied. The value of such information may influence the decision to test or not and should be studied.
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