Diagnostic tests for tubal pathology from a clinical and economic perspective
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Citation for published version (APA):
Verhoeve, H. R. (2013). Diagnostic tests for tubal pathology from a clinical and economic perspective

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Download date: 12 Dec 2018
Summary

Chapter 1
Tubal pathology is a common cause for subfertility. This chapter gives an overview of tubal patency tests from a historic perspective and gives an outline and description of the objectives of this thesis.

Chapter 2
The aim of the fertility work-up is to exclude recognized causes of infertility and to distinguish those couples who have good natural pregnancy prospects from those who have poor prospects. Information gathered by medical history, clinical findings and the results of the diagnostic tests should help the clinician in counselling subfertile couples. This chapter covers the most commonly used diagnostic tests in the fertility work-up and their utility in clinical practice is discussed.

Chapter 3
Guidelines recommend diagnostic laparoscopy in subfertile women with known co-morbidities in their medical history. Aggregated evidence underpinning these recommendations is, however, currently lacking. The objective of this study was to perform a systematic review and meta-analysis of the available evidence on the association between items reported during medical history taking and tuboperitoneal pathology. To do this we searched through MEDLINE (from 1966 to May 2007), EMBASE (from 1960 to January 2007) and used bibliographies of retrieved primary articles of all relevant studies that compared medical history with the presence or absence of tubal pathology. A diagnosis of tubal pathology had to be made by hysterosalpingography, laparoscopy or a combination of both. In the absence of invasive tubal testing, tuboperitoneal pathology was considered to be absent in case of intrauterine pregnancy. Homogeneity between studies was assessed, and the association between medical history and tubal pathology was expressed as a common odds ratio with a 95% CI. We included 32 studies. In cohort studies, strong associations were found for a history of complicated appendicitis (OR 7.2, 95% CI 2.2-22.8), pelvic surgery (OR 3.6, 95% CI 1.4-9.0) and pelvic inflammatory disease (PID) (OR 3.2, 95% CI 1.6-6.6), and in case-control studies, for a history of complicated appendicitis (OR 3.3, 95% CI 1.8-6.3), PID (OR 5.5, 95% CI 2.7-11.0), ectopic pregnancy (OR 16.0, 95% CI 12.5-20.4), endometriosis (OR 5.9, 95% CI 3.2-10.8) and sexually transmitted disease (OR 11.9, 95% CI 4.3-33.3).
Subfertile women reporting a history of PID, complicated appendicitis, pelvic surgery, ectopic pregnancy and endometriosis are at increased risk of having tuboperitoneal pathology.
CHAPTER 9

Chapter 4
In chapter 3 we performed a systematic review and meta-analysis of items in the medical history and their association with tubal pathology. For a history of induced abortion three case-control studies could be identified. Meta-analysis of these studies showed an increased risk of tubal pathology if the history revealed an induced abortion (OR 1.7, 95% CI: 1.3-2.1). Because case-control studies possibly overestimate such a relation, we evaluated this in a large cohort from our own hospital. For each couple, we registered the reproductive history. Tubal disease was diagnosed by hysterosalpingography and/or diagnostic laparoscopy. We assessed the association between reproductive history and the presence of tubal disease, by calculating odds-ratios (OR) and 95% confidence intervals. Data from 6,149 couples were available for analysis. The OR for tubal pathology after a previous induced abortion was 1.6 (95% CI: 1.3 to 1.9), after a previous ectopic pregnancy 8.4 (95% CI : 6.3 to 12), after a previous miscarriage 1.1 (95% CI: 0.87 to1.3), and after a previous live birth 1.0 (95% CI: 0.88 to 1.2).
A history of induced abortion is associated with an increased risk of tubal pathology in subfertile couples.

Chapter 5
The aim of tubal testing is to identify women with bilateral tubal pathology in a timely manner, so they can be treated with IVF or tubal surgery. In this study we presented two models which were developed to identify women in whom early tubal testing may be indicated, and in whom it may be deferred. Data of 3716 women who underwent tubal patency testing as part of their routine fertility work-up were used to relate elements in their medical history to the presence of tubal pathology. With multivariable logistic regression, we constructed two diagnostic models. One in which tubal disease was defined as occlusion and/or severe adhesions of at least one tube, whereas in a second model, tubal disease was defined as the presence of bilateral abnormalities. Both models discriminated moderately well between women with and women without tubal disease with an area under the receiver-operating characteristic curve (AUC) of 0.65 (95% CI: 0.63-0.68) for any tubal pathology and 0.68 (95% CI: 0.65-0.71) for bilateral tubal pathology, respectively. However, the models could make an almost perfect distinction between women with a high and a low probability of tubal pathology. A decision rule in the form of a simple diagnostic score chart was developed for application of the models in clinical practice.

This study provides two easy to use decision rules that can accurately express the women’s probability of (severe) tubal pathology at the couple’s first consultation. They could be used to select women for tubal testing more efficiently. However, external validation of these models is still required.
Chapter 6

Laparoscopy has been claimed to be superior to hysterosalpingography (HSG) in predicting fertility. Whether this conclusion is applicable to a general subfertile population can be questioned as data in support of this claim were collected in third line centres. The aim of this study was to assess the prognostic capacity of HSG and laparoscopy in a general subfertile population.

In 38 centres, we prospectively studied a cohort of patients referred for subfertility between 2002 and 2004, who underwent HSG and/or laparoscopy as part of their subfertility work-up. Follow-up started immediately after tubal testing and ended 12 months thereafter. Time to pregnancy was censored at the date of last contact, when the woman was not pregnant or at the start of treatment. Kaplan-Meier curves for the occurrence of spontaneous intra-uterine pregnancy were constructed for patients without tubal pathology, those with unilateral tubal pathology and patients with bilateral tubal pathology at HSG and laparoscopy. Multivariable Cox regression analysis was used to calculate fecundity rate ratios (FRRs) to express associations between tubal pathology and the occurrence of an intra-uterine pregnancy. Of the 3,301 included patients, 2,043 underwent HSG, 747 underwent diagnostic laparoscopy and 511 underwent both. At HSG, 322 (14%) patients showed unilateral tubal pathology and 135 (5%) showed bilateral tubal pathology. At laparoscopy 167 (13%) showed unilateral tubal pathology and 215 (17%) showed bilateral tubal pathology. Multivariable analysis resulted in FRRs of 0.81 (95% confidence intervals (CI): 0.59-1.1) for unilateral- and 0.28 (95% CI: 0.13-0.59) for bilateral tubal pathology at HSG. The FRRs at laparoscopy were 0.85 (95% CI: 0.47-1.52) for unilateral- and 0.24 (95% CI: 0.11-0.54) for bilateral tubal pathology.

Patients with unilateral tubal pathology at HSG and laparoscopy had a moderate reduction in pregnancy chances whereas those with bilateral tubal pathology at HSG and laparoscopy had a severe reduction in pregnancy chances. This reduction was similar for HSG and laparoscopy, suggesting that HSG and laparoscopy have a comparable predictive capacity on natural conception.

Chapter 7

Guidelines are not in agreement on the most effective diagnostic scenario for tubal patency testing, i.e. there is no consensus on which test should initially be used, and there is no consensus on the sequence of tests in the fertility work-up. Therefore we evaluated the cost-effectiveness of invasive tubal testing in subfertile couples. We performed a cost-effectiveness analysis, using a decision analytic framework based on a computer-simulated cohort of subfertile women. We evaluated six diagnostic and treatment scenarios: [1] No tests or treatment [2] Direct treatment without tubal testing [3] Delayed treatment without tubal testing [4] Hysterosalpingogram (HSG), followed by direct or delayed treatment, according to diagnosis (tailored treatment) [5] HSG and a diagnostic laparoscopy (DL) in case HSG does not prove tubal...
patency, followed by tailored treatment [6] DL followed by tailored treatment. Main outcome was expected cumulative live birth after three years. Secondary outcomes were cost per couple and the incremental cost-effectiveness ratio. For a 30 year old woman, with otherwise unexplained subfertility for 12 months, three year cumulative live birth rates were 51.8%, 78.1%, 78.4%, 78.4%, 78.6% and 78.4% and cost per couple were € 0, € 6,968, € 5,063, € 5,410, € 5,405 and € 6,163 for scenario 1, 2, 3, 4, 5 and 6, respectively. The incremental cost-effectiveness ratio compared with scenario 1 (reference strategy), were € 26,541, € 19,046, € 20,372, € 20,150 and € 23,184 for scenario 2, 3, 4, 5 and 6, respectively. Sensitivity analysis showed the model to be robust over a wide range of values for the variables.

Invasive diagnostic tubal tests in the fertility work-up are not cost-effective. If an invasive diagnostic test is planned, HSG followed by tailored treatment or HSG and a DL in case HSG does not prove tubal patency, are the most cost-effective scenarios.

**Chapter 8**
In this chapter the findings of this thesis are discussed, clinical implications are given and future research recommendations are made.

**Chapter 10**
Provides an epilogue in which the results of three different theses on tubal pathology from our study group are integrated.