Tubal subfertility and ectopic pregnancy. Evaluating the effectiveness of diagnostic tests

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1. Introduction

Subfertility is defined as failure of conception after at least one year of unprotected intercourse. In the United States, about 8% of all women between 15 and 44 years are suffering from subfertility.\(^1\) In the Netherlands, the percentage couples suffering from subfertility is estimated to be between 12% and 17%, depending on the age of the female partner of the couple.\(^2\)

With sperm defects and ovulation disorders, tubal pathology ranks among the most frequent causes of subfertility. Tubal pathology can be defined as any abnormality of the fallopian tube, a structure of 8 to 20 centimeters length that connects the abdominal cavity with the uterine cavity. The function of the fallopian tube is to facilitate transport of sperm to the abdominal cavity and of the zygote back to the uterus, after fertilization of the oocyte has taken place in the ampulla. The inside of the tube is covered with cilia that beat in the direction of the uterus, thereby probably facilitating egg transport. Apart from the cilia, the muscular wall of the fallopian tube is facilitating transport by causing peristaltic movements.

The most important cause of tubal pathology is infection. Pelvic inflammatory disease is caused by sexually transmitted infectious agents, of which \textit{Neisseria gonorrhoea} and \textit{Chlamydia trachomatis} are the most common. In the Netherlands, experts estimate the incidence of \textit{C. trachomatis} to be between 2 and 300 per 10,000 women.\(^2\) Although \textit{C. trachomatis} can cause fulminant pelvic inflammatory disease, the course of the infection is asymptomatic in the majority of the cases. Tubal function can be compromised after either symptomatic or asymptomatic infection, thereby increasing the risk of tubal subfertility and ectopic pregnancy. The prevalence of subfertility after pelvic inflammatory disease varies between 6% and 60%, depending on the severity of the infection, the number of infections and the age of the woman.\(^3\)

Several tests exist for the evaluation of tubal pathology. At hysterosalpingography (HSG), (first performed with lipiodol in 1925\(^5\)), oil or water based dye is injected slowly through the cervical canal into the uterine cavity. Subsequent X-ray imaging visualizes the uterine cavity, the fallopian tubes and, in case of tubal patency, the abdominal cavity. Apart from its diagnostic value, HSG is also thought to improve 'spontaneous' fertility chances.\(^6\) Hysterosalpingography is performed as an outpatient procedure, but is sometimes painful. The main complication of HSG is the occurrence of pelvic infection, which is reported in 1-3% of all cases.\(^7\) The risk of infection can be decreased by an adequate medical history for previous infections, \textit{Chlamydia} culture of the cervix and prophylactic antibiotics.\(^8\)

Laparoscopy with dye, first performed in the 1960s, allows direct visualization of the tubes, but also of peritubal adhesions and endometriosis.\(^9\) Laparoscopy with dye is generally regarded as the best test in the evaluation of tubal pathology.\(^10\) There is no knowledge on the effect of laparoscopy on 'spontaneous' fertility chances, but if HSG improves fertility chances by perturbation of the fallopian tubes, laparoscopy might also have beneficial effect on spontaneous conception chances. Furthermore, laparoscopy enables treatment of endometriosis grade I/II, which is also beneficial for fertility prospects.\(^11\)
Chapter 1

Chlamydia antibody testing (CAT) was introduced in the work-up for subfertility in the 1980s. Acute infection is diagnosed with detection of immunoglobulin (Ig) M in serum. High serum titers of IgG antibodies against Chlamydia indicate a previous Chlamydia infection, and are therefore especially of use in the assessment of the fallopian tubes. In contrast to HSG and laparoscopy, CAT does not allow visualization of tubal abnormalities.

At this moment, there is no consensus on which tests to use for the diagnostic work-up of tubal pathology. Whereas many authors have advocated the use of HSG, a recent guideline of the Dutch College of Obstetrics and Gynecology advised to start the work-up with CAT, and perform HSG only at indication. Laparoscopy should be performed for an evaluation of possible tubal pathology in case the CAT is increased.

The aim of this part of the thesis is to assess the test performance of HSG, CAT and laparoscopy, and to provide guidelines for the work-up of tubal pathology.

Chapter 2 focuses on the reproducibility of the interpretation of HSG with respect to proximal and distal tubal occlusion, hydrosalpinx and peritubal adhesions. A low reproducibility of the interpretation of one these items would seriously limit the use of HSG in the diagnostic work-up for tubal pathology.

Chapter 3 provides a systematic review of the published literature in which HSG is compared with laparoscopy with respect to the diagnosis of tubal pathology and peritubal adhesions. The performance of HSG is expressed in terms of sensitivity and specificity.

Chapter 4 provides a systematic review of the published literature in which CAT is compared with laparoscopy. The performance of CAT is expressed in terms of sensitivity and specificity.

Chapters 5 and 6 deal with the capacity of HSG and laparoscopy to predict fertility outcome. Chapter 5 focuses on the question which HSG findings have a significant impact on fertility outcome, using a cohort of over 350 women undergoing HSG in the Academic Medical Center in Amsterdam, The Netherlands. The prognostic impact of one- and two-sided tubal pathology as observed at HSG is expressed using fecundity rate ratios. The impact of potential bias caused by informative censoring is assessed. In chapter 6, a direct comparison is made between the prognostic capacity of HSG and laparoscopy in a cohort of over 800 patients, using data collected in the Canadian Infertility Treatment Evaluation Study (CITES).

In chapter 7, the results of the studies from chapter 2 to 6 are used in a cost-effectiveness analysis of the diagnostic work-up of tubal subfertility. The central question of this chapter is which strategy is expected to reveal the highest live birth rates (effectiveness) at the lowest possible cost per live birth (cost-effectiveness). The results of this chapter are used to formulate guidelines for the diagnostic work-up for tubal subfertility.

1.1 References


