Tubal subfertility and ectopic pregnancy. Evaluating the effectiveness of diagnostic tests
Mol, B.W.J.
17. Summary and clinical implications

The aim of the second part of the thesis was to assess the diagnostic performance of transvaginal sonography and serum human chorionic gonadotrophin (hCG) in the diagnosis of ectopic pregnancy, and to evaluate in which clinical situations these diagnostic tools can be used.

Chapter 10 and 11 focused on the diagnostic performance of initial and repeat serum hCG measurement in patients with suspected ectopic pregnancy in whom transvaginal sonography is inconclusive.

In chapter 10 it was shown that initial serum hCG measurement performed better in patients with sonographic evidence of an ectopic mass or fluid in the pouch of Douglas than in those without sonographic abnormalities. The interpretation of serum hCG levels should therefore depend on additional findings at transvaginal sonography. This is especially of interest if one takes into account that the prevalence of ectopic pregnancy differed strongly between patients with additional sonographic findings and patients without such findings. In patients with additional sonographic findings the prevalence of ectopic pregnancy was 72%. In contrast, in absence of additional sonographic findings this prevalence was only 24%. Consequently, the discriminative capacity of serum hCG measurement in absence of these findings should be better to compensate for the lower pre-test probability. Unfortunately, the latter does not seem to be true.

In chapter 11 it was shown that the course of the serum hCG concentration, be it the absolute or the percentual difference in serum hCG concentration between initial and repeat measures, performed better in the diagnosis of ectopic pregnancy and viable intra-uterine pregnancy than the absolute serum hCG concentration at repeat measurement. A rise in serum hCG concentration < 50% had a likelihood ratio (LR) for ectopic pregnancy of 3.4. A rise in serum hCG concentration > 50% had a LR for ectopic pregnancy of 3.2. However, after two days all viable intra-uterine pregnancies also had a rise of percentual serum hCG levels > 50%. Four days after the start of the diagnostic process only one viable intra-uterine pregnancy was not detected at sonography, whereas by then any rise in serum hCG levels made the diagnosis ectopic pregnancy very likely (LRs > 10).

In chapter 12 a diagnostic algorithm was described that used probabilistic decision rules in which cutoff levels for test-positivity are flexible, for the evaluation of women with suspected ectopic pregnancy. This algorithm was compared with an algorithm that used rigid cutoff levels. In the flexible algorithm, ectopic pregnancy was diagnosed whenever the post-test probability for ectopic pregnancy exceeded 95%, whereas ectopic pregnancy was rejected if the calculated post-test probability fell under 1%. The inflexible algorithm was associated with a fixed sensitivity of 93% and a fixed specificity of 97%, whereas the sensitivity and specificity of the individualized algorithm using probabilistic decision rules depended on the prevalence of ectopic pregnancy. Consequently, predictive values varied strongly when the inflexible algorithm was used, whereas they were much more stable after using the flexible algorithm. For five possible valuations of false-positive and false-negative
diagnoses, the flexible algorithm was shown to be able to reduce disutility, compared to the inflexible algorithm. Therefore, clinicians should incorporate probabilistic decision rules in algorithms used for the diagnosis of ectopic pregnancy.

Chapter 13 evaluated whether non-invasive diagnostic tools can predict the presence of tubal rupture or active bleeding in patients with tubal pregnancy. Among 288 consecutive patients with suspected tubal pregnancy scheduled for confirmative laparoscopy, 65 (23%) showed tubal rupture and/or active bleeding at laparoscopy. Presence of abdominal pain, rebound tenderness at abdominal examination, fluid in the pouch of Douglas at transvaginal sonography, and a low serum hemoglobin were independent predictors of tubal rupture and/or active bleeding. Presence of fetal signs or an ectopic mass at sonography reduced the risk of tubal rupture. Abdominal pain was the most sensitive predictor with a sensitivity of 95%, although its specificity was rather limited (37%). Since abdominal pain was present in 70% of the patients with tubal pregnancy, systemic methotrexate without confirmative laparoscopy can only be offered safely to a limited number of patients.

Chapters 14, 15 and 16 tried to answer the question if screening for ectopic pregnancy is indicated. Screening for ectopic pregnancy consists of inviting symptom-free women at increased risk for ectopic pregnancy to undergo diagnostic tests for ectopic pregnancy as soon as they know that they are pregnant.

Chapter 14 reviewed current knowledge on the risk of ectopic pregnancy by means of a meta-analysis. The results of 30 case-control studies and 10 cohort studies were analyzed. Previous ectopic pregnancy, previous tubal surgery, documented tubal pathology and in utero diethylstilbestrol (DES) exposure were found to be strongly associated with the occurrence of ectopic pregnancy. Women becoming pregnant after sterilization or while using an Intra Uterine Contraceptive Device (IUCD) were also at increased risk for ectopic pregnancy.

In chapter 15, 143 consecutive symptom-free women at increased risk for having an ectopic pregnancy were included in a prospective study. All women were offered transvaginal sonography and serum hCG measurement to detect ectopic pregnancy before the onset of symptoms. Eight had an ectopic pregnancy, 129 had an intra-uterine pregnancy, and six had a non-viable pregnancy, resulting in a prevalence of ectopic pregnancy of 5.6% (95% CI 2.5% to 10.7%) of the women screened. This prevalence was remarkably at odds with the 24% that was reported previously in a Finnish study. Although the different ectopic pregnancy rates could be caused by differences in the incidence of ectopic pregnancy between Finland and The Netherlands, it is more likely that women who fulfilled the inclusion criteria, but in whom initial transvaginal sonography showed an intra-uterine pregnancy, were not systematically included in the Finnish study.

In chapter 16 a decision-analytic approach was used to compare screening programs incorporating transvaginal sonography, serum hCG measurement and serum Progesterone measurement, with a ‘watchful waiting’ strategy. The strategies were compared on the expected number of prevented tubal ruptures, the expected number of false-positive diagnoses and costs. Both the number of false-positive diagnoses that were made to prevent one case of tubal rupture and the costs appeared to be strongly dependent on the
prevalence of ectopic pregnancy. At a prevalence of ectopic pregnancy of 6%, a screening program with transvaginal sonography and serum hCG measurement would reduce the number of patients with ruptured ectopic pregnancy from 2.1 to 0.61 per 100 screened women, whereas screening with transvaginal sonography, serum hCG measurement and serum Progesterone measurement would reduce the number patients with tubal rupture to 1.2 per 100 screened women. The number of false-positive diagnoses would be lower after screening with serum Progesterone measurement as compared to screening with transvaginal sonography and serum hCG measurement only, 0.92 and 1.1 per 100 screened women, respectively. The total costs of both strategies were comparable at approximately US$ 18,000 per 100 screened women. In terms of cost-effectiveness, screening with transvaginal sonography and serum hCG measurement was expected to cost approximately US$ 1,200 per prevented tubal rupture, whereas screening with transvaginal sonography, serum hCG measurement and serum Progesterone measurement was expected to cost US$ 2,100 per prevented tubal rupture. Screening with transvaginal sonography and serum hCG measurement alone was expected to generate 0.64 false-positive diagnosis for each prevented tubal rupture, whereas for screening with serum Progesterone measurement this number was 0.84. Screening reduced costs compared to watchful waiting at prevalences of 7.9% and 8.8% for screening without and screening with serum Progesterone measurement, respectively.

Although from these perspectives screening for ectopic pregnancy does not seem to be a very attractive option, one should also take into account that many women with a history of fertility problems want to be informed about the condition of their pregnancy. As a consequence, sonography can be considered on psychological and emotional grounds. Our analysis showed that one should be very careful with making a diagnosis and starting treatment in these situations. The merit of such sonographies is not the early detection of ectopic pregnancy, but rather the early reassurance that nothing is wrong with a viable intra-uterine pregnancy. The possibility of a false-positive diagnosis in symptom free women should especially be considered in women that are offered screening after IVF-ET, since the diagnostic performance of serum hCG measurement is strongly reduced in pregnancies that occur through in-vitro fertilization and embryo-transfer.

The main issue in the diagnosis of ectopic pregnancy in the near future is to identify which patients with an ectopic pregnancy should be treated, and which patients could be managed expectantly. In a previous study in which patients with serum hCG levels < 1,500 IU/L were managed expectantly it was shown that treatment was required in a very limited number of patients. This was confirmed in the study on 800 patients with suspected ectopic pregnancy reported in this thesis. The only randomized study comparing expectant management with systemic methotrexate found no difference between these two strategies in patients with a serum hCG concentration < 5,000 IU/L. Unfortunately, no cutoff value of serum hCG measurement was reported below which expectant management did not fail. This is a subject for future research. Such studies might show that patients with low serum hCG levels that are currently treated do not require treatment at all.
Another issue for further study is the mutual independence between serum hCG measurement and serum Progesterone measurement. Some authors, especially in the United States, have advocated the use of serum Progesterone measurement in the early detection of ectopic pregnancy.\textsuperscript{6,7} In a recent meta-analysis, serum Progesterone levels were found to be predictive for pregnancy failure, but not for the presence of ectopic pregnancy.\textsuperscript{8} Stovall \textit{et al.} reported in 1992 that single serum Progesterone measurement had a slightly better diagnostic performance as compared to serial serum hCG measurement.\textsuperscript{9} However, in that study serum hCG measurement was not interpreted in relation to findings at transvaginal sonography, according to the 'discriminatory zone' principle as defined by Kadar \textit{et al.}\textsuperscript{10} Chapter 16 showed that serum Progesterone measurement was unlikely to have additional value to diagnosis with transvaginal sonography and serum hCG measurement only in case it was used as triage. However, the comparison of serum hCG measurement and serum Progesterone measurement in the diagnosis of ectopic pregnancy in patients that also were subject to sonography might alter this conclusion.

17.1 References