Tubal subfertility and ectopic pregnancy. Evaluating the effectiveness of diagnostic tests
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The diagnostic management of suspected ectopic pregnancy has been subject to dramatic changes over the last decade. Before the introduction of reliable non-invasive diagnostic tests, ectopic pregnancy was often only recognized in its classical clinical picture, i.e., intermittent abdominal pain with a sudden onset and presence of irregular vaginal bleeding in a woman who might be pregnant. As the clinical signs and symptoms were usually inconclusive for a diagnosis of ectopic pregnancy, laparoscopy was mandatory to establish the diagnosis of ectopic pregnancy. Consequently, many laparoscopies were performed in patients without ectopic pregnancy, whereas at the time a diagnosis of ectopic pregnancy was made, the clinical situation had often deteriorated because of tubal rupture or active intra-abdominal bleeding. Consequently, 15 to 20% of the patients were in shock at the moment of first presentation.

Introduction of urine pregnancy tests with sensitivities and specificities both above 99% allowed a distinction between pregnant and non-pregnant women, offering the possibility to reject the diagnosis of ectopic pregnancy in women who were not pregnant. The introduction of transvaginal sonography in the mid 1980s made it possible to visualize the uterine cavity, allowing the diagnosis of an intra-uterine pregnancy from a gestational age of five to six weeks onwards, whereas it also allowed to scan the adnexal region for presence of an ectopic pregnancy.

At the same time, serum Progesterone and serum human chorionic gonadotrophin (hCG) were introduced as biochemical markers for first-trimester pregnancy. Progesterone is a cholesterol derivative produced by the corpus luteum until about 10 weeks of gestation, and from then on by the placenta. During normal pregnancy serum Progesterone levels increase from 20 ng/mL at a gestational age of 6 weeks to 100 to 200 ng/mL at term. Human chorionic gonadotrophin, a glycoprotein that is secreted by the syncytiotrophoblast, is necessary for the survival of the corpus luteum, thus creating a symbiotic relation between the young pregnancy and the corpus luteum until the placenta starts steroidogenesis. In normal pregnancy, serum hCG levels increase from 100 IU/L at a conceptional age of 14 days to 100,000 IU/L at 8 to 10 weeks.

Both serum Progesterone measurement and serum hCG measurement have been used in the diagnostic management of suspected ectopic pregnancy. Low serum Progesterone concentrations are predictive for pregnancy failure, thereby offering the possibility to select women at increased risk for having an ectopic pregnancy. Serum hCG measurement can be used in patients with inconclusive sonographic findings. In 1981, Kadar et al. proposed the use of a discriminatory zone for serum hCG levels, defined as the minimal hCG concentration above which the sac of an intra-uterine pregnancy can always be identified at sonography.

Since then several authors have developed algorithms for the clinical interpretation of transvaginal sonography and serum hCG measurement, sometimes preceded by serum Progesterone measurement. These algorithms have shown excellent sensitivity and specificity in women with suspected ectopic pregnancy, thereby reducing the number of
unnecessary laparoscopies. A questionnaire among Dutch gynecologists in 1995 showed that transvaginal sonography and serum hCG measurement were implemented in the vast majority of the hospitals in The Netherlands.\textsuperscript{11} Apparently, these new algorithms filled up a gap in clinical practice. Despite their widespread use, individual parts of the new algorithms have not been subject to extensive research. The ‘discriminatory zone’ of serum hCG measurement introduced by Kadar \textit{et al.} has never been subjected to Receiver Operating Characteristic (ROC) analysis. Such an analysis has also not been performed for repeat serum hCG measurement in patients in whom serum hCG measurement does not reveal an immediate diagnosis.

The introduction of non-invasive diagnostic tools has several consequences for clinical practice. First, the use of non-invasive tools incorporated in diagnostic algorithms has made it possible to diagnose ectopic pregnancy at an earlier stage of the disease, sometimes even before the onset of symptoms. Despite this fact, there remains a considerable part of patients with ectopic pregnancy who present at a later stage, several days or even weeks after the onset of clinical symptoms. As a consequence, the population of patients presenting with suspected ectopic pregnancy has become heterogeneous. This has had consequences for the diagnostic work-up of patients with suspected ectopic pregnancy, not only because the pre-test probability of patients presenting with suspected ectopic pregnancy is likely to depend on the clinical picture, but also because the performance of the available diagnostic tests can differ, depending on the type of ectopic pregnancy. Consequently, it can be useful to adjust the present algorithms by taking into account the heterogeneity of patients with suspected ectopic pregnancy.

Second, non-invasive diagnosis of ectopic pregnancy has paved the way for non-invasive treatment, of which systematic methotrexate at present is the best evaluated. A recently performed randomized clinical trial comparing systemic methotrexate and laparoscopic salpingostomy has ruled out a large difference in quality of life, preservation of tubal patency and future fertility.\textsuperscript{12,15} Nevertheless, systemic methotrexate without confirmative laparoscopy is thought to reduce direct and total costs in patients with a serum hCG concentration \textless 3,000 IU/L, whereas a majority of the patients preferred non-surgical treatment if this treatment were to be available without confirmative laparoscopy.\textsuperscript{16}

Third, non-invasive diagnosis has introduced the possibility of screening women at increased risk for ectopic pregnancy.\textsuperscript{17} Although such a screening program might prevent complications of ectopic pregnancy, in particular tubal rupture or even circulatory instability, an explicit weighting of these potential advantages against potential disadvantages, such as false-positive diagnoses or costs, has never been made.

This part of the thesis deals with the clinical consequences of the introduction of non-invasive diagnostic tools in women with suspected ectopic pregnancy. Data of more than 800 women presenting with suspected ectopic pregnancy in the Academic Medical Center and the Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands were collected. All
women underwent transvaginal sonography and serum hCG measurement according to a previously developed protocol.9

Chapters 10 and 11 focus on the diagnostic performance of serum hCG measurement in patients with suspected ectopic pregnancy in whom transvaginal sonography is inconclusive. Chapter 10 assesses the performance of initial serum hCG measurement by means of ROC analysis, and evaluates if patient characteristics do influence the diagnostic performance of serum hCG measurement. Chapter 11 assesses the performance of repeated serum hCG measurement in the diagnosis of ectopic pregnancy and viable intra-uterine pregnancy in patients with suspected ectopic pregnancy, in which initial transvaginal sonography and serum hCG measurement can not establish a definite diagnosis. The distinction between viable intra-uterine pregnancy and non-viable pregnancy is especially important if one considers treatment of ectopic pregnancy with systemic methotrexate without performing laparoscopy. Chapter 12 evaluates if differences in pre-test probabilities should be taken into account in the diagnostic work-up for suspected ectopic pregnancy.

Chapter 13 evaluates the capacity of non-invasive diagnostic tools to detect tubal rupture and/or abdominal bleeding in patients with ectopic pregnancy. If systemic methotrexate is offered to patients in whom the diagnosis is made without laparoscopy, it is of imminent importance that tubal rupture and/or active bleeding are ruled out. A model predicting the probability of tubal rupture and/or abdominal bleeding with non-invasive diagnostic tools will be presented.

Chapter 14, 15 and 16 try to answer if screening for ectopic pregnancy is useful. In chapter 14 the current knowledge on the risk of ectopic pregnancy will be evaluated by means of a meta-analysis of published cohort and case-control studies evaluating possible risk indicators for ectopic pregnancy. In chapter 15 the prevalence of ectopic pregnancies among symptom-free women at increased risk undergoing a screening program will be determined. In chapter 16 two screening programs for ectopic pregnancy in symptom-free women are compared with a strategy in which women are instructed to contact their gynecologist only when clinical symptoms occur by means of a decision-analytic model. Outcomes are prevention of tubal rupture, number of false-positive diagnoses, and costs.

In chapter 17 the results will be summarized, clinical guidelines will be formulated and issues for future research will be pointed out.

9.1 References


