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Screening for Ectopic Pregnancy in Symptom-Free Women at Increased Risk

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Objective: To determine the ectopic pregnancy rate among symptom-free women at increased risk undergoing a screening program involving transvaginal sonography and serum hCG testing.

Methods: Consecutive symptom-free women at increased risk for ectopic pregnancy were studied prospectively by transvaginal sonography and serum hCG measurement to detect ectopic pregnancy before the onset of symptoms.

Results: Between September 1993 and May 1996, 143 symptom-free pregnant women with pregnancies of a gestational age of less than 7 weeks were screened. Eight had ectopic pregnancies, 129 had intrauterine pregnancies, and six had trophoblast in regression. Among the eight women with ectopic pregnancies, one was initially diagnosed as having an intrauterine pregnancy. This woman returned 1 week later with abdominal pain, and an ectopic pregnancy with intra-abdominal bleeding was found. Ectopic pregnancies were present in 5.6% (95% confidence interval 2.5%, 10.7%) of the women screened. This was significantly lower than reported in a previous study.

Conclusion: The ectopic pregnancy rate in the population that was offered screening was low. Thus, it is questionable whether the possible benefits (prevention of complications and reassurance of the woman) outweigh possible detriments (false-positive diagnosis, financial costs, and emotional stress that could be induced by screening). (Obstet Gynecol 1997;89:704-7. © 1997 by The American College of Obstetricians and Gynecologists.)

Ectopic pregnancy occurs in 17 per 1000 pregnancies in the United States,¹ in 8.3 per 1000 pregnancies in the United Kingdom,² and in 10.2 per 1000 live births in the Netherlands (National Medical Register of the Organization for Dutch Health Care Information, 1992. Utrecht, The Netherlands). It can lead to serious com-

plications, and continues to be an important cause of maternal death. An early diagnosis usually allows intervention before tubal integrity is lost and before the patient's condition has deteriorated, thereby preventing complications and improving clinical outcome.³

Recently, two meta-analyses^{4,5} of case-control and cohort studies on risk indicators for ectopic pregnancy showed that pregnant women with a previous ectopic pregnancy [odds ratio (OR) 8.3], previous tubal surgery (OR 21), intrauterine exposure to diethylstilbestrol (DES) (OR 5.6), previous sterilization (OR 9.3), and women currently using an intrauterine device (IUD) (ORs 4.2-45) are at greatly increased risk for ectopic pregnancy. Pregnant women with previous pelvic inflammatory disease (PID) and infertile women showed a twofold increased risk. In all of these women, screening early for ectopic pregnancy might be useful.

In The Netherlands, screening for ectopic pregnancy is currently offered to high-risk pregnant women by 83% of all gynecologists.⁶ Although the accuracy of transvaginal sonography and serum hCG testing is well established, the application of these tests for screening purposes in symptom-free women is not. There is only one cohort study,³ in which 225 symptom-free pregnant women with a previous ectopic pregnancy, previous tubal surgery, a history of PID, or an IUD in situ were screened for ectopic pregnancy with transvaginal sonography and serum hCG assays. Fifty-five women (24%) had an ectopic pregnancy, of whom 52 were treated surgically and three were managed expectantly.³ Due to early detection, the risk of complications could be reduced and conservative treatment could be facilitated. The authors advocated screening for ectopic pregnancy in symptom-free pregnant women at increased risk.³

Nevertheless, assuming a tenfold increased risk for ectopic nidation in presence of a risk indicator and a baseline risk of ectopic pregnancy of 1%, the expected frequency of ectopic pregnancy in a screening program

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for pregnant women at increased risk is unlikely to exceed 10%,^{4,5} an ectopic pregnancy rate remarkably at odds with the incidence in Finland. Therefore, we studied prospectively the ectopic pregnancy rate in a screening program among consecutive symptom-free women at increased risk.

Materials and Methods

Between September 1993 and May 1996, 168 consecutive symptom-free pregnant women at increased risk for ectopic pregnancy in the Academic Medical Center in Amsterdam were entered in a prospective study. Since 1989, we have instructed women at increased risk for ectopic pregnancy to contact our clinic for screening purposes as soon as they thought they were pregnant. Pregnant women with a history of ectopic pregnancy, tubal surgery or PID; women known to have tubal disease detected by hysterosalpingography or laparoscopy; women with intrauterine DES exposure, sterilized women, and women with an IUD in situ at the moment of conception were regarded as being at increased risk.

Pregnancy was diagnosed with the Icon urine test (Hybrytech Inc., San Diego, CA). Gestational age was estimated from day 1 of the last menstrual period. Women with pregnancy of a certified gestational age of 7 weeks or more were excluded from the study, because at that gestational age an ectopic pregnancy is likely to be symptomatic.

Inclusion of women in the study was monitored continuously by a dedicated clinical investigator (PJH), who was responsible for the protocol. This clinical investigator instructed staff members and residents of the department about the protocol. Furthermore, nurses from the infertility clinic were instructed separately about the protocol. During office time, the clinical investigator was notified whenever a woman met the inclusion criteria.

The diagnostic strategy was based on transvaginal sonography and serum hCG monitoring, as reported previously.⁷ Transvaginal sonography was performed with Hitachi equipment (Hitachi EUB 415/515, Hitachi Medical Corporation, Tokyo, Japan) provided with 6.5- or 7.5-MHz transducers. Serum hCG was measured with the Microparticle Enzyme Immunoassay (IMx analyzer, Abbott Diagnostics Division, Chicago, IL) and expressed in IU/L according to the Third International Reference Preparation.

Transvaginal sonography was used to scan the uterine cavity and adnexa. If an intrauterine sac was visible, intrauterine pregnancy was diagnosed. If no intrauterine pregnancy was detected, the adnexal area was scanned thoroughly. When an ectopic gestational sac or ectopic mass with fluid in the pouch of Douglas was

clearly visible, ectopic pregnancy was diagnosed. If neither an intrauterine nor an ectopic pregnancy was detected at sonography, further management depended on the measurement of serum hCG. A serum hCG level above 1500 IU/L was assumed to be conclusive for ectopic pregnancy. If serum hCG was 1500 IU/L or lower, no definite diagnosis was made at that time; rather transvaginal sonography and serum hCG were repeated at 2-day intervals until a definite diagnosis was made. The cutoff value used at repeated serum hCG measures was 1000 IU/L. When transvaginal sonography did not show an intrauterine pregnancy or an ectopic pregnancy and when serum hCG concentrations were declining, a diagnosis of trophoblast in regression was made.

The three possible diagnoses were verified as follows. When ectopic pregnancy was suspected, a confirmatory laparoscopy was performed. If a diagnosis of intrauterine pregnancy was made, this was confirmed by repeated sonography at 12 weeks' gestation, or by histopathology in the case of abortion. When a diagnosis of trophoblast in regression was made, serum hCG was measured repeatedly until it declined to the detection threshold.

The ectopic pregnancy rate was calculated by dividing the number of ectopic pregnancies by the total number of women in the study. A 95% confidence interval (CI) of the ectopic pregnancy rate was calculated using the computer program Confidence Interval Analysis (CIA, British Medical Journal, London, United Kingdom).⁸

Results

Of the 168 women screened, 25 women were excluded because the gestational age of their pregnancies was 7 weeks or more. None of them appeared to have an ectopic pregnancy. Of the 143 women included in the study, 58 women had one risk factor, 44 had two risk factors, and 41 had three or more risk factors. In 16 women, the gestational age was unknown. The mean gestational age of the pregnancies of the remaining 127 women was 5.5 weeks.

Ectopic pregnancy was diagnosed in seven women: in one woman at initial transvaginal sonography, in two women because of a serum hCG level above 1500 IU/L, in one woman at repeat transvaginal sonography, and in three women because repeated hCG exceeded 1000 IU/L. In all seven women, ectopic pregnancy was confirmed at laparoscopy. None had intra-abdominal bleeding or tubal rupture. Three patients were treated with systemic methotrexate and four with laparoscopic salpingostomy. In 130 women, intrauterine pregnancy was diagnosed (118 after the first sonography, seven

Table 1. Distribution of the Ectopic Pregnancies per Risk Factor

Risk factor	Included women (<i>n</i> = 143)	Ectopic pregnancies (<i>n</i> = 8)
Previous ectopic pregnancy	72	4 (6%)
Previous tubal surgery	37	0
Previous PID	31	2 (6%)
Known tubal pathology	97	5 (5%)
Previous intrauterine DES exposure	8	1 (13%)
Sterilization	2	0
IUD in situ	4	0

Data are presented as *n* or *n*(%). Percentages are based on the total number of pregnancies within each risk factor. Some women had more than one risk factor.

PID = pelvic inflammatory disease; DES = diethylstilbestrol; IUD = intrauterine device.

after the second sonography, and five after the third sonography). The diagnosis was confirmed in 129 women, whereas one patient, DES-exposed in utero, returned 1 week after transvaginal sonography with abdominal pain and vaginal bleeding; an ectopic pregnancy with intra-abdominal bleeding was found and treated by laparoscopic salpingostomy. In six women, a diagnosis of trophoblast in regression was made. All of these women had an uneventful clinical course with declining serum hCG concentrations. The overall ectopic pregnancy rate was 5.6% (8/143) (95% CI 2.5%, 10.7%), and did not vary with gestational age. This was a statistically significant difference from the ectopic pregnancy rate of 24% (95% CI 18.8%, 30.1%) reported by Cacciatore and colleagues.³

The sensitivity of the diagnostic algorithm in this study was 88% (7/8; 95% CI 47%, 99%), with a specificity of 100% (135/135; 95% CI 97%, 100%). Table 1 shows the distribution of the ectopic pregnancies among the different risk indicators. There was no subgroup in which the ectopic pregnancy rate exceeded 10%, except for previous intrauterine exposure to DES, in which one ectopic pregnancy was diagnosed among eight women. All patients with ectopic pregnancy either had a previous ectopic pregnancy, were known to have tubal disease, or were previously DES exposed in utero. Among 58 women with only one risk factor, the ectopic pregnancy rate was 5% (3/58); among 44 women with two risk factors, the ectopic pregnancy rate was 5% (2/44); and among 41 women with at least three risk factors, the ectopic pregnancy rate was 7% (3/41).

Discussion

The ectopic pregnancy rate of 5.6% as detected in this study is statistically significantly lower than the 24% reported previously.³ One explanation for this differ-

ence is that women who fulfilled the inclusion criteria, but in whom initial transvaginal sonography showed an intrauterine pregnancy, were not systematically included in that study. In general, studying the number of detected cases in a screening program in a clinical setting is not without difficulties. It has to be made sure that every woman meeting the inclusion criteria is entered into the study. Analogous to the intention-to-treat principle, analysis should be from the intention-to-diagnose principle.⁹ In the present study, several measures were taken to guarantee this intention to diagnose, including continuous monitoring by a dedicated clinical investigator.

Efforts to initiate a similar study in a second hospital in Amsterdam with less-intensive monitoring failed. Over time, the absolute number of ectopic pregnancies detected in the screening program was stable, whereas the number of registered intrauterine pregnancies dropped. This decline could be traced back to a decreased willingness to fill out case-record forms for women with intrauterine pregnancies, leading to a biased, highly inflated rate of ectopic pregnancy. In an earlier study⁷ on the discriminative capacity of transvaginal sonography and serum hCG monitoring performed in our hospital between 1989 and 1992, we also included symptom-free women at increased risk. In that study, eight ectopic pregnancies were detected in 26 symptom-free women, indicating an ectopic pregnancy rate of 31%, which is comparable with the ectopic pregnancy rate reported in the Finnish cohort study.³ Apparently, the same phenomenon happened in our hospital in that particular study.

Another explanation for the different ectopic pregnancy rates could be a difference in incidences of ectopic pregnancy between the two populations. In Finland, the incidence of ectopic pregnancy is 20.9 per 1000 live births, whereas the incidence in the Netherlands is 10.3 per 1000 live births.¹⁰ However, the fivefold difference in rates in this study and an earlier report³ cannot be explained solely by the difference in incidences in the two countries, because the latter incidence differs only by a factor of two.

Based on the results of the meta-analysis of risk indicators for ectopic pregnancy and a baseline ectopic pregnancy risk in the Netherlands of 1%, the upper limit of the frequency of ectopic pregnancy in symptom-free pregnant women at increased risk would be approximately 10%.^{4,5} A 10% ectopic pregnancy rate will only be seen if pregnancy is always suspected before the onset of symptoms. Therefore, it is likely that the ectopic pregnancy rate is lower than 10%, which is entirely in accordance with our findings.

We found no additive or synergetic effect in women with multiple risk factors. Furthermore, we could not

identify a subgroup of risk factors in which the number of ectopic pregnancies was substantially increased. Because the Finnish cohort study³ does not provide data on the distribution of risk factors in their population, a comparison between them and our population on the possible differences in type, number, and multiple risk indicators cannot be made.

The discriminative capacity of transvaginal sonography and serum hCG in this study was good, with a sensitivity of 88% and a specificity of 100%. This accords with an earlier report.⁷ The value of a diagnostic test in a clinical situation, however, depends not only on its discriminative capacity, but also on the pretest probability of disease. This study shows that the rate of ectopic pregnancy in the screened population was rather low, thereby questioning its value in this high-risk population. The value of a screening program will also depend on the improvement in prognosis that is established in patients with ectopic pregnancies that are detected early, as compared to patients in whom ectopic pregnancies are diagnosed after the onset of symptoms. In our study, all seven patients with ectopic pregnancies detected early showed no complications, and they could all be treated conservatively. Another potential beneficial effect of screening is that women with an intrauterine pregnancy are reassured, once the diagnosis of intrauterine pregnancy has been made. These possible benefits of screening should be weighed against the number of screened women with false-positive diagnoses, the financial costs, and the emotional stress induced by screening symptom-free women before the final diagnosis is made. The question of whether an ectopic pregnancy rate of 5.6% justifies screening for ectopic pregnancy can only be answered fully if all of these arguments are included.

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