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

Objective: The purpose of this study was to review current knowledge on the risk of ectopic pregnancy by means of a meta-analysis.

Methods: Case-control and cohort studies reporting on risk indicators for ectopic pregnancy and published between 1978 and 1994 in English, French, German, or Dutch language retrieved by MEDLINE search, search of references from the papers obtained, and hand-search on recent medical journals were included. Detected studies on each potential risk indicator were tested for homogeneity. If homogeneity could not be rejected, Mantel-Haenszel common odds ratios (OR) and 95% confidence intervals were calculated.

Results: 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. Previous genital infections (pelvic inflammatory disease [PID], Chlamydia, gonorrhea), infertility and a lifetime number of sexual partners > 1 were associated with a mildly increased risk. For gonorrhea, PID, previous ectopic pregnancy, previous tubal surgery and smoking, a higher common OR was calculated when using pregnant controls compared to using non-pregnant controls. All assessed contraceptive methods protect against ectopic pregnancy. Women becoming pregnant after sterilization or while using an Intra Uterine Contraceptive Device (IUCD) are at increased risk for ectopic pregnancy.

Conclusions: The increased risk in women with a previous ectopic pregnancy, previous tubal surgery, current IUCD-use, sterilization, PID, documented tubal pathology or in utero DES exposure justifies the exploration of a screening policy for ectopic pregnancy among these women. If a risk indicator reduces fertility chances, the OR detected when using pregnant controls is higher than the OR calculated using non-pregnant controls.
14.1 Introduction

Current non-invasive diagnostic methods allow an early diagnosis of ectopic pregnancy, even before the onset of any symptoms, thereby possibly improving prospects for the patient. Intervention before tubal integrity is lost and before the patient's condition has deteriorated improves clinical outcome. To enable early diagnosis, a screening program for women in early pregnancy could be considered. Therefore, a proper understanding of the risk indicators associated with ectopic pregnancy is a prerequisite. Although many risk indicators for the development of ectopic pregnancy have been identified, none of the available review articles has tried to summarize and interpret these risk indicators in a systematic, quantitative way. The present study aims to do so by means of a meta-analysis of published case-control and cohort studies.

14.2 Materials and Methods

Search strategy

A computerized MEDLINE search was undertaken to identify relevant literature. Search conditions for titles and abstracts were 'ectopic pregnancy' together with 'risk factors'. The search was restricted to literature published in English, French, German, and Dutch between January 1978 and January 1994. Furthermore, a hand search was performed for 1993 and 1994 issues of the top 10 gynecological journals and the top 5 epidemiological journals of the Science Citation Index. From the reference lists of the articles obtained, a further search was carried out.

The available articles had to meet predefined inclusion criteria. They should either report on a case-control or a cohort study. In case-control studies, cases should be women with ectopic pregnancy, confirmed either at surgery or by histopathological examination. Controls should be defined as non-pregnant or pregnant women. Cohort studies should compare women exposed to a risk indicator with non-exposed controls. A two-by-two table should be available from the articles, either directly or retraceable from the data supplied. All reported potential risk indicators were analyzed. Because the analyzed studies did not provide data on individual patients the common odds ratio (OR) could not be adjusted for confounders.

Statistical analysis

From each study two-by-two tables were constructed for pregnant and non-pregnant controls. Odds Ratios and their 95% confidence intervals (CI) were calculated. Homogeneity was tested by means of the Breslow-Day test. P-values < 0.05 were considered to indicate statistical significance. If homogeneity could not be rejected, a Common OR with 95% CI was calculated for each exposure by means of the Mantel-Haenszel method, thus pooling the ORs of the evaluated studies. If homogeneity had to be rejected, the range of point estimates was reported.
Meta-analysis of risk indicators for ectopic pregnancy

Risk indicator (reference) | Number OR/COR (95% CI) | P-value |
--- | --- | --- |
Previous genital infections | | |
Gonorrhea (13 21 25 36) | 4 | 2.9 (1.9 to 4.4) | 0.12 |
Chlamydia IgG > 1:16 (11 26 27 32 34) | 5 | 0.72 (0.7 to 7.1) | < 0.05 |
Chlamydia IgG > 1:32 (13 24 32 35) | 4 | 2.8 (2.0 to 4.0) | 0.30 |
Chlamydia IgG > 1:64 (21 25 26 32 34 36) | 6 | 3.7 (2.9 to 4.7) | 0.15 |
PID (12 13 15 17 20 25 27 31 34 36) | 10 | 2.5 (2.1 to 3.0) | 0.26 |
Previous surgery | | |
Ectopic pregnancy (12 13 16 20 26 30 31 34 36) | 10 | 8.3 (6.0 to 12) | 0.29 |
Pelvic/ abdominal surgery (15 20 31 36) | 4 | 0.93 (0.9 to 3.8) | 0.02 |
Tubal surgery (20 31 36) | 3 | 2.1 (9.3 to 47) | 0.96 |
Previous abortion | | |
Medical abortion (12 16 20 25 30 34 36) | 7 | 0.95 (2.4) | 0.03 |
Spontaneous abortion (16 20 25 30 31 34 36) | 8 | 0.33 (3.3) | 0.01 |
Contraceptives | | |
Current OC-use (12 16) | 2 | 1.8 (0.6 to 3.4) | 0.50 |
Past OC-use (14) | 1 | 1.0 (0.72 to 1.4) | 1.0 |
Current IUCD-use (12 14 15 17) | 4 | 4.2 (4.5) | < 0.01 |
Past IUCD-use (14) | 1 | 1.4 (1.0 to 1.2) | 1.0 |
Sterilisation (12 17 20) | 3 | 9.3 (4.9 to 18) | 0.75 |
Condom use (16) | 1 | 0.97 (0.24 to 4.0) | 1.0 |
Infertility (13 16 17 20 25 31 34 36) | 8 | 2.5 (21) | 0.01 |
Tubal pathology (17 20) | 2 | 3.5 (25) | 0.03 |
Lifestyle factors | | |
Current smoking (12 17 30 34 36 37) | 6 | 2.3 (2.0 to 2.8) | 0.50 |
Ever smoking (17 33) | 2 | 2.5 (1.8 to 3.4) | 0.56 |
Vaginal douching (25 34 35) | 3 | 1.1 (3.1) | 0.01 |
Lifetime no sexual partners > 1 (26 34) | 2 | 2.1 (1.4 to 4.8) | 0.65 |
Age first sexual intercourse < 18 (26 34 36) | 3 | 1.6 (1.1 to 2.5) | 0.41 |

Figure 1: Case-control studies using pregnant controls
14.3 Results

Study characteristics

A total of 211 papers meeting the search conditions were obtained from the MEDLINE search. The cross-references of selected articles revealed another 20 studies, whereas 2 studies were detected by hand search. Among these 233 papers there were 46 case-control and 23 cohort studies that met the inclusion criteria. The other 164 papers were inappropriate for our purpose; 17 papers reported on the incidence and mortality of ectopic pregnancy, while 23 were review articles, 19 observational studies, 29 studies on diagnosis, three editorials, 18 case reports and 23 letters. Another 32 papers concerned a variety of other subjects. Of the 46 case-control studies thus obtained, 4 papers were duplicates of other reports on the same study, while another 12 did not meet the inclusion criteria, leaving 30 papers available for analysis. Of the 24 cohort studies obtained, 4 were duplicates of other studies and 10 did not meet the inclusion criteria, leaving 10 studies available for analysis.

The detected studies reported on one or more of the following possible risk indicators: previous genital infections (gonococcal infection, pelvic inflammatory disease [PID], positive Chlamydia serology), previous surgical interventions (previous ectopic pregnancy, abdominal or pelvic surgery and tubal surgery), previous spontaneous or medical abortion, contraceptive methods (current and previous oral contraceptives (OC), current and past Intra-Uterine Contraceptive Device (IUCD) use, sterilization and condom use), previous subfertility, tubal pathology documented by hysterosalpingography or diagnostic laparoscopy, in utero diethylstilbestrol (DES)-exposure and several lifestyle indicators (smoking, vaginal douching, lifetime number of sexual partners, age at first sexual intercourse).

Case-control studies using pregnant controls

The results of the analysis of case-control studies that used pregnant controls are shown in Figure 1. A common OR could be calculated for the exposures gonorrhea, Chlamydia immunoglobulin G (IgG) antibodies > 1:32 and > 1:64, PID, previous ectopic pregnancy, previous tubal surgery, current OC-use, sterilization, smoking, lifetime number of sexual partners > 1 and age of first sexual intercourse < 18 years. Common ORs varied from 1.6 for age of first sexual intercourse < 18 years to 21 for previous tubal surgery. Homogeneity was rejected for Chlamydia IgG antibodies > 1:16, previous pelvic and/or abdominal surgery, medical abortion, spontaneous abortion, current IUCD-use, infertility, documented tubal pathology and vaginal douching. For Chlamydia IgG antibodies > 1:16, the range of ORs of four studies varied from 3.9 to 7.1, whereas one study reported an OR of 0.72. For pelvic and/or abdominal surgery the range of ORs varied from 0.93 to 3.8. For medical abortion the range of seven studies varied between 0.95 and 2.4. Three of these studies reported a significantly increased risk. For spontaneous abortion, six of the eight detected studies showed no significant association with ORs between 0.63 and 1.5. One study showed a mildly increased OR of 3.3, whereas another study showed a mildly decreased OR of 0.33. Point estimates of the four studies reporting on current IUCD-use varied between
Point estimates of the OR in the eight studies reporting on infertility varied between 2.5 and 23, with seven of these eight studies reporting a significantly increased risk. Two studies reporting on tubal pathology had significant ORs with point estimates of 3.8 and 21. One of three studies reporting on vaginal douching showed a significant association, with an OR of 3.1. For each of the risk indicators past OC-use, past IUCD-use and condom use only one study was found.

Case-control studies using non-pregnant controls

The results of the analysis of case-control studies using non-pregnant controls are shown in Figure 2. A common OR could be calculated for the exposures PID, previous ectopic pregnancy, medical abortion, current OC-use, past IUCD-use, sterilization and current smoking. Common ORs varied between 0.48 for sterilization to 6.6 for previous ectopic pregnancy.

Homogeneity was rejected for the two studies reporting on spontaneous abortion and for the four studies reporting on current IUCD-use. Only one of the two studies reporting on spontaneous abortion showed a significantly increased OR with a point estimate of 2.0. Three of four studies reporting on current IUCD-use showed a significantly decreased OR with point estimates between 0.36 and 0.72. For each of the risk indicators gonorrhea, Chlamydia IgG antibodies > 1:16, previous pelvic and/or abdominal surgery, previous tubal surgery, past OC-use, condom use, infertility, ever smoking, vaginal douching, lifetime number of sexual partners > 1 and age of first sexual intercourse < 18 years, only one study was found.

Cohort studies

Figure 3 shows the results of the analysis of cohort studies. One study reported on two cohorts of women who delivered with secion caesarea. The common OR calculated from these cohort was 1.5. In 5 studies reporting on DES exposure, homogeneity was not rejected, and a common OR of 5.6 was calculated. The ORs of PID, medical abortion, past OC-use and infertility, each derived from a single study, are also shown.

14.4 Discussion

This meta-analysis assesses current knowledge of risk indicators for ectopic pregnancy. Previous ectopic pregnancy, tubal surgery, sterilization, current IUCD-use, documented tubal pathology and in utero DES exposure were strongly associated with the occurrence of ectopic pregnancy. Previous genital infections (PID, positive Chlamydia antibodies, gonorrhea), infertility and a lifetime number of sexual partners exceeding one were associated with a mildly increased risk. Previous pelvic and/or abdominal surgery, smoking, vaginal douching and an early age of first sexual intercourse were associated with a slightly increased risk. There seemed to be no impact of medical abortion, spontaneous abortion, OC-use and condom use on the occurrence of ectopic pregnancy. It should be noted that the traditional meta-analysis used in the present study does not
<table>
<thead>
<tr>
<th>Risk indicator (reference)</th>
<th>Number of studies</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous genital infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonorrhoea (33)</td>
<td>1</td>
<td>2.0 (1.5 to 3.1)</td>
<td></td>
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<tr>
<td>Chlamydia IgG &gt; 1:16 (11)</td>
<td>1</td>
<td>0.16 (0.6 to 3.8)</td>
<td></td>
</tr>
<tr>
<td>PID (8 12 18 39 24)</td>
<td>5</td>
<td>1.7 (1.5 to 1.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Previous surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy (8 12 18 24 39)</td>
<td>5</td>
<td>6.6 (5.2 to 8.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>Pelvic/ abdominal surgery (24)</td>
<td>1</td>
<td>1.4 (1.0 to 2.4)</td>
<td></td>
</tr>
<tr>
<td>Tubal surgery (24)</td>
<td>1</td>
<td>4.7 (2.4 to 9.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Previous abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical abortion (12 18 33)</td>
<td>3</td>
<td>1.2 (1.0 to 1.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Spontaneous abortion (18 33)</td>
<td>2</td>
<td>0.98 (0.3 to 2.5)</td>
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<tr>
<td>Contraceptives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current OC-use (8 12 29)</td>
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<td>0.19 (0.15 to 24)</td>
<td>0.95</td>
</tr>
<tr>
<td>Past OC-use (29)</td>
<td>1</td>
<td>1.5 (1.0 to 232)</td>
<td></td>
</tr>
<tr>
<td>Current IUCD-use (8 12 18 39 29)</td>
<td>4</td>
<td>0.36 (1.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Past IUCD-use (8 29 39)</td>
<td>3</td>
<td>1.6 (1.4 to 1.8)</td>
<td>0.87</td>
</tr>
<tr>
<td>Sterilisation (12 24 29 39 42)</td>
<td>5</td>
<td>0.48 (0.40 to 0.59)</td>
<td>0.07</td>
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<td>Condom use (28)</td>
<td>1</td>
<td>0.18 (0.11 to 0.25)</td>
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<tr>
<td>Infertility (40)</td>
<td>1</td>
<td>3.6 (2.6 to 4.9)</td>
<td></td>
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<tr>
<td>Tubal pathology</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking (12 24)</td>
<td>2</td>
<td>1.6 (1.4 to 2.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ever smoking (24)</td>
<td>1</td>
<td>1.7 (1.2 to 2.2)</td>
<td></td>
</tr>
<tr>
<td>Vaginal douching (23)</td>
<td>1</td>
<td>1.8 (1.2 to 2.2)</td>
<td></td>
</tr>
<tr>
<td>Lifetime no sexual partners &gt;1 (33)</td>
<td>1</td>
<td>2.5 (1.7 to 3.7)</td>
<td></td>
</tr>
<tr>
<td>Age first sexual intercourse &lt; 18 (23)</td>
<td>1</td>
<td>1.5 (1.0 to 2.1)</td>
<td></td>
</tr>
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</table>

Figure 2: Case-control studies using pregnant controls
Meta-analysis of risk indicators for ectopic pregnancy

<table>
<thead>
<tr>
<th>Risk indicator (reference)</th>
<th>Number of studies</th>
<th>OR/COR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic and/or abdominal surgery (14)</td>
<td>2</td>
<td>1.5 (1.1 to 2.6)</td>
<td>0.90</td>
</tr>
<tr>
<td>In utero DES-exposure (4-7 10)</td>
<td>5</td>
<td>5.6 (2.4 to 13)</td>
<td>0.49</td>
</tr>
<tr>
<td>PID (37)</td>
<td>1</td>
<td>5.7 (2.5 to 13)</td>
<td></td>
</tr>
<tr>
<td>Medican Abortion (9)</td>
<td>1</td>
<td>1.2 (0.78 to 1.2)</td>
<td></td>
</tr>
<tr>
<td>Infertility (22)</td>
<td>1</td>
<td>2.0 (1.2 to 3.4)</td>
<td></td>
</tr>
<tr>
<td>OC (past use) (3)</td>
<td>1</td>
<td>1.0 (0.52 to 2.1)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3: Cohort studies provide an insight in the interplay between risk indicators, which may be highly correlated. We would have preferred using a multivariable approach in estimating the risk of ectopic pregnancy conditioned on the absence or presence of risk indicators in combination. Unfortunately, the individual papers do not report sufficient data to allow such a strategy.

The majority of papers available for the meta-analysis were case-control studies. The fundamental problem in the interpretation of case-control studies reporting on risk indicators for ectopic pregnancy is control definition. If a risk indicator interferes with fertility, the OR for the occurrence of ectopic pregnancy is dependent on the selection of the control group. This is explained by the cumulative effect of two probabilities involved in the occurrence of ectopic pregnancy. First, there is the probability of achieving conception. Conditional on the probability of achieving conception, there is the probability of subsequent ectopic nidation. Most risk indicators in this meta-analysis interfere with both. For example, a history of tubal surgery leads to a decreased probability of conception, but increases the probability of ectopic nidation once a pregnancy occurs. Studies using pregnant controls describe the risk of ectopic pregnancy only for those who are currently pregnant. Therefore, ORs from these studies assess only the second probability, i.e., ectopic nidation, conditional on the presence of a pregnancy. Studies using non-pregnant controls, however, incorporate both probabilities mentioned earlier, i.e., the probability of conception and the probability of subsequent ectopic nidation. Consequently, ORs in these studies express the joint occurrence of two events. This implies that common ORs from studies using pregnant controls are higher than those from studies using non-pregnant controls, whenever risk indicators reduce the chance of achieving a pregnancy. For instance, for tubal surgery the OR of ectopic pregnancy compared to non-pregnant controls is 4.7, while it is 21 compared to pregnant controls. The fact that the latter common OR is significantly higher reflects the decreased
fertility prospects after tubal surgery. This mechanism might also explain the difference in common ORs calculated for studies with pregnant and non-pregnant controls for gonorrhea, PID, previous ectopic pregnancy and smoking.

The same mechanism explains the differences between studies using pregnant and studies using non-pregnant controls, when they report on contraceptive methods. Because contraceptive methods reduce the chance of pregnancy, the OR strongly depends on the selection of the control group. In assessing the risk for a woman who yet has to make a choice between contraceptive methods, non-pregnant controls should be considered. On the other hand, when considering the situation where a woman became pregnant during contraceptive use, one should focus on pregnant controls.

All contraceptive methods protect against ectopic pregnancy. However, once the method fails and pregnancy occurs, the risk of ectopic pregnancy depends on the contraceptive method used. Condom use shows no increased risk. Use of oral contraceptives show a slightly increased risk, in contrast to IUCD use and tubal sterilization, which both show a strongly increased risk. Apparently, the latter two protect better against intrauterine pregnancy than against ectopic pregnancy. The trend towards an increased risk of ectopic pregnancy whenever oral contraceptives fail, is difficult to understand. The increase could be explained by the effect on tubal motility of progesterone-only pills, as has been suggested previously.\textsuperscript{12} The explanation provided by Weiss et al. addressing it as a matter of control definition seems more plausible. While for women with ectopic pregnancies - the cases - , a medical abortion was no option, the controls with ongoing pregnancies did have the choice to terminate the pregnancy.\textsuperscript{44} This might explain the increased rate of current OC use among women with ectopic pregnancy as compared to pregnant controls, thus representing a bias by control definition. However, this hypothesis is not confirmed by the study reporting the risk of condom use.\textsuperscript{16}

If OC or condom use is discontinued, no increased risk for ectopic pregnancy occurred. After discontinuation of an IUCD, however, the risk continues to be increased, suggesting a relation between IUCD use and subsequent tubal damage.\textsuperscript{45} An increased risk on PID during IUCD use has been reported.\textsuperscript{46} This risk was shown to be higher in the first 20 days after insertion.\textsuperscript{47} The findings from the cohort studies are in concordance with those from case-control studies. In PID, however, there seems to be a discrepancy: the cohort study reports an OR of 5.7, while the common OR from case-control studies using non-pregnant and pregnant controls were 1.7 and 2.6 respectively. The difference might result from lack of statistical power as the 95% CIs are overlapping. It could also be explained by a different definition of PID: in the cohort study the diagnosis was made laparoscopically, whereas in case-control studies it was obtained from interviews or medical records.

Risk estimation in the current meta-analysis is based on case-control studies and cohort studies, in which the outcome is related to exposures. Case-control studies using pregnant controls compare the odds of ectopic nidation in cases and controls, whereas case-control studies using non-pregnant controls compare the odds of pregnancy and subsequent ectopic nidation. Risk estimation of ectopic pregnancy can also be done by
Meta-analysis of risk indicators for ectopic pregnancy
calculating absolute risks of ectopic pregnancy for different contraceptive methods from cohort studies without a control group, assuming ectopic pregnancy to be the product of pregnancy rate and ectopic nidation. This was done in a previous study, of which the results are in agreement with the results of the present study.48

The common denominator in the etiology of ectopic pregnancy seems to be the fallopian tube. Previous ectopic pregnancy, sterilization, tubal surgery, documented tubal pathology, PID, gonorrhea and in utero DES exposure, which show the highest ORs, all affect the fallopian tube directly. The same pathophysiologic mechanism seems involved in infertility and previous pelvic/abdominal surgery, although apparently these risk indicators not by definition affect the tube.

Smoking is thought to affect tubal motility, thus increasing the risk of ectopic nidation, but might also represent a certain lifestyle, associated with an increased risk. The observed influence of lifestyle-indicators in the occurrence of ectopic pregnancy is most likely explained by confounding. Sexually transmitted diseases probably play an important role in this respect.

In conclusion, this meta-analysis shows previous ectopic pregnancy, previous tubal surgery, sterilization, current IUCD-use, documented tubal pathology and in utero DES exposure to be the strongest risk indicators associated with the occurrence of ectopic pregnancy. Screening women with these risk indicators for ectopic pregnancy could therefore be promising. However, the success of such a screening program depends not only on the OR of the risk indicator, but also on the pre-test chance for ectopic pregnancy. A low pre-test chance reduces the benefit from screening, whereas a high pre-test chance may justify the screening of women with mildly increased risk indicators. The cost-effectiveness of such a screening policy will be evaluated in the next two chapters.

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14.5 References


