Surgical management of tubal pregnancy
Mol, Femke

Citation for published version (APA):
Mol, F. (2013). Surgical management of tubal pregnancy

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Ectopic pregnancy and pelvic inflammatory disease: a renewed epidemic?

Femke Mol, Norah M. van Mello, Ben W. Mol
Fulco van der Veen, Willem M. Ankum, Petra J. Hajenius

ABSTRACT

OBJECTIVE: The incidence of ectopic pregnancy (EP) was reported to rise during the 1970s and 1980s; thereafter it remained stable or even declined. We studied whether changes in the incidence of pelvic inflammatory disease (PID) have had an impact on the incidence of EP and we hypothesise about the incidence of EP in the near future.

STUDY DESIGN: EP and PID hospital admissions from 1980 to 2005 were derived from Dutch Medical Registries and incidence trends were calculated and analysed by joinpoint regression.

RESULTS: The peak incidence of EP in 1988 (11/1000 live births) was preceded by a peak incidence of admissions for PID in 1983 (0.6/1000 women of all ages). The EP rate declined towards 2005 (7.3/1000 live births) mainly due to a decrease in EP in urban regions and in older aged women (≥ 35 years). Presently, women <25 years and born between 1985 and 1990 are again at an increased risk of EP (12/1000 live births) but this rise was not preceded by a peak incidence of admissions for PID.

CONCLUSION: On a population level, the peak incidence of EP in The Netherlands was preceded by a peak incidence of PID. A renewed rise in the incidence of EP is observed for young women. This may be related to the significant increase in positive tests for genital Chlamydia trachomatis during recent years.
INTRODUCTION

In many countries a considerable rise in the incidence of ectopic pregnancy (EP) was reported during the 1970s and 1980s (1-3). Since the late 1980s to the early 1990s, the incidence of EP no longer increased but remained stable (4-6) or even declined (7-9). An important risk factor for EP is pelvic inflammatory disease (PID) (10). Nowadays, genital Chlamydia trachomatis – frequently asymptomatic in women – has been identified as another major risk factor (10). This paper explores whether changes in the incidence pattern of PID have had an impact on the incidence of EP in the Netherlands in a 25-year period. In addition, we investigated whether we can expect a trend change in the incidence of EP in The Netherlands in the near future due to changes in demography, life style or sexual behaviour.

MATERIAL AND METHODS

Data sources

Hospital admissions of women diagnosed with EP and PID between 1980 and 2005 were identified from the Dutch National Medical Registration (Prismant, Institute for Healthcare Management, The Netherlands) by using the International Classification of Disease code (ICD-9) Clinical Modification Dutch extension (http://www.cdc.gov/nchs/icd9.htm). From 1992 onwards, this registry also contains data on date of admission, region and women’s age. The following ICD-9 CM codes were used to identify women with EP; abdominal EP, tubal EP, ovarian EP or other EP. For PID, these codes were acute PID, chronic PID, PID not specified, acute parametritis, chronic parametritis, acute peritonitis female pelvis, adhesions female pelvis, chronic peritonitis female pelvis, infection female pelvis or infection female pelvis not specified. Demographic data were provided by Statistics Netherlands on region-specific live birth numbers, maternal age during delivery and total number of women in specific birth years. Similar to the National Medical Registration, this registry has a nationwide coverage.

Analysis

The absolute numbers of hospital admissions for EP and PID were calculated over the period 1980–2005. The incidence of EP was calculated as an EP rate (95% confidence intervals), defined as the number of admissions for EP per year as numerator and live birth per 1000 women in the same year as denominator. In line with earlier studies, live birth was selected as the best denominator available since an adequate registry of the total number of conceptions, including early pregnancy loss and termination, is not available in The Netherlands. The PID rate (95% confidence intervals) per year was calculated per 1000 women for the whole study period. For the period 1992–2005, the PID rate was also calculated as the number of admissions of women between 15 and 45 years of age, expressed per 1000 women of similar age in the same year. EP and PID incidence trends were analysed by joinpoint
regression analysis (http://srab.cancer.gov/joinpoint/, version 3.0). Joinpoint regression analysis estimates the annual percentage change (APC) and 95% confidence intervals in rates by selecting the best fitting regression line segment. Joinpoint selects time periods within an overall time frame, ensuring uniformity of incidence trends within each selected time period. A maximum of three join points, each denoting a statistically significant change in trend, were allowed for each model (11). For example, an APC of −3.0 denotes an average decline of the EP rate of 3% per year over the selected time period.

Subgroup analyses were performed per region, per age group, and per five-year birth cohort using joinpoint analysis. For the subanalysis on region, we used the common distinction (as provided by Statistics Netherlands) between the urban regions with more than 250,000 inhabitants (Amsterdam, The Hague, Rotterdam and Utrecht, located in the central western part of The Netherlands) and the other less intensively populated parts of The Netherlands, e.g. non-urban regions. We distinguished three different age groups; women under 25 years, women between 25 and 35 years and women 35 years and older. EP rates were calculated per year per age group. EP rates were also calculated per five-year birth cohort for women born between 1945 and 1990 and who conceived between 1992 and 2005.

RESULTS

The absolute numbers of hospital admissions for EP and PID were calculated for the period 1980–2005. A total of 45,799 hospital admissions for EP were registered. The absolute number rose from 1292 admissions in 1980 to a peak incidence of 2045 in 1988 and declined to 1375 in 2005. For PID, a total of 72,088 hospital admissions were registered. Like EP, after an initial rise in the incidence a decline was observed. The absolute number of PID rose from 3356 admissions in 1980 to a peak incidence of 4084 in 1983 and a decline thereafter to 2105 in 2005. The EP rate and PID rate between 1980 and 2005 are shown in Figure 1.

The EP incidence rate increased from 7.1 EPs per 1000 live births in 1980 to a peak incidence of 11.0 in 1988. Between 1980 and 1983 the increase was statistically significant (APC 11.1), indicating an annual increase of EP rate by 11.1%. Between 1983 and 1988, the increase was no longer significant and slowed down to an APC of 2.8. Thereafter, a consistent significant decline occurred to an EP rate of 7.3 per 1000 live births in 2005 (APC −2.3). The PID rate, expressed as a rate per 1000 women of all ages, increased from 0.47/1000 to 0.56/1000 between 1980 and 1983 (APC 5.5) and then decreased to 0.26/1000 in 2005. The PID rate of fertile women between 15 and 45 years of age, showed a similar significant decline (APC −2.4) (data not shown in Figure 1). The EP rate in urban versus non-urban regions over time is shown in Figure 2.

In 1992, the EP rate for women who lived in urban regions was 13.5/1000 compared to 8.9/1000 for women from nonurban regions, resulting in a 40% higher risk of EP in urban
Figure 1. Left axis: EP rate (EP/1,000 Live Births with 95% CI); right axis: PID rate (PID/1,000 Women with 95% CI).

Figure 2. 1992–2005 EP rate: urban and non-urban regions. Left axis: EP rate (EP/1,000 Live Births with 95% CI).
Figure 3. 1992–2005 EP rate: per age group. Left axis: EP rate (EP/1,000 Live Births with 95% CI).

Figure 4. 1992–2005 EP rate: per 5 year birth cohort, per age group. Left axis: EP rate (EP/1,000 Live Births with 95% CI).
regions. The nationwide decline of EP was mainly explained by the decline in urban regions of 4.1% per year compared to only 1.4% per year in non-urban regions (APC −4.1 versus APC −1.4). In 2005, no difference in EP rate could be demonstrated between urban (7.2/1000) and non-urban regions (7.4/1000; 95%). Whereas the EP rate was stable during the study period for women under 25 years of age (APC 0.3) and for those between 25 and 35 years (APC −1.9) at approximately 8/1000 live births, there was a significant decline in the EP rate in women over 35 years of age from 16.3/1000 in 1992 to 8.6/1000 in 2005 (APC −4.8). In 2005, differences in EP rate between the three age groups were no longer observed Figure 3. The incidence of EP for women born between 1945 and 1990 and who conceived between 1992 and 2005 is summarised in Figure 4. Women born between 1950 and 1960 had the highest incidence of EP while most of these women conceived at an older age (≥35 years) (1950–1954: 13.8/1000; 1955–1959: 13.6/1000). Women born between 1965 and 1970 and who also conceived at a relatively advanced age had almost half the risk (8.7/1000 live births). Women who conceived early (<25 years) and were born between 1980 and 1985 had a comparable risk of 7.8/1000 live births. However, women who conceived early (<25 years) but were born more recently (between 1985 and 1990) had again an increased risk of EP of 12.0/1000 live births (APC 18.7, 95% CI 5.1–34.1).

COMMENT

Our data on the incidence pattern of EP covering the period 1980–2005 show an increase of EP rates up to 1988, followed by a decrease towards 2005. This pattern is analogous with other reports from regions in Scandinavian countries, in New South Wales, Australia and in California, United States of America (1, 4-9).

The strength of our study, compared to these earlier studies reporting on incidence rates on EP, is that this study provides nationwide rates instead of reports in a circumscribed part of a country. Moreover, we were also able to report sub-analyses on urban versus non-urban regions and birth cohorts. A limitation of our study is that the number of admissions is registered, instead of individual patient data for the diagnosis of EP or PID as is done in registries from Scandinavian regions. However, similar to most other countries, the Dutch Medical Registration System does not employ personal identifiers because of national privacy legislation. Thus, we were unable to review medical records to verify the diagnosis of EP or PID, but we believe that large-scale complete coverage of all Dutch hospitals and internal validation of the Medical Registration System compensate for this. The quality of the data collected is nevertheless dependent upon the standard of coding and the accuracy of clinical diagnoses upon which this is based.

The peak incidence of EP in 1988 may be related to the preceding peak incidence of PID in 1983. Although causality between the relation of PID rates and EP rates cannot be inferred
from this ecological analysis, this analysis of the time trends is the only tool available to generate hypotheses about explanations for the observed changes and to point to the need for possible interventions (12).

To express the EP rate, we used Live Birth as the denominator. Other but less frequently used denominators are the number of all known pregnancies (live births, miscarriages and terminations of pregnancy (TOP)), the number of all viable pregnancies (live birth and TOPs), or the number of women of reproductive age (15–44 years) (13). Although the number of women of reproductive age is unaffected by fluctuations in miscarriages and TOPs, it is influenced by the fertility rates and contraceptive practices in these women, for which population-based studies are needed. These data are not available for our study. The number of TOPs has been low in The Netherlands for the past years (14). Therefore, we find that expressing the EP rate per 1000 live births is suitable for presenting time trends of EP in The Netherlands. Since the registries only document hospital admissions, we cannot exclude incomplete coverage. Concerning EP, progress in the diagnostic approach, e.g. better diagnostic tests (quantitative serum hCG and high resolution ultrasound) might have influenced the admission rates.

From the mid-1990’s, outpatient medical treatment with systemic methotrexate and expectant management was installed for selected EPs and pregnancies of unknown location according to the recommendations of the Dutch national guideline and international reviews (15, 16). We observed that only 5% of women with EP are treated as such (17). Concerning PID, changes in the therapeutic approach might have influenced the admission rates. PID cases are no longer hospitalized except for complicated cases. Uncomplicated PID are either treated as outpatients or undiagnosed in the case of asymptomatic PID. In this study an estimate of the proportion of outpatient treatment for women with PID in later years could not be made. In other countries, it was estimated that between 75% and 90% of women with PID are treated on an outpatient basis (18). This outpatient policy is incorporated in international guidelines (19). It is therefore doubtful that the admission rate of PID is still an advanced indicator for EP.

Changes in sexual behaviour might have influenced trends in PID and EP rates. During the 1960s and 1970s, women who lived in urban regions demonstrated more liberal sexual behaviour (“sexual revolution”) and consequently were at increased risk of developing tubal pathology with ensuing EP compared to women living in non-urban regions. Our data show that women born in the 1950s were at the highest risk of EP. In the 1980s, sexual behaviour changed dramatically as a response to the HIV epidemic (“safe sex”). Since then, other sexual transmitted infections (STI), such as gonorrhoea, became almost extinct in The Netherlands resulting in a decline in EP (20). The introduction of STI clinics, mainly located in the urban regions with their easy accessibility and outpatient antibiotic treatment, may also have attributed to the decline in EP. Our data support this hypothesis; the declining EP
rate was mainly due to a decrease of EP rates in urban regions, which eventually resulted in equal EP rates in urban and nonurban regions.

Although the changes in sexual awareness and behaviour certainly had their impact on the incidence of EP, incidence patterns of other risk factors, i.e. increasing maternal age, parity and induced abortion, could also have contributed (21, 22). The mean maternal age of women with a live birth increased from 27.5 years in 1980 to 31.1 in 2005 (Statistics Netherlands). It is however difficult to estimate to what degree this increase in maternal age contributed to the peak incidence in EP observed in 1988, especially since maternal age increased further, whereas EP rate declined. Minor changes in parity during the study period were observed. Parity varied between 1.6 (1980) and 1.5 (1983) and increased to 1.7 in 2005. No further increase is expected in the near future (23). The number of induced abortions per 1000 women (15–44 years) was as low as 6.5 in 1996. This number slightly increased to 8.4/1000 women in 2001. This rise was explained by an increase of induced abortions in young women (<15 years) only and in women from different ethnic backgrounds (14). The effect of other risk factors for EP, like previous EP, tubal surgery, diethylstilbestrol exposure, infertility, prior infertility treatment or contraception failure with an intrauterine device, is not known.

Although not a nationwide coverage, the Dutch National Institute for Public Health and Environment registered 2200 positive tests for genital Chlamydia trachomatis infection in 1992 rising to 15,150 positive tests in 2007. These data comprise positive laboratory tests of individuals who presented with clinical symptoms in family practices, STI clinics or hospitals, as well as individuals who requested testing after unsafe sex. This rise is most likely biased by increased testing and data are lacking on the total number of tests performed. The STI clinic in the Amsterdam region, which diagnosed approximately 50% of all STIs recorded in The Netherlands, was able to report on Chlamydia positive testing rates for the period 1999–2002 and observed a slight increase of positive Chlamydia test rates among women (OR 1.05 per year, 95% CI 1.03–1.07) (24).

What is more worrying is that in Amsterdam a prevalence of genital Chlamydia trachomatis infection among young women (<20 years) of 20% was found (24). Since 2004, all STI clinics have participated in a national surveillance. From their data, nationwide trends in positive testing Chlamydia rates in time are available. The positive test rate in women increased from 9.7% in 2004 to 10.6% in 2008 (25, 26). In 2008, 88,000 consultations were registered and 9433 cases of Chlamydia were seen in this surveillance; an absolute increase of 21% compared to 2007. In 2007 and 2008 the highest positive test rate was again seen in young heterosexuals aged less than 25 years (14.1% and 17%, respectively). Since April 2008, a pilot study for a large scale population-based Chlamydia screening program has started in two urban and one non-urban region among individuals aged 16–29 years of age. Preliminary data show an overall positive test rate of 4.3%, whereas women under 20 years
again showed the highest positive test rate (7.0%) (27). The question is whether a renewed rise in the incidence of EP can be anticipated. In our birth cohort analyses, we did observe an increased risk of EP in young women (conceiving < 25 years and born between 1985 and 1990), but without a preceding rise in the number of admissions for PID in this birth cohort. This may be mimicked because these women were treated on an outpatient basis.

Sexual behaviour again seems to have undergone dramatic changes since the introduction of anti-retroviral therapy. A more liberal sexual behaviour is observed reflected by the increase of registered genital Chlamydia trachomatis infections. Although we are conscious of the limitations of the registration of genital Chlamydia trachomatis infection and the risk of screening bias, the increase in positive tests cannot be ignored and is of clinical significance. To prevent a future increase in the incidence of EP, health policy makers should seriously consider the launch of a new series of STI awareness campaigns among young people. Whether this also merits the start of a genital Chlamydia trachomatis screening program is subject to debate (28, 29).

Conflict of interest
None.

Funding
This study is supported by grants of The Netherlands Organization for Health Research and Development (Agiko stipendium grant 920-03-328, Clinical fellow grant 40-00703-97-05-154). The sponsors had no involvement in the study.

Acknowledgement
We acknowledge the contribution of PRISMANT, Institute for Healthcare Management, Utrecht, The Netherlands.
REFERENCE LIST


