The aetiology and pathogenesis of appendicitis, the most common abdominal emergency, is not known. According to the most favoured theory, appendicitis is caused by mechanical obstruction of the appendix lumen, either because of faecal stasis, kinking, peritoneal adhesions or infection-induced swelling of the mural lymphoid tissue. Other possible mechanisms include a breakdown of the mucosal barrier in the appendix by the direct invasion of a pathogen, or by an inflammatory response that has been triggered by an infectious agent or some other stimulus. Geographical differences in the incidence of appendicitis and secular trends have been related to differences and changes in dietary intake of fibre and in standards of hygiene.

A relation with female sex hormones has been proposed because of a lower incidence among women and incidence variations during the menstrual cycle, but studies have given inconsistent results. Pregnancy constitutes a period of dramatic increases in levels of female sex hormones, but the incidence of appendicitis during childbearing is not known.

The study of the influence of pregnancy on the incidence of appendectomy and appendicitis is a methodological challenge. The incidence of appendectomy and appendicitis and childbearing are strongly related to age, with a peak in the middle of the second decade for appendicitis and appendectomy and a peak in the third decade for childbearing. The incidence of appendicitis and appendectomy shows regional variations and a secular trend with a decreasing incidence. Secular and regional variations are also seen for the incidence of childbirth. The influence of these variations on the incidences of appendectomy, appendicits and pregnancy is complex which makes it difficult to determine the expected incidence of appendectomy and appendicitis during pregnancy for comparison purposes. The aim of this study was to analyse if pregnancy has any influence on the risk to the fetus, ranges from 0.15 to 2.10 cases with appendicitis per 1000 pregnancies. Most of these estimates have been based on small, retrospective studies of patients with a discharge diagnosis of appendectomy combined with a diagnosis of pregnancy. The incidence of appendicitis during pregnancy has been estimated by relating the number of pregnant women having an appendectomy to the number of deliveries in the same time-period. Only one previous study has been based on population-based registries.

The aim of this study was to analyse if pregnancy has any influence on the risk of having appendicitis. To overcome the mentioned difficulties we chose a population-based case-control approach to analyse the difference in the pregnancy status at the time of appendectomy of 53 058 women and of 53 058 population-based age-matched controls. Cases and controls were identified by linkage of the Swedish Inpatient Register and the nationwide census. Pregnancy status at the time of operation was obtained by linkage with the Swedish Fertility Register. Differences in pregnancy status were analysed using conditional logistic regression and expressed as odds ratios (OR) with 95% CI.

Fewer patients than expected with appendicitis were pregnant compared with the controls, especially in the third trimester (OR = 0.49, 95% CI: 0.30–0.79 for perforated and OR = 0.33, 95% CI: 0.28–0.39 for non-perforated appendicitis). The reduced incidence of appendicitis suggests a protective effect of pregnancy, especially in the third trimester.

Keywords: Appendicitis, aetiology, pathogenesis, pregnancy, female sex hormones, case-control study

Accepted 2 March 2001

Background

Methods

Results

Conclusions

Keywords
the time of appendectomy among cases that had an appendectomy compared to that among controls matched on age, time-period and township of residence. This approach also allowed a more detailed analysis of the relation within each trimester of the pregnancy and in the 3-month period following childbirth.

Patients and Methods

The study population

Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in the Inpatient Register. Besides a national registration number (uniquely identifying every resident of Sweden), each record contains medical data, including surgical procedures performed (coded according to the Swedish Classification of Operations and Major Procedures) and diagnoses at discharge (coded up to 1968 according to the International Classification of Diseases, Seventh Revision [ICD-7], according to the Eighth Revision [ICD-8] in 1969 to 1986 and according to Ninth Revision [ICD-9] thereafter). At the start in 1964, the register covered only six counties, representing 20 per cent of the Swedish population, but successively more counties have been added, and since 1987 all Swedish hospitals are included. Since there is virtually no private hospital care in Sweden, any study using the Inpatient Register is, in effect, population-based.

The cases

All women in the Inpatient Register with a discharge diagnosis of appendectomy (operation code 4510 or 4511) between 1964 and 1993 were not included (Table 1). Patients with ‘appendectomy en passant’ were not included. Only patients in the most fertile period, aged 15–39 years at appendectomy, were included. Based on the discharge diagnosis the patients were divided into: perforated appendicitis (ICD-7: 550.10, 550.11, 550.12, 550.13; ICD-8: 540.00, 540.01, 540.02, 540.03; ICD-9: 540A, 540B), non-perforated appendicitis (ICD-7: 550.00, 550.02, 550.03, 551.99, 552.00, 552.10, 552.90; ICD-8: 540.90, 540.91, 540.99, 541.99, 542.00, 542.01, 542.02; ICD-9: 540X, 541X, 542X) and negative appendectomy. In the latter group the appendix was unaffected with no signs of inflammation. The discharge diagnoses in this group included mesenteric lymphadenitis, non-specific abdominal pain and a large number of other diagnoses.

Table 1 Characteristics of women who had appendectomies aged 15–39 years (cases) and age-matched controls

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, SD)</td>
<td>23.4 (6.8)</td>
<td>23.4 (6.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age of last child (years, SD)</td>
<td>3.98 (2.74)</td>
<td>3.92 (2.72)</td>
<td>0.78</td>
</tr>
<tr>
<td>No. of pregnant women</td>
<td>2077 (3.7%)</td>
<td>2503 (4.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of women in the puerperium</td>
<td>784 (1.5%)</td>
<td>818 (1.5%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Parity (mean, range)</td>
<td>0.61 (0–9)</td>
<td>0.59 (0–9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Parity distribution

<table>
<thead>
<tr>
<th>Parity</th>
<th>Cases (n = 35 525)</th>
<th>Controls (n = 35 950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (no., %)</td>
<td>35 525 (67.0)</td>
<td>35 950 (67.8)</td>
</tr>
<tr>
<td>1 (no., %)</td>
<td>6936 (13.0)</td>
<td>6909 (13.0)</td>
</tr>
<tr>
<td>2 (no., %)</td>
<td>7403 (14.0)</td>
<td>7185 (13.5)</td>
</tr>
<tr>
<td>3+ (no., %)</td>
<td>3194 (6.0)</td>
<td>3014 (5.7)</td>
</tr>
</tbody>
</table>

The controls

For each eligible patient, one control without a history of appendectomy according to the Inpatient Registry was matched by age, gender and township of residence. The township of residence at the time of the operation was obtained from the nation-wide census that was closest in time to the operation, using the censuses from 1970, 1980 and 1990. Consequently matching was carried out using the census that preceded the operation: by up to 5 years for cases that were operated on in the first half of the decade. During the interval from the census to the operation 28 controls had died or emigrated and were therefore not eligible. After the matching had been done we further excluded 457 women who had had an ‘appendectomy en passant’ prior to the appendectomy among the cases. From the census we identified 6477 cases and 7135 controls who were not born in Sweden. These women were also excluded as their appendectomy status, parity and pregnancy status was not known. The corresponding cases and controls were also excluded from the analysis. Only complete pairs of cases and controls were kept for the analysis.

Exposure

Exposure in this study was pregnancy (divided into trimesters) and the puerperium (the 3-month postpartum period). Exposure information was obtained by linkage with the nation-wide Swedish Fertility Register, which provides information on the date of all births to all women who were Swedish citizens in 1960, or who were born in Sweden thereafter. Stillbirths were also included. At the moment of the data compilation the register had been updated to 31 December 1995. The quality of the Fertility Register is generally high.12

The pregnancy status at the moment of operation was assessed from the interval between the date of the operation and the date of childbirth assuming a normal length of gestation of 9 months, i.e. women who gave birth within 9 months of an operation were regarded as pregnant. This approach thus necessitated 9 months of follow-up after the operation. During this period 28 cases and 8 controls were lost to follow-up due to death or emigration and were excluded from the analysis together with the matched women. To analyse the frequency of appendectomy during the puerperium we also analysed the non-pregnant women who had given birth within 3 months before the operation.
Analysis

The differences in the exposures at the moment of operation (trimester of pregnancy and 3 months of puerperium) for the matched set of cases and controls was analysed using conditional logistic regression. For multiparous women the date of the childbirth that was closest to the time of operation was used. Differences in exposure were expressed as odds ratios (OR) with 95% CI. Separate analyses were done for perforated and non-perforated appendicitis and negative appendectomy. Differences in parity (parity 0, 1, 2 and 3+) and in the age of the last child (in 6-month intervals up to 3 years) at the moment of the operation were adjusted for by including these factors as dummy variables in a second set of regression models. Differences in means, rates and proportions were analysed with the Student’s t-test, the $\chi^2$-test and the rank-sum test where applicable. A P-value <0.05 was regarded as significant.

Results

A total of 53 058 matched pairs of cases and controls were included in the analysis. The characteristics of the cases and the controls at the time of the operation are presented in Table 1.

For the cases with a negative appendectomy there were fewer appendectomized women in the first and third trimester of pregnancy (OR = 0.70, 95% CI: 0.58–0.85 and OR = 0.55, 95% CI: 0.44–0.68, respectively). Operation for negative appendectomy was significantly more common in the second trimester (OR = 1.42, 95% CI: 1.21–1.68), compared with the controls.

The frequency of operations for perforated or non-perforated appendicitis in the 3 months that followed childbirth (i.e. during the puerperium) was not different from the controls (OR = 1.25, 95% CI: 0.88–1.78 and OR = 0.99, 95% CI: 0.87–1.12, respectively). Negative appendectomy was less common among women in the puerperium (OR = 0.77, 95% CI: 0.64–0.94). Figure 1 illustrates a comparison of pregnancy status at time of surgery in women who had an appendectomy compared with matched controls.

The cases and the controls were matched on age but the primary analysis revealed that the cases had a higher parity at the moment of operation. This may influence the probability of being pregnant at a certain moment. Adjustment for parity and age of the last child in conditional logistic regression models gave, however, almost identical results with regard to the association between pregnancy status and appendectomy (data not presented).

Table 2 Diagnosis and pregnancy status among cases and controls at operation. Differences in pregnancy status was analysed by conditional logistic regression and expressed as odds ratios (OR) with 95% CI

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Perforated appendicitis</th>
<th>Non-perforated appendicitis</th>
<th>Negative appendectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR</td>
</tr>
<tr>
<td>Non-pregnant</td>
<td>3345</td>
<td>3318</td>
<td>1.00</td>
</tr>
<tr>
<td>Months pre-partum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–6</td>
<td>40</td>
<td>66</td>
<td>0.58</td>
</tr>
<tr>
<td>5–3</td>
<td>52</td>
<td>43</td>
<td>1.20</td>
</tr>
<tr>
<td>2–0</td>
<td>26</td>
<td>51</td>
<td>0.49</td>
</tr>
<tr>
<td>Months postpartum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>72</td>
<td>57</td>
<td>1.25</td>
</tr>
</tbody>
</table>
Discussion

This study shows that patients who had undergone appendectomy were less likely to be pregnant at the time of the operation compared with controls. This inverse relation was dependent on the period of gestation and the underlying diagnosis at the operation. Corroborating results from previous reports, the highest incidence of appendicitis and appendectomy was found in the second trimester of pregnancy.\(^9\)\(^-\)\(^11\),\(^13\)\(^-\)\(^18\) This pattern was seen for perforated appendicitis and negative explorations, whereas for non-perforated appendicitis the strength of the inverse relation increased continuously throughout pregnancy. This result does not support the commonly expressed opinion that the incidence of appendicitis is the same in pregnant as in non-pregnant women but rather suggests that pregnancy may protect against appendicitis.\(^9\)\(^,\)\(^11\),\(^19\)\(^-\)\(^21\)

The strength of the present study include its size and the population-based design. The age-matched case-control design overcomes the potential sources of bias from the age-related differences in both the incidence of appendicitis and in the birth rate, with a declining incidence of appendicitis from the later half of the second decade and a peak in the birth rate in third decade. Matching on township of residence and time-period controls for geographical differences and secular trends in the birth rate and the incidence of appendectomy.

Case-control studies can only show patterns of relations but cannot define the direction of these associations. Adverse effects of appendicitis and appendectomy on pregnancy with an increased risk of spontaneous abortion may at least partly explain the inverse association of perforated appendicitis and negative appendectomy with first trimester pregnancy. However, adverse effects of appendicitis and appendectomy on pregnancy cannot explain the low risk of appendicitis in third trimester pregnancy as preterm births and stillbirths of more than 27 weeks of gestation were included.

Unfortunately no information about the date of the last menstrual period was available. Therefore, the pregnancy status and length of gestation at the time of operation had to be assessed from the interval between the date of the operation and the date of the succeeding childbirth, assuming a normal length of gestation of 9 months. Women that experience abortion after appendectomy are therefore misclassified as non-pregnant. This will give a bias towards an inverse relation and may partly explain the inverse relation with perforated appendicitis and negative appendectomy in early pregnancy. Pre-term births after appendectomy are misclassified as term births. The number of operations that were assigned to the third trimester of pregnancy is therefore inflated and the true inverse relation with appendicitis and late pregnancy is underestimated.

One potential problem with register studies concerns the validity of the registered information. The specificity of the diagnosis of appendicitis is somewhat less pronounced than a diagnosis of non-inflamed appendix as the surgeon may over-diagnose macroscopic pathological changes. In a study of the Inpatient Register of the Jönköping County in Central Sweden, a region that is also covered by and included in the National Inpatient Register, appendicitis was a false-positive diagnosis in 10 per cent of patients and a false-negative diagnosis 6 per cent.\(^22\) These figures are probably representative for the whole register. These relatively small errors cannot explain the inverse relations seen in third trimester pregnancy.

We selected controls who had not been submitted to appendectomy according to the information available in the Inpatient Register. However, some controls may have been operated on at a time period, or in a geographical location, that was not covered by the register. We estimate that this proportion is less than 1 per cent. Contrary to common belief, appendectomy has no negative influence on fecundity.\(^23\) The possible bias from this error should be negligible.

The attitude to abdominal exploration for suspected appendicitis is probably more restricted during pregnancy leading to fewer negative explorations as well as a lower detection rate of milder cases of appendicitis.\(^22\) A more restrictive attitude to exploration may explain the inverse association of negative appendectomy and non-perforated appendicitis with pregnancy, but this cannot explain the inverse relation with perforated appendicitis as a more restrictive attitude to exploration would increase the risk of perforation. The relatively larger decrease that was observed for non-perforated appendicitis compared with the negative explorations in the third trimester also suggests that the decrease in the incidence of non-perforated appendicitis is real.

There was an increased risk of negative appendectomies in the second trimester. Abdominal pain suggesting a suspicion of appendicitis thus seems frequent in the second trimester of pregnancy. We have no information about the cause of this pain. The weaknesses in the study regarding the length of gestation and the pregnancy status cannot explain this association. The misclassification of abortions and premature births due to the appendectomy would rather give a deflated association. There was also a decreased risk of negative appendectomies in the puerperium. This indicates that puerperal women experience abdominal pain less frequently or are less prone to seek care for abdominal pain.

The most important result in this study is the inverse relation between pregnancy and appendicitis. This suggests that pregnancy protects against appendicitis, especially in the third trimester. During pregnancy a range of physiological changes take place that may influence the pathogenesis of appendicitis. The immune system is shifted towards a T-helper cell type 2 (TH2) dominated immunity with a depressed cellular inflammatory response and increased humoral immunity.\(^24\) A decrease in T-helper cell type 1 (TH1) mediated chronic inflammation, as in rheumatoid arthritis and multiple sclerosis, is observed during pregnancy.\(^25\),\(^26\) Appendicitis is an inflammatory process and the inverse relation between appendicitis and pregnancy may suggest that the inflammatory response in appendicitis is mediated by a TH1 mediated inflammatory response.

To conclude, our findings indicate that the incidence of appendicitis is reduced in pregnancy, particularly during the third trimester. The result suggests a protective effect of pregnancy on the development of appendicitis, which may have implications for the understanding of the pathogenesis of appendicitis.

Acknowledgements

The study was supported by a grant from The Health Research Council in the Southeast of Sweden and the Swedish Council for Social Research.
KEY MESSAGES

- The aetiology and pathogenesis of appendicitis remains unknown.
- A relation to female sex hormones has been proposed but results of previous studies have been inconsistent.
- In this study we found a strong inverse relation between appendicitis and pregnancy, especially in the third trimester. This suggests a protective effect of childbearing for appendicitis.

References