Endometriosis is associated with a decreased risk of pre-eclampsia

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BACKGROUND: We postulated that impaired endometrial differentiation in women with pelvic endometriosis predisposes for pre-eclampsia. METHODS: A retrospective case–control study set at the University of Ghent IVF centre. The incidence of pre-eclampsia and pregnancy-induced hypertension (PIH) following the clinical and/or laparoscopic diagnosis of endometriosis-associated infertility (case group; n = 245 pregnancies) was compared with the incidence of these obstetric complications in pregnancies following treatment for male-factor infertility (control group; n = 274 pregnancies). Pregnancy data were obtained by searching electronic databases and postal questionnaires. The case and control groups were matched for age, parity and multiple pregnancies. RESULTS: The incidence of pre-eclampsia and PIH was significantly lower in the case group (0.8%) when compared with control group (5.8%) (P < 0.002; odds ratio (OR) = 5.5, 95% confidence interval (CI): 1.7–33.3) than in pregnancies following endometriosis-associated infertility. PIH occurred in 3.5% and 8.7% of case and control pregnancies, respectively (P = 0.018; OR = 2.6, 95% CI: 1.2–6.0). The odds of developing pre-eclampsia were 5.67 times higher in the control group than in pregnancies following endometriosis-associated infertility. In multiple pregnancies, the odds of developing pre-eclampsia increased 1.93 times per additional child, with or without endometriosis. CONCLUSIONS: We found no evidence that endometriosis predisposes for pre-eclampsia. Instead, the risk of hypertensive disorder in pregnancy is significantly reduced in women with endometriosis-associated infertility.

Keywords: endometriosis; pre-eclampsia; pregnancy-induced hypertension; incidence; angiogenesis

Introduction

Although many studies have examined the effect of endometriosis on fertilization and implantation rates after IVF treatment, little is known about the incidence of late pregnancy complications such as pre-eclampsia. A recent meta-analysis of 22 published studies reported significantly decreased fertilization, implantation and pregnancy rates after assisted conception in women with endometriosis-associated infertility when compared with those with other causes of infertility (Barnhart et al., 2002). Whether this is attributable to impaired oocyte/embryo quality or to decreased endometrial receptivity remains to be elucidated (Garrido et al., 2003). Pregnancy outcome data in women with endometriosis-associated infertility is currently confusing as these patients are often grouped with those with unexplained infertility. After adjusting for age, parity and multiple pregnancies, Pandian et al. (2001) reported a significantly higher incidence of pre-eclampsia, placental abruption and preterm labour in women with unexplained infertility compared with the general obstetric population.

Gene expression analyses of timed endometrial biopsies have provided evidence that entire gene networks are perturbed in women with endometriosis during the putative window of endometrial receptivity when compared with fertile controls (Giudice, 2004). Coordinated endometrial gene expression is thought to be important not only for embryo implantation but also for controlled interstitial and endovascular trophoblast invasion and the establishment of a functional placenta (Damsky et al., 1994). In humans, trophoblast invasion encompasses the inner myometrium, also termed the junctional zone. Interestingly, recent studies have linked thickening and dysperistalsis of the junctional zone to endometriosis (Leyendecker et al., 2004). Combined with the available epidemiological data, these observations suggest that endometriosis may predispose for pre-eclampsia, which is characterized primarily by the defective remodelling of junctional zone myometrial spiral arteries in the placental bed (Brosens et al., 1972). We have tested this conjecture in this case–control study. Surprisingly, we found that risk of developing pre-eclampsia

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is significantly decreased in women with endometriosis-associated infertility.

**Material and Methods**

The study was approved by the Ethics Committee of the Faculty of Medicine, University Hospital Ghent, Belgium. In this matched case–control study, the incidence of pre-eclampsia and pregnancy-induced hypertension (PIH) was investigated in a cohort of women with or without pelvic endometriosis whom attended the University of Ghent IVF Centre between 1991 and 2004.

**Definitions**

PIH was defined as persistently raised blood pressure (≥140/90 mmHg) starting after the 20th week of gestation in an otherwise normotensive woman. Pre-eclampsia was defined as PIH with proteinuria (≥300 mg/24 h).

**Case and control groups**

For all patients, only the outcome of the first documented pregnancy following IVF treatment was included to ensure that the same woman was not analysed twice. The case group consisted of pregnancies in patients with endometriosis-associated infertility. The diagnosis of endometriosis was based on either laparoscopy performed at the University of Ghent IVF centre or on endometriosis being the reason for IVF referral. In the IVF referral group, the laparoscopic findings were often not available. The control group consisted of pregnancies following referral for male-factor infertility. This group also consisted of two subgroups. In the first subgroup, endometriosis was excluded laparoscopically, whereas the second subgroup, consisted of patients with no clinical symptoms or signs suggestive of endometriosis. The control and case pregnancies were matched for age at the time of delivery and parity. We aimed to obtain two control pregnancies for every case pregnancy.

**Inclusion and exclusion criteria**

The case group included infertile women with endometriosis, alone or combined with male-factor infertility. Women with additional causes of infertility were excluded. The control group consisted of pregnancies in normal women with male-factor infertility. Patients with other known causes of infertility were excluded.

**Study size**

After completing the data collection from patients and their practitioners, the study group included a total of 1102 pregnancies: 312 pregnancies in the case group and 790 in the control group. After applying the exclusion criteria, 675 pregnancies were further analysed, of which 271 were in the case group and 404 in the control group.

**Data collection**

The electronic database of the University of Ghent IVF centre often contained incomplete pregnancy outcome information, and therefore, with approval of the Ethics Committee, all initially selected patients in the case and control groups were sent a postal questionnaire. The response rate was 18% in both groups. This low response rate was largely due to change of address or incomplete address details. Returned questionnaires were incompletely filled out in 16 (41%) and 19 (20%) of the case and control groups, respectively. Whenever possible, the referring gynaecologist was contacted, resulting in additional information on 11 patients and 19 pregnancies. After exclusion of those pregnancies that did not meet the inclusion criteria, the response to the questionnaires provided additional information on 32.8% of the pregnancies in the case group and on 35.9% of pregnancies in the control group. Because of possible self-reporting bias, pregnancy information obtained from women who returned the questionnaire, referred to as ‘responders’, was analysed separately from outcome data based only on database search and examination of clinical records (‘non-responders’).

**Bias analysis**

Several potentially confounding factors were considered during data analysis. First, although all patients were treated at the University of Ghent IVF centre, many delivered at different hospitals in Belgium or The Netherlands. Although it would have been easier to restrict the study to those patients that delivered at the University Hospital of Ghent, this could introduce an overrepresentation of high-risk patients. Second, this study covered the period from 1991 until 2004 during which changes in antenatal care and data recording could have occurred. Therefore, the date of delivery was taken into account to ensure that both groups remained matched. Third, although each pregnancy satisfying the inclusion criteria was considered as an outcome measure, the incidence of pre-eclampsia is known to be higher in nulliparous than multiparous women. Again, this was taken in account in the analysis. Finally, the use of postal questionnaires introduces several potential biases, including non-response, incomplete response and subjective over- or under-estimation of complications. This approach was however necessary to ensure study size was adequate.

**Statistical analysis**

For comparison of incidence of pre-eclampsia or PIH in the unpaired case and control groups, the $\chi^2$ test and, where appropriate, the Fisher’s Exact test for $2 \times 2$ contingency tables were used and tested two-ways. A $P \leq 0.05$ was considered statistically significant. The above statistical analyses were performed with the Statistical Package for Social Sciences, Version 12.0 (SPSS Inc., Chicago, IL, USA). The association between pre-eclampsia and endometriosis was further verified using stepwise multiple logistic regression analysis, controlling for multiple pregnancies, age at time of delivery, year and place of delivery. Backward elimination was applied starting from a complex model containing high-order interaction terms for all variables and quadratic terms for mean-centred continuous variables. Observing marginality restrictions, only variables with $P \leq 0.05$ were kept in the final model. The analysis was performed using SAS software version 8.2 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Characteristics of the study populations**

After applying the inclusion and exclusion criteria, the study population consisted of 271 pregnancies in the case group and 404 pregnancies in the control group. The case and control groups were matched for age at the time of delivery, parity, year of delivery and multiple pregnancies. The mean age at the time of delivery in the case group was 32 years (range: 21–44 years) versus 33 years (range: 20–44 years) in the control group (NS). Parity was also comparable between both groups with a mean (±SD) of 1.41 ± 0.67 in the case group and 1.37 ± 0.61 in the control group (NS). In both groups, 75% of women delivered after 1996 and the median year of delivery was 1998. However, proportionally more deliveries in the case group took place at the University Hospital of Ghent or its affiliated hospitals than in the control group.
(37% versus 18%, respectively; P < 0.01). Multiple pregnancies are at increased risk of feto-maternal complications, including pre-eclampsia. However, the incidence of twin pregnancies in the case group was comparable to that of the control group (19.2% versus 18.8%, respectively; NS) as was the incidence of triplets (1.5% versus 1.0%, respectively; NS). Multiple pregnancies were analysed separately for the risk of pre-eclampsia.

**Incidence of pre-eclampsia**

Out of a total of 675 pregnancies, insufficient data were available on 156 (23.1%) pregnancies, resulting in 245 case and 274 control pregnancies for further analysis. The incidence of pre-eclampsia in the case group was 0.8% (2/245) versus 5.8% (16/274) in the control group (P = 0.002) (odds ratio (OR) = 7.5; 95% confidence interval (CI): 1.7–33.3) (Table 1). A total of 464 pregnancies occurred in nulliparous women but insufficient obstetric data were available on 107 pregnancies. However, pre-eclampsia occurred in 2 out of 170 (1.2%) pregnancies in the case group compared with 13 out of 187 (7.0%) pregnancies in the control group (P = 0.007) (OR = 6.3; 95% CI: 1.4–28.6) (Table 1). The overall incidence of pre-eclampsia in the nulliparous group was 4.2%. There were 211 pregnancies in multiparous patients but 49 were excluded because of missing information, thereby leaving 162 pregnancy outcomes available for analysis. Although pre-eclampsia occurred in 2 out of 170 (1.2%) pregnancies in the control group and in none in the case group, this did not reach statistical significance. To further validate the findings, we examined the incidence of pre-eclampsia in patients in which the presence or absence of endometriosis was based on laparoscopy. This group included 168 case pregnancies and 54 control pregnancies after exclusion of 33 pregnancies with insufficient data. The lower number of controls can be explained by the fact that laparoscopy is no longer systematically performed during fertility investigation in the absence of clinical signs or symptoms of endometriosis. Again, the incidence of pre-eclampsia in the case group (1.2%) was significantly lower when compared with the control group (7.4%) (P = 0.032; OR = 6.6; 95% CI: 1.2–37) (Table 1).

**Pregnancy-induced hypertension**

In the total study group of 675 pregnancies, information on blood pressure after the 20th week of gestation was inadequate in 181 (26.8%) pregnancies. The higher incompleteness of the data when compared with the pre-eclampsia cohort (23.1%) is explained by the fact that in the absence of proteinuria, blood pressure recordings were sometimes unsatisfactory. PIH occurred in 8 out of 229 (3.5%) pregnancies in the case group and in 23 out 265 (8.7%) pregnancies in the control group (P = 0.018; OR = 2.6; 95% CI: 1.2–6.0). The lower incidence of PIH in the case group was in agreement with the results obtained for pre-eclampsia. Next we examined the incidence of PIH in the cohort of patients with laparoscopic data. This analysis consisted, after exclusion of those pregnancies with insufficient information (14.9%), of 164 pregnancies in the case group and 53 in the control group and showed an incidence of PIH of 4.9% and 9.4%, respectively. Although there was a lower occurrence of PIH in the case group, the difference was not statistically significant (P = 0.314; OR = 2.0; 95% CI: 0.6–6.5).

**Multiple pregnancies and other variables**

Although 136 multiple pregnancies were included in the study, insufficient information precluded further analysis in 38 (27.9%) cases. Both the case and control groups included 49 pre-eclamptic pregnancies, which was not statistically significant (4.1% and 14.3%, respectively; P = 0.159). We further analysed the data to determine if the place of delivery influenced the incidence of pre-eclampsia. As shown in Table 2, the incompleteness of data was, for obvious reasons, lowest for deliveries at the University Hospital in Ghent. When analysed according to the place of delivery, there was a lower occurrence of PIH in the case group, the difference was not statistically significant in the case versus control group (P = 0.018). A similar trend was present in ‘responders’ but the smaller sample size precluded statistical significance.

**Table 1: Incidence of pre-eclampsia in control and case groups**

<table>
<thead>
<tr>
<th>Place of delivery</th>
<th>Case group (%)</th>
<th>Control group (%)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study group</td>
<td>2/245 (0.8)</td>
<td>16/274 (5.8)</td>
<td>0.002</td>
<td>7.5 (1.7–33.3)</td>
</tr>
<tr>
<td>Nulliparous women</td>
<td>2/170 (1.2)</td>
<td>13/187 (7.0)</td>
<td>0.007</td>
<td>6.3 (1.4–28.6)</td>
</tr>
<tr>
<td>Lap. confirmed</td>
<td>2/168 (1.2)</td>
<td>4/54 (7.4)</td>
<td>0.032</td>
<td>6.6 (1.2–37)</td>
</tr>
</tbody>
</table>

Lap. confirmed: presence or absence of endometriosis was confirmed by laparoscopy.

**Table 2: Incidence of pre-eclampsia according to the place of delivery**

<table>
<thead>
<tr>
<th>Place of delivery</th>
<th>Case group (%)</th>
<th>Control group (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghent, Belgium*a</td>
<td>0/90 (0.0)</td>
<td>3/62 (4.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Belgium*b</td>
<td>1/100 (1)</td>
<td>4/61 (6.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1/47 (2.2)</td>
<td>9/145 (6.3)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*aDeliveries at the University Hospital of Ghent.
*bIn centres elsewhere in Belgium.

**Table 3: Incidence of pre-eclampsia amongst ‘responders’ and ‘non-responders’ to a postal questionnaire**

<table>
<thead>
<tr>
<th>Place of delivery</th>
<th>Case group (%)</th>
<th>Control group (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Responders’</td>
<td>1/87 (1.1)</td>
<td>8/135 (5.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>‘Non-responders’*</td>
<td>1/158 (0.6)</td>
<td>8/139 (5.8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Outcome data was obtained from a database search and examination of clinical records.
Multiple regression analysis

Stepwise multiple regression analysis was applied to verify the effect of endometriosis on the incidence of pre-eclampsia in nulliparous women, controlling for age at time of delivery, multiple pregnancies and the year and site of delivery. In addition, the effect of responding to the postal questionnaire or not was tested. After backward elimination, only endometriosis and multiple pregnancies were kept in the final multiple logistic regression model. The odds of developing pre-eclampsia were 5.67 times higher in the control group than in pregnancies following endometriosis-associated infertility. In multiple pregnancies, the odds of developing pre-eclampsia increased 1.93 times per additional child, regardless of the presence or absence of endometriosis. Moreover, neither the reduced risk of pre-eclampsia associated with endometriosis nor the increased risk caused by multiple pregnancy was significantly influenced by the age of the woman at delivery, year or place of delivery or response to postal questionnaires regarding the diagnosis of endometriosis. Thus, this multivariate approach yielded comparable results as the univariate analysis and further supports the notion that endometriosis is associated with decreased risk of pre-eclampsia.

Discussion

On the basis of available epidemiological and endometrial gene expression data, we speculated that endometriosis prior to conception may predispose for pre-eclampsia. However, this case–control study provided no evidence in support of this assumption. Instead, we demonstrate that the incidence of pre-eclampsia is significantly lower in pregnancies following IVF treatment for endometriosis-associated infertility when compared with male-factor infertility. The risk of pre-eclampsia in women with endometriosis was 7.5-fold lower when based on the entire study population and 6.6-fold lower in the subgroup of patients with laparoscopic data, independently of age, parity and other potentially confounding factors such as year and place of delivery. Furthermore, the risk of PIH was also significantly decreased in women with endometriosis. Arguably, the observed differences could be accounted for by an increased likelihood of pre-eclampsia in patients treated for male-factor infertility rather than by a decreased risk associated with endometriosis. However, this appears most unlikely as the incidence of pre-eclampsia and PIH is generally increased in subfertile women (Thomson et al., 2005). Furthermore, male-factor infertility has been shown not to be associated with an altered risk of pre-eclampsia after IVF treatment (Ludwig and Katalinic, 2003).

The methodology of this study, however, necessitates cautious interpretation of the results. A potential problem is that detailed clinical data on pregnancy outcomes were mostly available only for those women who delivered at the University Hospital of Ghent. Pregnancy outcome data on other patients were obtained by questionnaire. The response to these postal questionnaires was low, although similar for both case and control groups. Although the study could be criticized on the grounds of recall bias and reporting errors, the careful analysis of the various subgroups and the application of univariate and multivariate analyses supports the conclusions. The selection criteria for case and control groups could also be considered controversial as laparoscopic data were not considered mandatory. For obvious reasons, invasive procedures such as laparoscopy are increasingly avoided in infertile women with no clinical symptoms of pelvic disease. Rather than being overly focussed on obtaining a certified disease-free control group, epidemiological studies are increasingly selecting for patients with or without clinical suspicion of disease, a valid approach as long as subjects are derived from the same population source (Zondervan et al., 2002). Furthermore, analysis of the total case group and the laparoscopic case subgroup showed a similar degree of protection against pre-eclampsia. Pregnancy outcome data can be a potential cause of bias for various reasons. For instance the risk of pre-eclampsia may be recurrent in some patients or be dependent upon the interval between pregnancies (Skjaerven et al., 2002). Finally, it is not known if medical, surgical or combined treatment for endometriosis prior to IVF impacts on subsequent pregnancy outcome. Because of these potentially confounding factors, it will be important to validate our findings in a prospective study and assess the impact, if any, of surgical or medical treatments for endometriosis on subsequent pregnancy outcome. Nevertheless, our findings, despite the limitations of the study, are in agreement with those reported by others. Isaksson et al. (2002) found a lower incidence of PIH in singleton IVF pregnancies in women with unexplained infertility when compared with other IVF singleton pregnancies. Kortelahti et al. (2003) examined the pregnancy outcome in a matched case–control study that included 137 women with biopsy-proven endometriosis and 137 controls. While these investigators failed to detect a significant effect of endometriosis on the obstetric outcome, it is noteworthy that the incidence of pre-eclampsia in patients with endometriosis was 6.6% compared with 11% in the control group.

The mechanism whereby endometriosis could protect against pre-eclampsia is unknown. Polymorphisms in angiogenesis-regulating genes are increasingly linked to susceptibility to reproductive disorders, including endometriosis, spontaneous abortion, spontaneous preterm delivery and pre-eclampsia. Vascular endothelial growth factor (VEGF) in particular is an important determinant of the angiogenic potential and its level of expression has a considerable effect on disease progression (Papazoglou et al., 2004). Endometriosis is one of the best-known conditions in which angiogenesis is inappropriately switched on. In addition to VEGF, the expression of several other angiogenic growth factors and cytokines, including interleukin-1, -6 and -8, epidermal growth factor, fibroblast growth factor, insulin-like growth factor and platelet-derived growth factor, is enhanced in both eutopic and ectopic endometrium in women with endometriosis (Taylor et al., 2002). On the other hand, pre-eclampsia is an example of a disorder characterized by an insufficient angiogenic switch, resulting in endothelial-cell dysfunction, vessel malformation or regression and impaired re-vascularization (Carmeliet, 2005). A variable degree of defective vascular remodelling at the feto-maternal interface also underpins other pregnancy complications, including recurrent spontaneous abortions, fetal
growth restriction and preterm labour (Brosens et al., 1980; De Wolf et al., 1986, 1987; Kim et al., 2002; Sebire et al., 2002).

Recent studies have provided further evidence of increased endometrial angiogenesis in women with endometriosis. A prospective observational study measuring sub- and intra-endometrial blood flow by power Doppler ultrasound found that endometriosis is associated with significantly higher endometrial perfusion rates during the late secretory phase of the cycle, providing in vivo evidence of excessive angiogenesis (Xavier et al., 2005). Furthermore, increased impedance of intra-placental blood velocity waveforms has been detected as early as the 8th week of gestation in women who subsequently develop pre-eclampsia or preterm labour (Makikallio et al., 2004). These observations suggest that the level of angiogenesis at the feto-maternal interface in early pregnancy may be an important determinant of obstetric outcome and indicate that haemodynamic studies on placental bed perfusion during early pregnancy may reveal differences between women with and without endometriosis.

In summary, we report for the first time that women with endometriosis have a significantly lower risk of pre-eclampsia than women without endometriosis. This unexpected finding may reflect increased local expression of angiogenic factors and enhanced endometrial vascular perfusion at the time of implantation in women with endometriosis. Although this explanation remains speculative, our findings do emphasise the importance of the endometrial milieu at the time of conception in determining pregnancy outcome.

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