

Should the patients with endometriosis be treated as a risk group of pregnancy complications? Single center experience and literature review

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ABSTRACT

Objectives: Multidirectional influence of endometriosis on fertility impairments is well known. Altered implantation and placentation among affected patients raised concerns regarding possible negative influence on the course of pregnancy. The primary objective of the study was to assess the course of gestation and the incidence of pregnancy complications among women with endometriosis. It also aimed to determine whether the method of conception might impact the primary results.

Material and methods: A single-center cohort study included 64 women with confirmed endometriosis and 296 healthy controls. Data concerning treatment of endometriosis related infertility, course of pregnancy and perinatal outcomes were evaluated.

Results: Patients with endometriosis were older than controls (33.6 +/- 4.2 y vs 31.8 +/- 4.6, p = 0.01) and more often gave birth for the first time (87.5% vs 43.9%, p = 0.001). The age at the time of first delivery was significantly higher within the study group (33.1 y +/- 4.1 vs 29.9 +/- 4.6, p < 0.001). In the study, 81.2% of patients with endometriosis had the diagnosis of infertility. Patients suffering from endometriosis were significantly more prone to spontaneous placental abruption during pregnancy and delivery (4.7 vs 0.3%, odds ratio = 14.5). Several complications occurred more often in endometriotic patients (gestational diabetes mellitus, small-for-gestational-age and anemia); however, without statistical significance. The risk of pregnancy complications was independent from stage of endometriosis and way of conception. The incidences of adverse neonatal outcomes (preterm delivery, low Apgar score, lower birth weight) were similar in both groups.

Conclusions: Endometriosis may adversely affect perinatal outcomes, especially due to increased risk of placenta abruption and operative delivery. Stage of endometriosis and method of conception does not enhance these complications.

Key words: cesarean section; endometriosis; infertility; placenta pathology; pregnancy complications

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INTRODUCTION

There are a multitude of possible reasons for decreased fertility among women of reproductive age. Among them is endometriosis, defined as presence of endometrial glands and stroma outside the uterine cavity [1]. Although the pathogenesis of endometriosis is still under debate, it is well known that it affects every part of a woman's reproductive system. The prevalence of endometriosis in the general population is estimated to be 10–15%; however, among infertile females the rate may increase up to 48% [2, 3]. Nevertheless, the symptoms of the disease do not correlate with its' stage, meaning that the real incidence in the general population remains unknown and the prevalence may be underestimated.

Endometriosis can affect the reproductive potential by means of reduced ovarian function, decreased oocyte quality, altered embryo development or implantation failure.

Current literature describes various defects of endometrial functions in patients suffering from endometriosis. Endometrial tissue is characterized by high sensitivity to autocrine and paracrine signaling factors, such as sex hormones or cytokines. Locally unbalanced production of estrogens and cytokines in ectopic endometrium leads to disordered growth and malfunctioning of the tissue [4]. All of the above are involved in altered gene expression in eutopic endometrium and myometrium [5]. Furthermore, inappropriate cytokine secretion causes chronic local and

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systemic inflammatory response and results in the most typical symptoms and signs of endometriosis, such as chronic pelvic pain (especially dysmenorrhea, dyspareunia), pelvic adhesions and distorted pelvic anatomy. Decreased sensitivity to progesterone, due to downregulation of progesterone receptors is the reason why endometriosis is also called 'progesterone-resistant disease' [6, 7]. The alterations in molecular and cellular profiles of the eutopic endometrium of women with endometriosis were detected. It has been, therefore, hypothesized that endometriosis may influence pregnancy outcomes [8].

There is a strict dependency between proper implantation and placentation. Both are critical for fetal growth and favorable pregnancy outcomes. Nowadays, the correlation between abnormal placentation and several pregnancy complications, such as pregnancy induced hypertension (PIH), preeclampsia, fetal growth restriction, placental abruption (AP) or placenta praevia (PP) is well established. Furthermore, most of them may lead to the iatrogenic preterm birth. All the above may explain why previous investigators raised concerns regarding possible negative influence of endometriosis on the course of pregnancy and possible early pregnancy loss.

Objectives

The primary objective of the presented study was to assess the course of gestation and the incidence of pregnancy complications among women with confirmed endometriosis. It also aimed to determine whether the way of conception might impact the primary results. According to the available literature this issue has not been investigated among the Polish population before.

MATERIAL AND METHODS

A single-center cohort study was carried out at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. Multiple gestations and pregnancies miscarried prior to 22 weeks were excluded from the study. The authors identified 64 women with endometriosis, confirmed during previous surgical intervention (laparoscopy or laparotomy), who delivered at the Department between January 2015 and December 2018. Women diagnosed with adenomyosis or other anatomical disorders within genital tract not related to endometriosis (e.g. myomas) were excluded from the final analysis due to the suggested additional negative impact on the course of gestation. Data concerning treatment of pre-existing endometriosis, infertility [especially with the usage of assisted reproductive technologies (ART)], course of pregnancy and perinatal outcomes were obtained from medical records. Assessed neonatal outcomes included preterm delivery, Apgar score and birth weight. The stage of endometriosis was conferred according to the revised

American Society for Reproductive Medicine classification (rASRM) [9].

The control group (C) consisted of healthy women (without any known chronic diseases before conception; no suspicion of endometriosis, nor the diagnosis of infertility) who delivered at the Department within the same time frame. Finally, the control group consisted of 296 participants.

The baseline and clinical characteristics of both groups were collected from the patients' medical records. Preterm delivery was defined as birth before 37 completed weeks of gestation, while fetal growth restriction (FGR) as estimated fetal weight (EFW) below the tenth percentile in ultrasound examination [10]. PE, PIH and gestational diabetes mellitus were recognized according to guidelines of The Polish Society of Gynecologists and Obstetricians and The Royal College of Obstetricians and Gynaecologists.

The study was conducted in accordance with the Declaration of Helsinki for Medical Research involving human subjects. The ethical approval was obtained from the Ethics Committee of Medical University of Warsaw (AKBE/99/2019).

Statistical analyses

Categorical variables were presented as percentages and continuous ones as means with SD (standard deviation). The baseline and clinical data were compared using parametric (t-Student) and nonparametric (Mann-Whitney U) tests. Univariate odds ratios (ORs) with 95% confidence intervals (95% CI) for the parameters that could affect the course of pregnancy were calculated by Chi-Square test. A multiple logistic regression model was built to estimate which factors influence the risk of pregnancy complications. Statistica 13 software was used for statistical analyses. P-values below the threshold of 0.05 were considered significant. Main calculations were performed for all women with endometriosis. Additional analyses included the adjustment for the stage of endometriosis and the way of conception.

RESULTS

Baseline characteristics of women with or without endometriosis are presented in Table 1. Patients diagnosed with endometriosis were significantly older ($p = 0.01$) than controls and more often gave birth for the first time ($p = 0.001$). Moreover, the age at the time of first delivery was significantly higher in the study group compared to controls (33.1 years, SD = 4.1 vs 29.9, SD = 4.6, $p < 0.01$).

All patients from the study group underwent at least one surgical procedure in the past (62.5% excision of endometrioma, 15.6% diagnostic laparoscopy due to pelvic pain or infertility, 6.3% removal of hydrosalpinx). The mean age at the diagnosis of endometriosis was 29.2 years (SD = 4.5). Most of the women suffered from moderate to severe endo-

Table 1. Baseline characteristics of the groups

	Study group (SD)	Control group (SD)	p value
Sample size	64	296	(–)
Age [years]	33.6 (4.2)	31.8 (4.6)	0.01
BMI before pregnancy [kg/m ²]	22.4 (3.8)	23.4 (4.6)	0.24
Gestational age at delivery [weeks]	38.6 (1.6)	38.7 (2.0)	0.25
Primiparous	87.5%	43.9%	< 0.001
Mean birth weight [g]	3301 (540)	3408 (580)	0.09

BMI — body mass index; SD — standard deviation

Table 2. Pregnancy complications and perinatal outcomes in studied groups

	Study group, n (%)	Control group, n (%)	OR (95% CI)
PIH	5 (7.8)	28 (9.5)	0.8 (0.3–2.2)
Preeclampsia	1 (1.6)	7 (2.4)	0.7 (0.1–5.4)
GDM	11 (17.2)	45 (15.2)	1.2 (0.6–2.4)
FGR	5 (7.8)	12 (4.1)	2.0 (0.7–5.9)
Hypothyroidism	11 (17.2)	69 (23.3)	1.1 (0.1–9.8)
Anemia during pregnancy	9 (14.1)	21 (7.1)	2.1 (0.9–4.9)
Placenta previa	1 (1.6)	0(0)	(–)
Placental abruption	3 (4.7)	1 (0.3)	14.5 (1.5–140)
Imminent fetal asphyxia during labor	6 (9.4)	20 (6.8)	1.4 (0.5–3.7)
Caesarean delivery	43 (67.2)	156 (52.7)	1.8 (1.1–3.2)
Preterm delivery	7 (10.9)	27 (9.1)	1.2 (0.5–2.9)

CI — confidence interval; GDM — gestational diabetes mellitus; OR — odds ratio; PIH — pregnancy induced hypertension; FGR — fetal growth restriction

metriosis (stage 4–15.2%, 3–42.4%, 2–30.3%, 1–12.1%). Patients' BMI significantly differed within subsequent stages of endometriosis [stage 1–22.2 (kg/m²), (SD = 4.9), 2–23.4 (4.8), 3–20.9 (2.6), 4–24.8 (3.2), $p = 0.02$]. Moreover, the incidence of overweight and obesity increased with the severity of disease (stage 1–0%, 2–30%, 3–14% and 40% in stage 4), however this factor did not reach statistical significance ($p = 0.1$). Patients BMI did not impact the severity of endometriosis. Due to comparable prognosis and recommendations concerning the treatment of infertility in patients with stage 1 and 2, as well as stage 3 and 4 of endometriosis, these cases were further evaluated together (called 1 + 2 and 3 + 4 endometriosis).

In the study, 81.2% of patients with endometriosis had the diagnosis of infertility before (65.6% primary and 15.6% secondary). The mean time to conception in the study group equaled 2.6 years (SD = 2.7). Also, 42.9% of women with 1 + 2 endometriosis conceived spontaneously, 21.4% after

Table 3. Pregnancy complications and perinatal outcomes adjusted for the stage of endometriosis and the way of conception

	1 + 2 vs 3 + 4 endometriosis OR (95% CI)	Natural conception/IUI vs IVF OR (95% CI)
PIH	0.4 (0.1–2.6)	0.3 (0.1–2.2)
Preeclampsia	(–)	(–)
GDM	0.4 (0.1–1.7)	0.6 (0.2–2.3)
FGR	1.1 (0.1–11.0)	2.4 (0.2–22.6)
Hypothyroidism	0.4 (0.1–1.5)	0.4 (0.1–1.5)
Anemia during pregnancy	0.4 (0.1–1.8)	0.1 (0.1–0.6)
Placenta previa	(–)	(–)
Placental abruption	(–)	1.1 (0.1–13.2)
Imminent fetal asphyxia during labor	0.5 (0.1–2.9)	1.1 (0.2–6.7)
Caesarean delivery	0.3 (0.1–1.5)	0.8 (0.3–2.5)
Preterm delivery	1.8 (0.2–16.0)	0.7 (0.1–3.5)

CI — confidence interval; GDM — gestational diabetes mellitus; IUI — intrauterine insemination; OR — odds ratio; PIH — pregnancy induced hypertension; FGR — fetal growth restriction

intrauterine insemination (IUI) and 35.7% after in-vitro fertilization (IVF). Finally, 72% of pregnancies in patients with 3 + 4 endometriosis were a result of IVF, 20% of IUI, while only 8% were conceived naturally. The incidence of spontaneous pregnancies was significantly higher in patients with stage 1 + 2 compared to stage 3 + 4 ($p = 0.01$).

The incidence of pregnancy complications among women from the study and control groups is presented in Table 2. Patients suffering from endometriosis were significantly more prone to spontaneous placental abruption during pregnancy and delivery (OR = 14.5). Several complications related to the course of pregnancy occurred more often in endometriotic patients (gestational diabetes mellitus, FGR or anemia); however, without statistical significance.

Endometriosis increased the risk of operative delivery (OR = 1.8). The most frequent indication for caesarean section (CS) in the study group was the previous history of infertility/ART (elective CS, 27.9%) and excessive bleeding/hemorrhage during labor (emergency CS, 13.9%). Moreover, placental abruption was the most frequent known reason of obstetric hemorrhage. On the contrary, the most frequent reasons to perform CS in the control group included previous caesarean section (18.3%) and labor arrest of (8.1%).

Further sub analysis assessed the risk of pregnancy complications adjusted for the stage of endometriosis and the method of conception (Tab. 3). The risk of the analyzed perinatal complications was not related to any of the above. The only feature that differed in patients with endometriosis was the decreased risk of anemia during IVF pregnancy (4.9% vs 30.4%, $p = 0.01$).

Most women in both groups delivered full-term newborns. The rate of preterm deliveries among women diagnosed with endometriosis equaled 10.9% compared to 9.1% in healthy controls ($p = 0.65$). Neonatal outcomes were similar among women with and without endometriosis. There was no significant difference in the mean fetal birth weight (3301 g vs 3408 g in controls, $p = 0.09$). There were no significant differences in the incidence of low Apgar scores (< 8 points in 1st and 5th minute of life between both studied groups (1.6 vs 3.4%, $p = 0.4$ and 0 vs 1.7%, $p = 0.3$ respectively).

DISCUSSION

Pregnancy and delivery related complication are the main reasons of maternal and neonatal morbidity [11]. Identifying and close monitoring of patients with increased risk of adverse perinatal outcomes provide an opportunity to improve the quality of maternity care [12].

According to our findings, endometriosis does not seem to increase the risk of most common pregnancy complications such as PIH, preeclampsia, GDM or FGR. The potential correlation between endometriosis and preeclampsia is still a subject of debate. Previous researchers did not find any association between these conditions either [13]. Hadfield et al. obtained similar results from the longitudinal observation of 3239 Australian women with endometriosis diagnosed prior to pregnancy. In comparison to the healthy controls, neither pregnancy hypertension, nor pre-eclampsia occurred more often in the study group [14]. The rate of complications was also independent from the severity of endometriosis. However, according to Berlac et al., women with endometriosis are more prone to suffer from hypertensive disorders during pregnancy: preeclampsia (OR 1.4), severe preeclampsia, eclampsia or HELLP syndrome (OR 1.7 95%) than healthy controls [15]. Data from Danish reports (82,793 singleton pregnancies) also suggest increased risk of pre-eclampsia in affected females (OR = 1.37, 95% CI 1.06–1.77), regardless of the way of conception (natural vs ART) [16]. The results were again confirmed in a cohort study by Farland et al. [17], where the risk of hypertensive disorders in women with endometriosis was also greater (RR 1.3; 95% CI 1.16–1.45).

Tobias et al. evaluated the risk of GDM among women with a history of infertility – they found no association for endometriosis [18]. Subsequent systematic review published by Perez-Lopez et al. [19] also confirmed no association (OR 1.14, 95% CI 0.86–1.51). However, Farland et al. concluded that endometriosis was associated with a significantly greater risk of GDM (RR 1.35; 95% CI 1.11–1.63). Therefore, even the results from large cohort studies are inconclusive [17].

The incidence of placental abruption differed most between both studied groups in the presented research. Wom-

en with endometriosis were at increased, over fourteen-fold, risk of the above complication compared to healthy controls. Moreover, the authors observed higher incidence of placenta previa in the study group (1.6% vs 0%), but the result did not reach significance. These conclusions are concordant with the findings of previous researchers (reported OR 2.0–3.99 for placental abruption and 3.9–15.1 for placenta previa) [13, 15, 20, 21].

According to our results, endometriosis seems to be positively correlated with the incidence of elective caesarean sections (OR = 1.8). This finding is concordant with previous studies (Porpora et al., Horton et al.) [21, 22]. Nevertheless, vaginal labor does not increase the risk of peritoneal injuries among women who underwent surgery for deep infiltrating endometriosis and may reduce the recurrence of endometriosis symptoms after delivery [23, 24].

Further sub-analyses of pregnancy complications regarding the stage of endometriosis and the method of conception did not show any significant differences between groups.

The incidence of most of the adverse perinatal outcomes increases with the age of the woman in general population. Patients with endometriosis were significantly older than controls (33.6 vs 31.8 years); however, this fact did not bias the end results.

The authors of the presented paper did not evaluate the course of early pregnancies ($< 22^{\text{nd}}$ week of gestation). Few publications hypothesize that endometriosis may be associated with early pregnancy losses (both spontaneous abortion and ectopic pregnancy), but these findings should be carefully interpreted (Farland et al., Porpora et al.) [21]. Further studies should also focus on these issues.

Neonatal outcomes (rate of preterm deliveries, birth weight and Apgar scores) did not differ between women with or without endometriosis. On the other hand, previous researchers gave evidence of increased risk for preterm delivery and neonatal unit admission following delivery among women diagnosed of endometriosis [22].

The women' age is the strongest indicator of fertility impairments in the future. Of women, 81.2% diagnosed with endometriosis, who delivered at our department, had been diagnosed with infertility before. Furthermore, the average age at the time of the first pregnancy ended with delivery was significantly higher among women with endometriosis compared to healthy controls. The same findings were presented by previous researchers [25]. According to the epidemiological data, endometriosis extends the time to conception (mean time from diagnosis to pregnancy equaled 2 years and 4 months). There is a clear association between endometriosis and infertility due to lower oocyte yield and lower implantation rates. The percentage of known fertility impairments is much higher than the rate observed

in the general population [26]. Previous studies have reported an inverse correlation between advanced stages of endometriosis and the prognosis for fertility treatments [27]. Apart from chronic pelvic pain and dyspareunia, fertility impairments are the most common symptoms among patients suspected of endometriosis [28]. Moreover, literature data proves an increased risk of infertility, over 8-fold, among endometriotic patients [29].

The problem is additionally enhanced by significant diagnostic delay in recognition of endometriosis. The average time from the onset of first symptoms to the final diagnosis of the disease varies greatly among countries (from 4.4 years in USA, up to 10.4 years in Germany and Austria) [30, 31]. The main factors contributing to the above are mainly limited access to gynecological care, time between consultations and high (up to 74%) rates of false diagnoses. The American Society for Reproductive Medicine classification is the most widely used tool for assessing the clinical stage of endometriosis. In the study group, a higher incidence of late forms of endometriosis was observed (stage III and IV). It may be due to the problem of underestimation of the disease prevalence; however, benefits from performing laparoscopy for minimal endometriosis prior to IVF are still under debate [32].

There are some limitations of the above study. It presents only single-center experience and the results regarding adverse perinatal outcome might not reach significance due to small sample size.

CONCLUSIONS

To conclude, the history of endometriosis may adversely affect perinatal outcomes, especially due to impaired placental and increased risk of operative delivery. However, it does not seem to influence neonatal complications as preterm birth, low Apgar score or low birth weight. Since stage of endometriosis have detrimental effect on female fertility, it seems reasonable to raise awareness of possible fertility impairments especially among women with symptoms typical for endometriosis.

Conflict of interest

The authors declare that there is no conflict of interest.

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