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Rate of caesarean sections is higher in endometriosis patients – experience of single tertiary obstetric clinic in the light of epidemiologic data

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Abstract

Introduction and Objective. Endometriosis is defined as the presence of endometrium-like tissue outside the uterine cavity which can cause chronic pelvic pain, dysmenorrhea, infertility, and obstetric complications. The study was undertaken to elucidate the influence of endometriosis on conception, pregnancy and course of Latour, as well as outcomes for the growth of the foetus.

Materials and method. A single centre study was undertaken of endometriosis patients who were followed-up for five years after laparoscopy. The study group consisted of 30 patients with endometriosis who conceived, of whom 120 underwent laparoskopy. The control group consisted of 30 healthy women who delivered children and were hospitalized in a two-month period in 2015. Each patient completed a questionnaire regarding endometriosis symptoms, infertility duration, gravidity, smoking habits, education, metod of conception, incidence of pre-term labour, foetal growth restriction (FGR), small for gestational age (SGA) and pregnancy-induced hypertension (PIH). Analysis of the data was carried out using STATISTICA v.10.

Results. A significant difference was observed in maternal age (34.7 ±4.7 for the study group vs. 29.8±4.9 years for the control group; p=0.001). In the study group, an increased incidence of caesarean section was noted (OR 4.9; 95% CI 1.61–15.07). No significant differences were observed in the incidence of preterm labour, FGR, SGA and PIH.

Conclusions. Delivering child at older age was observed in the endometriosis group, compared with controls, which suggests that endometriosis extends the time to conceiving. Higher maternal age at delivery and prolonged time to pregnancy may be the factors that influence the rate of caesarean section in endometriosis patients.

Key words

pregnancy, infertility, endometriosis, cesarean section

INTRODUCTION

Endometriosis is a disease found in 7–15% of women at reproductive age in the general population, whereas in the group of infertile women the prevalence of the disease is 21–47%, and among patients with menstruation-associated pain even as high as 71–97 % [1,2]. Endometriosis is one of the most cost-consuming diseases. Social costs paid because of work absences, other health related issues, medical and surgical therapies for patients with endometriosis, are very high and sometimes difficult to estimate. It may take many years from first symptoms to final diagnosis, which is burdensome for both the patients and the health care system [3].

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Endometriosis is defined as a pathology caused by the presence of foci of endometrial tissue outside the uterine cavity, so called 'endometrium-like' tissue. With the exception of the female genital organs, endometriosis can be also located on the uterosacral ligaments, on the recto-vaginal septum in the pouch of Douglas, on the uterovesical fold, and other organs, including the bowels and bladder. Nowadays, its pathology is one of the most studied of all human diseases, but through its complexity remains full of unknowns.

There are many hypotheses about endometriosis etiology, but despite extensive studies, the exact mechanism of endometriosis is not clearly understood. The complex pathogenesis and varied symptoms make the diagnostic and therapeutic process difficult [3]. Endometriosis is associated with many distressing symptoms, including dysmenorrhea, chronic pelvic pain, dyspareunia and infertility [4, 5, 6].

Infertility is often the only symptom of endometriosis. Only many years of unsuccessful attempts to conceive lead to the diagnostic process and, as a consequence, diagnosis of endometriosis. According to Radwan J. et al., in women with asymptomatic endometriosis the probability of conception in the natural cycle drops significantly to 0.02–0.1, while in healthy women – 0.15–0.2.

As a result of pathological processes occurring in endometriosis, pelvic anatomy disorders and adhesions may appear, as well as impaired function of the fallopian tubes, ovaries or implantation disorders in the endometrium [7]. These women also often need ART (artificial reproduction technique) procedures, what sometimes can generate a slightly higher risk of pregnancy complications and risk of caesarean section. According Ibiebele et al. Endometriosis and ART are independent risk factors of pregnancy outcomes, specially ante-partum haemorrhage [8]. Additionally, Stern et al. observed increased risk of plancetal disfunction [9]. The rate of caesarean deliveries in patients after ART is much higher than in patients who conceived naturally and in whom not only elective section is performed significantly more often, but also emergency incisions are performed (usually as a result of pregnancy complications). In addition, a different percentage of c-section was fund, depending on the assisted reproductive method used (more often after ICSI, and fresh or frozen embryo transfer) [10].

The percentage of caesarean deliveries in Poland is much too high, oscillating around 48%, while the WHO considers about 10% to be normal. The percentage of c-sections above 10% does not reduce maternal and neonatal mortality, which is the goal of caesarean sections [11] [12].

It is difficult to determine the exact cause, but taking into account the risk of operative delivery and possible complications in subsequent pregnancies, efforts should be made to reduce the cesarean section rate. So far, although some studies have not found any association between endometriosis and pregnancy complications, others have found such an association. Among them, a pre-term delivery and a higher caesarean section rate are reported predominantly.

Laparoscopy is usually the only method which enables to ascertain the expected diagnosis of endometriosis. Diagnosis should be reinforced by biopsy because visual diagnosis alone can lead to misdiagnosis even in 25% of cases. Symptom relief is achieved in most patients after successful ablation or resection of pathological tissues. Nevertheless, the recurrence rate is as high as 50–80% [13].

It is speculated that endometriosis may promote the occurrence of adverse obstetric outcomes in affected pregnant women. The eutopic endometrium and junctional zone have been reported to be abnormal at molecular and functional levels, which leads to impairment of endometrial growth, maturation and decidualization, endometrial receptivity, defective spiral artery remodeling, and defective deep placentation [6,14,15]. Defective artery remodeling is a typical feature of preeclampsia and associated with a spectrum of pregnancy complications, including preterm labour and FGR.

Progesteron resistance is also known in endometriosis patients as a disturbing factor for embryo implementation [16]. This is the result of a reduced expression of the progesterone receptor B/A due to the activity of pro-inflammatory immunomodulators in the peritoneal fluid in women with endometriosis [17].

The pathological mechanisms mentioned above are well known, but clinical data regarding pregnancy outcomes are highly ambiguous.

The current study was designed to examine the influence of endometriosis on pregnancy and course of labour in patients diagnosed with endometriosis in the Clinic of Foetal Medicine and Gynaecology at the Medical University in Łódź, Poland. Based on the results obtained, the authors discuss the current literature and highlight the necessity for the close observation of endometriosis patients at child bearing age.

OBJECTIVES

The aim of the study was to elucidate the influence of endometriosis on pregnancy and the course of labour, as well as outcomes for foetal growth.

MATERIALS AND METHOD

A retrospective case-control study was conducted in the 1st Department of Gynaecology and Obstetrics of Medical University in Łódź. 120 medical records were analyzed of women diagnosed laparoscopically for infertility or infertility and pelvic pain, who were followed-up for 5 years after initial diagnosis. The endometriosis group consisted of 30 women diagnosed and pharmacologically-treated for endometriosis at the above Gynaecological and Obstetrics Department, who became pregnant after confirmation and treatment of the disease. This group of patients was closely followed-up since the diagnosis because of their participation in a separate study on angiogenesis and danazol treatment in endometriosis. A control group consisted of 30 healthy mothers who were selected randomly from the patients hospitalized for labour – from the years corresponding the 5-year follow-up period for the endometriosis group. Endometriosis was excluded in these women during a routine interview and medical examination while they were hospitalized because of the labour. They denied painful periods, painful intercourses, any other pain symptoms in the pelvis, infertility, being diagnosed for ovarian endometrial cysts or deep infiltrating endometriosis. Exclusion criteria for both groups were also because of any other comorbidities, e.g. hypothyroidism, hypertension, anamnesis of cancer or pelvic inflammatory disease, auto-immunological disorders or impaired glucose tolerance before pregnancy.

The study was conducted in accordance with the Declaration of Helsinki for Medical Research involving human subjects. The study protocol was approved by the Bioethical Commission of Medical University of Łódź. Informed consent was obtained from the patients either on-site or during a phone call.

A questionnaire was applied in which following factors were evaluated:

- Demographic
- Obstetric
- Complications during pregnancy

Definitions. *Preterm labour* – the state of delivery 37 weeks prior to gestation. PIH(pregnancy-induced hypertension) includes gestational hypertension and preeclampsia.

Table 1. Demographic data in the questionnaire

1. Have you ever smoked cigarettes?	☐Yes, ☐No
2. What is your education?	☐Primary ☐Secondary ☐Higher
3. Age	
Pregnancy	
4. How did you conceive your baby?	☐natural ☐stimulation ☐insemination ☐*in vitro*
5. Was it your first pregnancy?	☐Yes, ☐No
If it was your first pregnancy, please go to question number 7.	
6. If it was not your first pregnancy, how many pregnancies have you had?	
7. Have you ever had:	
a) a miscarriage	a) ☐Yes, ☐No
b) an ectopic pregnancy	b) ☐Yes, ☐No
8. Was it a singleton pregnancy?	☐Yes, ☐No
9. How long have you been trying to conceive a baby after confirmation of the diagnosis?	
10. What symptoms of endometriosis occured before a pregnancy?	
Obstetric complications	
11. Were you suffering from a pregnancy-induced hypertension during pregnancy?	☐Yes, ☐No
12. Did you have a preeclapmsia?	☐Yes, ☐No
13. Did you have a placenta previa?	☐Yes, ☐No
14. Did you have a placental abruption?	☐Yes, ☐No
15. Did you have a preterm labour?	☐No ☐Spontaneous preterm delivery ☐Premature rupture of membranes ☐Maternal or fetal indications for cesarean section
16. Was the baby delivered by caesarean section?	☐Yes, ☐No
17. Was foetal growth restriction diagnosed in the USG examination?	☐Yes, ☐No
18. Was the state of small-for-gestation-age recognized in the newborn?	☐Yes, ☐No

Gestational hypertension – refers to elevated blood pressure ≥140/90 mmHg after 20 weeks of gestation in a previously normotensive woman.

Preeclampsia – gestational hypertension with proteinuria (≥300 mg/24 h).

Placenta previa – the presence of placental tissue that reaches or extends over the internal cervical os.

Placental abruption – bleeding at the decidual placental interface that causes partial or total placental detachment before delivery of the fetus.

FGR (Foetal Growth Restriction) – defined as an estimated foetal weight below the tenth percentile for gestational age and gender based on sonography when foetus is unable to achieve its genetically determined potential size due to various pathological conditions.

SGA (Small for Gestational Age) – birth weight below the tenth percentile for gestational age and gender (for term infants, the standard is <2500 g.).

PPROM – preterm premature rupture of membranes; rupture of membranes usually should occur during labour.

Statistical analysis. Analysis of the data was performed using STATISTICA version 10. The categorical variables were assessed using the Chi-square test with Yates correction. Contingency tables were used to evaluate the association between endometriosis and adverse obstetric outcomes. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using MedCalc. P<0.05 was considered to be statistically significant.

RESULTS

The exposed group with endometriosis and the control group without endometriosis were compared by age, gravidity, smoking and education. In the endometriosis group an increased risk of caesarean section was noted in comparison with women without endometriosis. (OR 4.9, 95% CI 1.61–15.07).

Table 2. Demographic characteristic of women with and without endometriosis

CHARACTERISTICS	WOMEN WITH ENDOMETRIOSIS n=30 (n [%])	WOMEN WITHOUT ENDOMETRIOSIS n=30 (n [%])	P
Maternal age (years) mean ± SD	34.7±4.7	29.8±4.9	0.001
Gravidity			
1	20 (66.7)	15 (50)	0.14
2	10 (33.3)	13 (43.3)	
3	0	2 (6.7)	
Smoking			
Yes	7 (23.3)	6 (20)	0.75
No	23 (76.7)	24 (80)	
Education			
Higher	26 (86.6)	21 (70)	0.13
Secondary/Primary	4 (13.4)	9 (30)	

A significant difference was observed in maternal age – women with endometriosis were older than those without endometriosis (34.7 ±4.7 vs. 29.8±4.9 years; p=0.001). Both groups were also compared by obstetric's complications (Tab. 3).

Table 3. Adverse obstetric outcomes in women with and without endometriosis

ADVERSE OBSTETRIC OUTCOME	WOMEN WITH ENDOMETRIOSIS n=30 (n [%])	WOMEN WITHOUT ENDOMETRIOSIS n=30 (n [%])	OR (95% CI)	*P*
Caesarean section	18 (60)	7 (23)	4.9 (1.61-15.07)	0.0052
Preterm labour	5 (16.7)	7 (23)	0.657 (0.18-2.36)	0.5
FGR	10 (33.3)	5 (16.7)	2.5 (0.735-8.5)	0.14
SGA	9 (30)	5 (16.7)	2.14 (0.62-7.39)	0.227
Placenta previa	1	0	-	-
Placental abruption	1	0	-	-
PIH	4 (13.3)	2 (6.67)	2.15 (0.36-12.76)	0.398

No significant differences were observed in the incidence of preterm labour, FGR, SGA and PIH between the two groups. Two outcomes: placenta previa and placental abruption could not be compared due to lack of cases in the control group.

DISCUSSION

Endometriosis is associated with a chronic pelvic inflammatory process, for which there are well documented studies confirming increased levels of neuromodulators and other markers in the peritoneal fluid of women with endometriosis [3,18]. Abnormal endometrial function and difficulties with implantation of pregnancies have also been described [7].

It is speculated that endometriosis may promote the occurrences of adverse obstetric outcomes in affected pregnant women. The results of current studies are conflicting: while some studies found no association, others did find an association. Kobayashi et al. summarized the current reports and concluded that there are more data on different complications during pregnancy in endometriosis patients. He also suggested that there is limited evidence from a few studies that surgical excision of endometriosis may not reduce the risk of adverse pregnancy outcomes [19].

Among those authors who did find an association, preterm labour is reported as being predominating [20,21,22,23]. However, according to Juang et al. and Shin et al., the risk of preterm birth is higher only in women with adenomyosis [24,25], whereas Fernando et al. came to the same conclusion only with endometrioma [26]. He pointed out that the rates of preterm birth and SGA babies doubled in infertility patients with ovarian endometriomata who required ART [26]. On the other hand, Bengalia et al. did not observe any relationship between preterm delivery and SGA in endometriosis patients, compared to healthy controls. Furthermore, he observed that neither endometriosis nor IVF increased rate of preterm births [27].

Conti et al. noticed that the frequency of diabetes and SGA is higher in patients with endometriosis in anamnesis [21]. On the other hand, Warzecha et al. found no increased risk of PIH, preeclampsia or FGR [28]. The same conclusion, that endometriosis is not a risk factor of pregnancy complications, was reached by Tzur et al. [29]. Both Warzecha and Tzur observed a higher rate of acesarean sections in patients identified with endometriosis.

Hong Lin et al., examining a group of 249 patients endometriosis, found that women with endometriosis were at a higher risk of preterm labour, placenta previa, and caesarean section during pregnancy [30]. Sorrentino et al, also attempted to show correlation between women with a history of endometriosis and further obstetric complications. They confirmed the relationship between the percentage of operative deliveries, and all the complications studied in the questionnaires used in the current study [1].

Borisova et al. summed up studies which confirmed a higher risk for miscarriage in endometriosis patients [31]. Only single studies by Gonzaleza et al. and Yanga et al. failed to find any such correlation [32,33]. Lalani et al. also observed an increased risk of PPROM [34]. An increased risk of PE or hypertensive conditions and placental abnormalities (placenta previa, placental abruption) is also debatable, although most studies confirm an increased risk.

Borisova summarized the likely pathogenesis of pregnancy complications by analyzing the available literature, and concluded that in patients with endometriosis as a result of chronic inflammation, the activity of immunomodulators (natural killers, macrophages, IL-6, IL-1ß, TNF-a, prostaglandin E2 and cyclooxygenase (COX)-2) occurs in estrogen dependent reactions. Also, the junctional zone (between endometrium and myometrium) becomes defective by modulation of the extracellular matrix by prostaglandin secretion, as well as the influence of hormones, cytokines, neurohormones, and growth factors (vascular endothelial growth factors – VEGF, by VEGFR receptor-1 or Soluble FMS-like tyrosine kinase-1 [sFlt-1]). Luteal phase deficiency, progesterone resistance and adhesions are also an important phenomenon that could be responsible for early pregnancy complications in endometriosis patients [31]. On the other hand, Perez-Lopez denied any increased risk of PE, HELLP or increased blood pressure in endometriosis pregnant population [35].

Almost all the cited papers confirm the increased percentage of caesarean sections performed in patients with a history of endometriosis. The current study also confirms an increased percentage of caesarean sections, but without analyzing the indications for caesarean section other than the outcomes studied.

Warzecha et al. described the differences between indications for caesarean section in endometriosis patients and healthy subjects. He confirmed a higher rate of caesarean sections in the study group, with the main indications being a previous history of infertility/ART (elective CS, 27.9%) and excessive bleeding/ haemorrhage during labour (emergency CS, 13.9%). In the study group, the most frequent known reason for obstetric haemorrhage was placental abruption. On the contrary, the most frequent indications for performing an operative delivery in healthy subjects was previous caesarean section and labour arrest [28]. Zullo et al. also confirmed the increased risk of caesarean delivery and pregnancy complications [23].

On the basis of the above-mentioned data, it is easy to conclude that one of the indirect causes of the operative delivery is long infertility and conceiving through ART procedure. Women with endometriosis are significantly older when they become pregnant, they are also often after prolonged infertility treatment which is also sometimes an indication for caesarean section

Some studies report that the advanced age of the mother is a risk for pregnancy complications that require a quick termination by caesarean section [36]. Moreover adenomyosis in anamnesis is a risk factor of operative delivery [15,37]. There are unfortunately only very low quality data concerning endometriosis resulting in a highest risk emergency delivery due to intra-labour haemorrage.

Some limitations of the current study have to be recognized: 1) although the sample size was relatively small, some significant results were obtained. 2) The women with endometriosis selected for the study were treated with danazol, and then followed-up in another study for five years. 3) Both methods of conception: spontaneous and artificial were reported by the patients. In the study group seven of the 30 patients tried assisted reproductive technology, whereas in the control group, all 30 patients embraced natural methods. 4) Finally, the study is was a single-center analysis. In the light of the most recently published opinion, this could be the most biasing factor.

From 1997–2014, Berlac et al. conducted retrospective research based on a national cohort in Denmark that included all delivering women and their newborns; they concluded that almost all pregnancy complications occurred more frequently in women with endometriosis [38]. However, while analyzing such a large study, one should keep in mind that it is a study on data gathered for a national healthcare system which could not exactly reflect the severity of the complications. Another limitation of Berlacs' study is that data were adjusted for maternal age and obesity, but not for other important factors, such as previous surgery on the uterus (i.e. caesarean section, myoma excision) which could have biased the rate of placental complications in women with endometriosis.

The women in the current study were closely monitored both during and after treatment (surgical and pharmacological) for endometriosis. This fact may be responsible for the small rate of other complications during pregnancy in the studied endometriosis patients. Many researchers have considered the effects of endometriosis at each stage of pregnancy, and many studies have been carried out done on this topic; however, most studies have been conducted in small centres with small groups of patients, which makes it impossible to draw uniform general conclusions about the relationship of the effects on complications.

The increasing percentage of caesarean sections worldwide is worrying in the context of long-term effects for the women and the children born. Caesarean delivery is a procedure, combined with risk during the operation and after procedure (bleeding, surgical complications, infections, prolonged hospitalization), as well as the long-term effects for the women and children: risk of future uterine rupture in the next pregnancy or abnormal placentation of the gestational sac or trofobast, adhesions, formation of new endometriosis foci, infertility, and many others [37].

The benefits of caesarean section, e.g. lowering the risk of perinatal hypoxia, urinary incontinence in the mother, or prolapse of the reproductive organ, do not outweigh the possible risks of a too high rate of operative deliveries when taking the whole population into consideration [39]. In order to reduce the rate of caesarean sections in endometriosis patients, this population should be very closely monitored, even before pregnancy. Special attention should also be given them during pregnancy to lower the patient's fear combined with possible complications. Prospective studies on prophylaxis, psychological help or the influence of cooperation with midwifes on endometriosis women are highly required to prove whether the rate of operative deliveries can be reduced in this special group of patients.

CONCLUSION

The study suggests that women with endometriosis are at higher risk of caesarean section as a method of delivery. These females concerned also need more time to conceive, with the implication that they are at an older age at the time of pregnancy.

Prospective studies on a large and diverse group of patients are needed to establish clear associations between different endometriosis forms and pregnancy complications, and to find the best management strategy for this special group of patients during pregnancy.

Conflict of interest

The authors have no conflict of interest to declare.

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