ORIGINAL ARTICLE

CONTENTS

Pregnancy outcomes after assisted reproductive technology among women with endometriosis in Ukraine: results a multicenter study

Aidyn G. Salmanov[1,2], Volodymyr V. Artyomenko[3], Victor O. Rud[4], Olena A. Dyndar[5], Oleksandra Z. Dymarska[5], Svitlana M. Korniyenko[3], Orusia A. Kovalyshyn[6], Anastasia S. Padchenko[7], Vitalii S. Strakhovetskyi[8]

[1]SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE
[2]INSTITUTE OF PEDIATRICS, OBSTETRICS AND GYNECOLOGY OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE, KYIV, UKRAINE
[3]ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE
[4]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE
[5]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[6]LVIV MEDICAL INSTITUTE, LVIV, UKRAINE
[7]KYIV PERINATAL CENTER, KYIV, UKRAINE
[8]MEDICAL CENTRE "ASHERA", KHARKIV, UKRAINE

ABSTRACT

Aim: To evaluate the association between adverse pregnancy outcome, assisted reproductive technology (ART) and a previous diagnosis of endometriosis in Ukraine.

Materials and Methods: We conducted a multicentre retrospective cohort study was based on infertility surveillance data among women reproductive age from January 1st, 2017 to December 31st, 2021 in Ukraine. The patients from 10 Ukrainian regions who achieved singleton pregnancy by ART were included in this study. Linked hospital, pregnancy/birth and mortality data were used. Logistic regression analysis was performed to calculate odds ratios (OR) and 95 % confidence interval (CI) for the rates of adverse pregnancy outcomes.

Results: During study period within the cohort of 11,271 singleton births, 94 women with endometriosis diagnosed before birth delivered 102 infants. Compared with women without endometriosis, women with endometriosis had higher risks of preterm birth [adjusted odds ratio 1.33, 95% confidence interval (CI), 1.23-1.44]. Women with endometriosis had higher risks of antepartal bleeding/placental complications, pre-eclampsia and Caesarean section. There was no association between endometriosis and risk of SGA-birth or stillbirth.

Conclusions: Endometriosis and ART use are both independently associated with increased risk of preterm birth, antepartum haemorrhage, placenta praevia and planned birth. These findings are clinically relevant to obstetricians for distinguishing high- and low-risk pregnancies. Pregnant women with endometriosis require increased antenatal surveillance.

KEY WORDS: assisted reproduction technology, endometriosis, adverse pregnancy outcome, reproductive epidemiology, Ukraine

Wiad Lek. 2024;77(7):1303-1310. doi: 10.36740/WLek202407101 DOI

INTRODUCTION

Women infertility is one of the most important complications in gynecology. The World Health Organization has identified infertility as a global public health problem. The global prevalence of infertility among females is reported to be 3.5% -16.7% [1]. The high prevalence of infertility worldwide, implies that the current assessment of the women reproductive system is far from perfect.

According to the literature, as a result of advances in technology and provision of services, an increasing number of infants are born as a result of assisted reproductive technology (ART) therapy. In developed countries, ART pregnancies represent 1.7% to 4.0% of all births [2], while 0.7% to 1.5% of all births in Ukraine are the result of ART. An estimate of at least 12 million births have resulted from assisted reproduction techniques, as announced by International Committee Monitoring Assisted Reproduction Technologies (ICMART) in the European Society of Human Reproduction and Embryology (ESHRE) meeting in 2023. Incorporating techniques such as intracytoplasmic sperm injection

(ICSI) and testicular sperm extraction (TESE), the rate of Assisted Reproduction Technique (ART) births is expected to surpass 4% of total births [3,4].

One of the causes of female infertility is a history of endometriosis [5]. Endometriosis is common gynecological disease in Ukraine, affecting 20% of reproductive age women and 50% of women seeking infertility evaluation. Recent epidemiological studies reported an association between endometriosis and adverse pregnancy outcomes. Some studies reported increased incidences of preterm birth, pregnancy-induced hypertension (PIH), and small for gestational age (SGA) babies in women with endometriosis, suggesting that endometriosis affects pregnancy outcomes [6,7].

Women with endometriosis are more likely to have difficulty conceiving and tend to receive infertility treatment, including assisted reproductive technology (ART) therapy, which in itself is a risk factor for preterm birth, PIH, and SGA babies [8,9]. However, concern is mounting over the safety of ART and its effect on maternal and fetal well-being. ART pregnancies have a significantly higher risk of multiple pregnancy and adverse perinatal outcomes, including preterm delivery, low birth weight, and birth defects. The most studies have suggested an increased risk of preeclampsia, gestational hypertension, placenta previa, and gestational diabetes in ART pregnancies [10, 11]. There is increasing evidence that pregnancies after Assisted Reproduction Techniques (ART) are associated with pre-term birth, low birthweight, congenital defects, and increased mortality rates [12].

Currently, no cohort study has yet examined the effects of endometriosis on pregnancy outcomes in pregnant Ukrainian women. Furthermore, it is unclear whether pregnancy outcomes in women with endometriosis are affected by ART. To our knowledge, only a few studies were conducted to study infertility in Ukraine within narrow clinical features [13, 14].

AIM

The aim of this study was to evaluate the association between adverse pregnancy outcome, ART and a previous diagnosis of endometriosis in Ukraine.

MATERIALS AND METHODS

DESIGN, SETTING AND STUDY POPULATION

We conducted a multicentre retrospective cohort study was based on infertility surveillance data among women reproductive age from January 1st, 2017 to December 31st, 2021 in Ukraine. We compiled list of the 15 Privat medical centers for family planning and reproductive health and 20 public maternity hospitals. Of these, only 12 medical centers and 14 maternity hospitals from 10 regions of Ukraine agreed to take part in our study. Participants: all female residents of Ukraine aged 19-45 years and their index singleton pregnancy of at least 20 weeks gestation or 400 g birthweight. The patients with endometriosis and without endometriosis who achieved singleton pregnancy by ART were included in this study. Exclusion criteria: complications before pregnancy including endometrial cancer, cervical cancer and post-canization.

DEFINITION

The definitions used in this study for the diagnosis of these complications was as follows. Antepartal haemorrhage/placental complications were defined as placental abruption, placenta praevia and other reasons for antepartal bleeding. Preterm birth was defined as delivery before 37 complete weeks of gestation. Placenta previa was defined as the condition in which the placenta at least partially covered the internal ostium. SGA defined as an infant weight less than the 10th percentile for the gestational age. Gestational age was determined on the basis of menstrual history, a prenatal examination, and ultrasound findings, such as gestational sac diameter, crown rump length, and biparietal diameter. ART includes information on vitro fertilization (IVF) treatment for the present pregnancy. Parity was categorized into nulliparous or parous women. Maternal age was defined as age in completed years at the time of delivery and was categorized as ≤20, 21–25, 26–30, 31–35 or 36 years and older. Women were categorized according to the Body mass index (BMI) as lean (BMI < 20.0 kg/m^2), normal (BMI 20.0–24.9), overweight (BMI 25.0–29.9) and obese (BMI of 30.0 or more). Women were categorized as non-smokers, moderate smokers (one to nine cigarettes per day), or heavy smokers (at least10 cigarettes per day).

DATA COLLECTION

In Ukraine, maternal characteristics are recorded in a standardized manner during a woman's first visit for antenatal care, which occurs before the 15th week of gestation in more than 95% of the pregnancies. Linked hospital, pregnancy/birth and mortality data were used. Infant outcomes were derived from birth data and included preterm birth. Data on endometriosis is based on diagnosis of discharge or out-patient visits at hospitals in Ukraine before delivery. The demographic data included the patient's age, parity, past medical

Table 1. Characteristics of women delivering singleton infants and univariate associations with risk of preterm birth in Ukraine, 2017-2021

Variable	Number of births (n= 11219)	Preterm birth (≤36 Weeks)		
		No. of cases (n= 560)	Rate per 100 births (%)	OR (95% CI)
Endometriosis				
Yes	102	7	6.86	1.39 (1.30–1.49)
No*	11,117	553	4.97	1.00
Age (year)				
≤20	225	15	6.66	1.28 (1.22–1.34)
21–25*	1,755	94	5.36	1.00
26–30	3,867	183	4.73	0.88 (0.86–0.90)
31–35	3,571	165	4.62	0.86 (0.84–0.88)
≥36	1,791	100	5.58	1.05 (1.02–1.07)
Data missing	10	2	–	
Parity				
0	4,833	299	6.19	1.54 (1.51–1.56)
≥1*	6,386	261	4.09	1.00
BMI (kg/m^2)				
≤19.9	982	53	5.39	1.22 (1.19–1.26)
20·0–24·9*	5,220	233	4.46	1.00
25·0–29·9	2,181	105	4.81	1.08 (1.06–1.10)
≥30·0	862	50	5.80	1.32 (1.29–1.36)
Data missing	1,974	119	–	–

Note:
OR, odds ratio; CI, confidence interval.
*The births with this characteristic served as the reference group. Values are based on live births.

history including surgical records, suspected causes of infertility, the number of transferred embryos and pregnancy outcomes. Data collection was performed by extracting data from medical records. We analyzed following adverse pregnancy outcomes: preterm birth, placenta previa, and SGA birth, stillbirth, Caesarean section, pre-eclampsia and antepartal haemorrhage. The women who had laparoscopically diagnosed endometriosis and women who were suspected to have endometriosis by transvaginal ultrasound or medical history but did not undergo laparoscopy were categorized as endometriosis. The other women who were not suspected to have endometriosis by transvaginal ultrasound or in whom the presence of endometriosis was denied by laparoscopy were categorized as denied presence of endometriosis. Gestational age was primarily based on prenatal ultrasound measurement if present or otherwise estimated on the recorded date of the first day of the last menstrual period. Information about stillbirth at 28 weeks of gestation or later, birthweight, and infant sex was obtained from the standardized paediatric record, routinely filled out immediately after delivery. The current study limited the analysis to women who delivered a singleton live birth or stillbirth at ≥22 weeks of gestation.

ETHICS

The study was approved by Shupyk National Healthcare University of Ukraine. The board did not require the women to provide informed consent. Ethical principles such as discretion and confidentiality, and beneficence and nonmaleficence to participants were strictly adhered to.

STATISTICAL ANALYSIS

All statistical analyses were performed using the SAS software (SAS Institute Inc., Cary, NC, USA). Fisher's exact test was used to calculate p values for the comparison of maternal characteristics with or without endometriosis. We used unconditional logistic-regression analysis to evaluate the association between diagnosis of endometriosis and preterm delivery and SGA birth. We also investigated the possible association between endometriosis and stillbirth, Caesarean section, pre-eclampsia

Table 2. Maternal characteristics associated with endometriosis among women delivering singleton infants in Ukraine, 2017-2021

Variable	Endometriosis			
	Yes		No	
	Number of births (n= 102)	Percentage of births, %	Number of births (n= 11,169)	Percentage of births, %
Age (year)				
≤20	–	–	227	2.03
21–25	6	5.88	1,757	15.73
26–30	25	24.5	3,856	34.52
31–35	40	39.2	3,547	31.75
≥36	31	30.39	1,771	15.85
Data missing	–	–	11	–
Parity				
0	47	46.07	4,815	43.11
≥1	55	53.93	6,354	56.89
BMI (kg/m^2)				
≤19.9	9	8.82	1,185	10.61
20.0–24.9	60	58.86	6,302	56.42
25.0–29.9	25	24.61	2,633	23.57
≥30.0	8	7.71	1,049	9.39

Note: BMI, Body mass index.

and antepartal bleeding. Odds ratios (OR), presented with 95% confidence intervals (CI) were calculated before and after adjustments for maternal characteristics. The estimates were adjusted for maternal age, parity, education, BMI, smoking and calendar year of birth of the child. In order to adjust for the effect of repeated pregnancies, estimates were calculated using the generalized estimating equation method with no major differences in the results. A *P* value of <0.05 was considered statistically significant.

RESULTS

During study period (2017-2021) within the cohort of 11,271 singleton births, 94 women with endometriosis diagnosed before birth delivered 102 infants. Among the 11,271 singleton births 37 cases of stillbirth (rate 3.28 per 1000 births). In this study the rate of preterm birth was higher among women with endometriosis compared with women without endometriosis. Women with low and high maternal age, with high or low BMI, and nulliparous women had higher rates of preterm birth. Characteristics of women delivering singleton infants and univariate associations with risk of preterm birth in Ukraine are presented in Table 1.

In this study compared with women without endometriosis, women with endometriosis were of higher maternal age and were more likely to be primiparous. There were no major differences in BMI and parity between women with and without endometriosis. Maternal characteristics associated with endometriosis in women giving birth to singleton children in Ukraine are shown in Table 2.

In the multivariable analysis we adjusted for confounders known to be associated with adverse pregnancy outcome, such as maternal age, parity and BMI. In the adjusted model, the OR for preterm birth was 1.33 (95% CI, 1.23–1.44). For preterm birth we also categorized deliveries into spontaneous and induced (Caesarean section) preterm birth. In present study the risk associated with endometriosis was higher for induced preterm birth, OR 1.61, 1.41–1.83, compared with spontaneous preterm birth, OR 1.22, 1.11–1.34. Crude and adjusted odds ratios (AORs) for adverse pregnancy outcome in women with and without endometriosis among singleton births in Ukraine are presented in Table 3.

In the multivariate analysis, endometriosis disease was not associated with risk for SGA birth or stillbirth. In this study as compared with women without endometriosis, women with endometriosis were at increased risk of pre-eclampsia. Among women with endometriosis the risk of antepartal bleeding including placental disorders was increased. Caesarean section was more common among women with endometriosis compared with women without endometriosis, and the risk was highest for prelabour Caesarean section. The use of ART was more prevalent in women with endometriosis compared with women without endometriosis (data not shown).

Table 3. Crude and adjusted odds ratios (AORs) for adverse pregnancy outcome in women with and without endometriosis among singleton births in Ukraine, 2017-2021

Adverse pregnancy outcome	Endometriosis (n=102)		No endometriosis (n=11,169)		Crude (95% CI)	Adjusted (95% CI)
	n	%	n	%		
Preterm Birth (≤36 Weeks)*	7	6.86	556	4.98	1.39 (1.30–1.49)	1.33 (1.23–1.44)
SGA-Birth	3	2.94	266	2.38	1.17 (1.05–1.30)	1.04 (0.92–1.17)
Stillbirth	1	0.98	36	0.32	1.23 (0.94–1.61)	1.02 (0.74–1.40)
Pre-eclampsia	4	3.92	322	2.88	1.17 (1.06–1.29)	1.13 (1.02–1.26)
Antepartal bleeding/placental complications	3	2.94	151	1.35	1.95 (1.75–2.18)	1.76 (1.56–1.99)
Caesarean section*	22	21.57	1,506	13.48	1.76 (1.69–1.84)	1.47 (1.40–1.54)

Note

SGA: small-for-gestational-age

Odds ratios have been adjusted for maternal age, BMI, parity, and year of birth of the child.

*For preterm birth and Caesarean section values are based on live births.

DISCUSSION

The results presented multicentre retrospective cohort study was based on infertility surveillance data among women reproductive age in Ukraine. In this study including 11,271 singleton births we assessed the association between adverse pregnancy outcome (preterm birth, SGA birth, stillbirth, Caesarean section, pre-eclampsia and antepartal haemorrhage), ART and a previous diagnosis of endometriosis in Ukraine. This study expands upon the previous reports [5, 11, 13, 14] and is the first study to publish the association between adverse pregnancy outcome, ART and a previous diagnosis of endometriosis in Ukraine. In the present study we found an increased risk of preterm delivery among women with endometriosis. We also found that women with endometriosis more frequently were affected by pre-eclampsia and antepartal haemorrhage. Moreover, delivery through Caesarean section was almost twice as common in this group as compared with women without endometriosis. In this study there was no association between endometriosis and risk of SGA-birth or stillbirth. The results from this study are accordance with previous studies [7, 15, 16].

ART pregnancy is known to carry a high risk of adverse pregnancy outcomes, compared with natural conception. However, the underlying mechanism of the increased risk for adverse outcomes in ART pregnancy remains unclear. Previous studies on obstetrical complications among women with endometriosis have demonstrated an increased risk of placental complications, leading to a higher risk of obstetrical hemorrhage in pregnancy and during labor. They also indicate a possible increased risk of preeclampsia, preterm birth (PTB) and low birthweight (LBW) [7,15-19]. Wennberg AL, et al. reported that the risk of placenta previa, cesarean delivery, PTB, and low LBW higher in ART than in spontaneous conception (SC) pregnancies for most maternal ages. In both ART pregnancies, the risk of hypertensive disorders in pregnancy (HDP), placenta previa, cesarean delivery, PTB, LBW, and SGA changed significantly with age. The AORs for adverse neonatal outcomes at advanced maternal age (>35 years) showed a greater increase in SC than in ART. The change in risk with age did not differ between ART for maternal outcomes at advanced maternal age [20]. However, these results have been inconsistent and often are based on small study populations. Also, the increased use of artificial reproductive techniques means that the women with endometriosis who become pregnant are different from populations studied earlier. Current consequences of endometriosis for pregnancy, birth and neonatal outcome therefore need to be clarified in a large contemporary cohort of women with endometriosis.

According to the literature, there are contradictory findings on the association between endometriosis and several adverse pregnancy outcomes, for example, some studies suggest increased risk of preterm birth, pregnancy hypertension and small-for-gestational age among women with endometriosis [7, 9]. However, many large studies including population-based cohorts have not considered the effect of ART use. This is important because women with endometriosis are more likely to have difficulty conceiving and are more likely to undergo treatment with ART, which has been shown to be associated with adverse pregnancy outcomes. Ibiebele I, et al. found increased risk of placenta praevia among women who used ART as well as among women who had endometriosis [15]. These

findings concur with studies among women who used ART that have consistently reported that those who also had endometriosis had increased risk of placenta praevia compared to those without endometriosis [16, 21]. The mechanisms underlying these observations are not entirely clear, although factors related to ART have been implicated. It has also been suggested that perturbed uterine peristalsis in women with endometriosis may influence the site of implantation and increase the risk of placenta praevia [22].

In this study we found endometriosis and ART use, separately and together, were independently associated with increased risk of antepartum haemorrhage. This finding was partially supported by Ibiebele I, et al., 2022 [15] and other studies that found increased odds of antepartum haemorrhage among women with endometriosis compared to those without endometriosis but further analysis among the subgroup of women who conceived using ART found no association between endometriosis and antepartum haemorrhage [23].

Our study found increased risk of planned birth (caesarean delivery or induction of labour) with both endometriosis and ART use independently and this may reflect the higher rates of placenta praevia in the endometriosis and ART groups. However, other studies did not find an association between endometriosis and induction of labour [23]. We found increased risk of preterm birth associated with endometriosis as well as ART use. This concurs with other cohort studies that found increased risk of preterm birth in women with endometriosis compared to women without endometriosis in both spontaneous and ART pregnancies [24]. Inflammation has been suggested as a possible pathway between endometriosis and preterm birth, while the underlying causes of infertility and ART procedures have been found to be associated with adverse pregnancy outcomes [15]. We observed an increased risk of pre-eclampsia among women with endometriosis. This finding is in contrast with other study, where pre-eclampsia surprisingly was found to be reduced in women with endometriosis [25]. However, several methodological aspects, including low response rate and possible selection bias may account for this result. In the present study, women with endometriosis generally had a lower BMI compared with women with no endometriosis, which is supported by other cohort study [26].

Our results suggest that women with endometriosis including those who used ART to achieve pregnancy are a higher-risk obstetric group requiring appropriate surveillance and management during their pregnancy. Against the background of the demographic crisis in Ukraine, which is characterized by a decrease in the birth rate and population depopulation, it is important to improve the reproductive health of the population, treat infertility, and help solve the problem of postponing the birth of children in wartime conditions. Improving the quality and accessibility of ART should become one of the priorities of the state's demographic policy.

STRENGTH AND LIMITATIONS

Our study has several strengths. To our knowledge, this is the first report in Ukraine to suggest the correlation of adverse pregnancy outcome, ART and a previous diagnosis of endometriosis in Ukraine. This study was only included ART pregnancies to avoid the influence of conception methods. This study expands upon the previous reports and is the first study to publish the association between adverse pregnancy outcome, ART and a previous diagnosis of endometriosis in Ukraine. No prior study on this issue is as large, up to date, or comprehensive in Ukraine. A limitation of this study was that we were not able to follow all women throughout their entire reproductive period. Therefore, the total number of deliveries and other pregnancy outcomes does not represent the full lifelong reproductive history. Some of the women with endometriosis were diagnosed solely based on clinical suspicion, some of which, therefore, could be misclassified. We were unable to assess the effect of endometriosis stage or typology on the study outcomes.

CONCLUSIONS

Pregnancies resulting from ART are associated with an increased risk of adverse perinatal outcomes compared with those following natural conception. We found that endometriosis to be a risk factor for preterm birth, irrespective of ART. Women with endometriosis may be more likely to be delivered by Caesarean section and to suffer from antepartal haemorrhage/placental complications and pre-eclampsia. These findings are clinically relevant to obstetricians for distinguishing high- and low-risk pregnancies. This information might be helpful for women and their providers when managing these pregnancies. Pregnant women with endometriosis require increased antenatal surveillance. Further studies are required to assess whether any modification is needed to conventional pregnancy monitoring for patients with endometriosis.

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The authors wish to acknowledge all the study subjects who provided us with the information required for conducting this study. The findings and conclusions in this study are those of the authors.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Aidyn G. Salmanov
Shupyk National Healthcare University of Ukraine,
9 Dorohozhytska St., 04112, Kyiv, Ukraine
e-mail: mozsago@gmail.com

ORCID AND CONTRIBUTIONSHIP
Aidyn G. Salmanov: 0000-0002-4673-1154 A C D E F
Volodymyr V. Artyomenko: 0000-0003-2490-375X B C D F
Victor O. Rud: 0000-0002-0768-6477 B C D F
Olena A. Dyndar: 0000-0002-0440-0410 B C D F
Oleksandra Z. Dymarska: 0009-0006-7275-9405 B C D F
Svitlana M. Korniyenko: 0000-0003-3743-426X B C D F
Orusia A. Kovalyshyn: 0000-0002-9710-0694 B C D F
Anastasia S. Padchenko: 0009-0007-6382-8955 B C D F
Vitalii S. Strakhovetskyi: 0000-0002-7528-1498 B C D F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.02.2024
ACCEPTED: 21.06.2024