REVAZ SULUKHIA [1,2], LARISA MELIA [1,2], NINO DAVIDOVA [2,3], LALI PKHALADZE [2,3]

PREGNANCY COMPLICATIONS IN PATIENTS WITH ENDOMETRIOSIS

[1]Gudushauri National Medical Centre, Department of Obstetrics and Gynecology; [2] Ivane Javakhishvili Tbilisi State University; [3] Zhordania and Khomasuridze Institute of Reproductology

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რევაზ სულუხია [1,2], ლალი მელია [1,2], ნინო დავიდოვა [2,3], ლალი ფხალაძე [2,3]

ორსულობის გართულებები ენდომეტრიოზის მქონე ქალებში

[1]ღუდუშაურის სახელობის ეროვნული სამედიცინო ცენტრი, მეანობა-გინეკოლოგიის დეპარტამენტი; [2]ივანე ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი; [3]ჟორდანიას და ხომასურიძის რეპროდუქტოლოგიის ინსტიტუტი

რეზიუმე

შესავალი: ენდომეტრიოზი არის ქრონიკული დაავადება, რომელიც იწვევს უნაყოფობას შემთხვევათა 40%-ში. არაეფექტური მედიკამენტური თერაპიის დროს ნაჩვენებია ინ ვიტრო განაყოფიერება (IVF). ენდომეტრიოზი არის დამოუკიდებელი რისკ-ფაქტორი დედისა და ბავშვის ავადობისთვის. ადრეული პრენატალური მონიტორინგი მნიშვნელოვანია ორსულობის გართულებების პრევენციისათვის.

მიზანი: ორსულობის გართულებების სიხშირის შეფასება და შედარება ენდომეტრიოზის მქონე ორსულ ქალებში უნაყოფობის მკურნალობის ტრადიციული მეთოდებისა და IVF-ის შემდეგ.

მეთოდები: რეტროსპექტული კვლევა მოიცავდა ორსულობამდე ლაპაროსკოპიით დიაგნოსტირებული სხვადასხვა ლოკალიზაციის ენდომეტრიოზის მქონე და უნაყოფობის გამო ნამკურნალევ 320 პაციენტს, რომელთა ასაკი იყო 28-46 წელი. პაციენტები დაიყო ორ ჯგუფად: I ჯგუფი - 170 ორსული, რომელთაც ჩაუტარდათ IVF და II ჯგუფი - 150 ორსული ქალი, რომელთაც ჩაუტარდათ ტრადიციული მკურნალობა. ორსულობის გართულება შეფასდა და გაანალიზდა სტატისტიკურად.

შედეგები: ქალებში ენდომეტრიოზით, IVF მკურნალობის შემდეგ, ორსულობის ყველაზე გავრცელებული გართულება იყო საკეისრო კვეთა - 79.4%, როგორც გადაუდებელი, ასევე არჩევითი. პრეეკლამპსიის სიხშირე ასევე მაღალი იყო - 54,7%. მომატებული იყო ნაადრევი მშობიარობის რისკიც - 49,4%, რაც არ განსხვავდებოდა II ჯგუფის მაჩვენებლისგან - 52,0%. იშვიათი გართულება იყო პლაცენტის წინამდებარეობა ორივე ჯგუფში: 10,6% და 4.0%. პლაცენტის აშრევების მხოლოდ რამდენიმე შემთხვევა გამოვლინდა ორივე ჯგუფში: 3.5% და 2%. ზოგადად, ორსულობის გართულებები ART ჯგუფში მნიშვნელოვნად მაღალი იყო ბუნებრივად ჩასახულ ორსულებთან შედარებით, ნაადრევი მშობიარობისა და პლაცენტის აშრევების გარდა.

დასკვნა: ინ ვიტრო განაყოფიერების შედეგად მიღებული ორსულობა ენდომეტრიოზის მქონე პაციენტებში უნდა ჩაითვალოს მაღალი რისკის ორსულობად ისეთი გართულებების მაღალი სიხშირის გამო, როგორებიცაა: საკეისრო კვეთა, პრეეკლამპსია და ნაადრევი მშობიარობა. აღნიშნული გართულებები შესაძლოა დაკავშირებული იყოს ენდომეტრიოზთან და უნაყოფობასთან და არა დამხმარე რეპროდუქციულ ტექნოლოგიებთან.

Introduction. Endometriosis is a chronic disease that affects between 5 to 15% of reproductive-aged women [1]. It may be more prevalent as up to 25% of cases are asymptomatic and can be a secondary finding during pelvic surgery or exploration for other reasons. Pelvic endometriosis is present in 6% to 43% of women undergoing sterilization, in 12% to 32% of women undergoing laparoscopy for pelvic pain, and in 21% to 48% of women undergoing laparoscopy for infertility. Endometriosis generally occurs at age 30-40. Delayed diagnosis by ±7 years is common [2].

According to medical statistics, infertility occurs in 40% of women with endometriosis [3]. The exact pathogenic mechanisms of endometriosis-related infertility remain unclear. Several factors have been proposed to account for this problem such as distorted tubo-ovarian anatomy, mechanical stretching, alteration in follicular microenvironment, impaired endometrial receptivity, chronic inflammatory changes in the pelvic cavity, and reduced oocyte and embryo competence [1].

For over a century, pregnancy has been considered to have beneficial effects on endometriosis and 'pseudopregnancy' induced through hormonal therapies has been recommended as a way to manage symptoms [4]. The coexistence of endometriosis and pregnancy was first described in 1904-1905. In the early 1920s, regression of endometriosis cysts during pregnancy or during lactation was observed in small case series. Beecham (1949) declared pregnancy as an efficient prophylactic and curative measure against endometriosis [5], however, it's hard to achieve for such patients.

At the same time, there are data concerning the increase in the incidence of pregnancy complications-intrauterine growth restriction, preeclampsia, antepartum hemorrhage, spontaneous hemoperitoneum in pregnancy, caesarean section and early pregnancy loss in women with endometriosis [6,7].

Bonavina and Tanbo described the mechanisms of infertility in the context of endometriosis, which is orientated towards four main directions: mechanical obstruction due to pelvic adhesions; local/systemic inflammatory processes accompanied by elevated cytokines in the peritoneal fluid; altered hormonal profile and genetic polymorphisms [8,9].

Other factors are responsible for poor implantation and pregnancy complications in patients with endometriosis. Glycosylation of the proteins of the endometrium is altered which causes less thick endometrium, thus - poor implantation. Progesterone receptor isoforms PR-A and PR-B on the stromal cell secrete paracrine factors and 17 beta-hydroxylase D2 which convert estradiol (E2) to estrone (E1). In endometriosis, there is downregulation of 17 beta-hydroxylase D2 and less expression of PR-B in the stromal cell which causes increased estrogen called progesterone resistance state [10]. The increased estrogen causes a positive feedback loop via COX -2 enzyme which causes an increase in prostaglandin E2 (PGE2) and prostaglandin F2A (PGF2A). So, these high inflammatory mediators cause uterine contractions, cervical ripening and preterm birth [6]. Endometriosis is also associated with abnormalities in the inner myometrium, a highly specialized and functionally distinct uterine structure known as the "Junctional Zone" (JZ).

Normal placentation is characterized by a full conversion of the spiral arteries into large uteroplacental vessels at the level of the JZ. Defective placentation is characterized by an absent or incomplete remodeling of these arteries and the primary site of the vascular abnormalities responsible for defective placentation has been suggested to lie in the JZ.

Defect in placentation is induced by part or complete lack of remodeling which may become the main reason for pre-eclampsia, preterm labor, premature rupture of membranes (PROM), intrauterine growth restriction (IUGR) [11]. Oxidative stress - reactive oxygen species ROS rise in endometriosis and cause adverse outcomes in pregnancy as pre-eclampsia [12].

High iron levels in ovarian endometriomas affect oocyte development and cause miscarriage in nulliparous.

According to Ghaheh et al., the incidence of placenta previa is ten times higher in endometriosis than in the general population. The coexistence of adenomyosis and endometriosis, and in particular the high prevalence of adenomyosis in patients with deep endometriosis, could act as a confounder in the placentation anomalies [13].

Unfortunately, a long period of unsuccessful tries of pregnancy establishes advanced maternal age, over 40 years and it became an independent risk factor for adverse pregnancy outcomes, particularly for the mother. Pregnancies in women over 40 years should be considered at risk and carefully monitored with individualized care protocols [14].

As endometriosis can cause fertility issues, such as blocked fallopian tubes, adhesions, or ovarian cysts, which can make it difficult to conceive physiologically, in such cases, in vitro fertilization (IVF) can be a more effective option for achieving pregnancy. IVF offers higher success rates for individuals with endometriosis-related infertility compared to natural conception. The key to successful IVF is embryo implantation. However, the average success rate of implantation is about 20% in the common population [15]. IVF may improve the conception rate in women with endometriosis by avoiding contact with the gametes and embryos with potentially toxic peritoneal and oviductal factors. At the same time, existing data confirmed, that women with IVF-conceived singletons are at increased risk of preeclampsia,

gestational diabetes, placenta previa, and perinatal mortality, Cesarean section (CS), both emergency and elective [16].

Many studies have been conducted on the treatment of endometriosis-associated infertility but very limited studies are available on the obstetric outcomes in pregnant women with endometriosis. Pregnancy complications are public health problems worldwide, which negatively impact health systems, and present a major reservoir of future disease. Early initiation of prenatal care and monitoring of pregnancy, are key to helping to prevent and treat severe pregnancy-related complications.

Objective. The objective of our study was to evaluate and compare the frequency of pregnancy complications in pregnant women with endometriosis after traditional treatment methods of infertility and after IVF.

Patients and Methods. The study was retrospective and included an analysis of 320 patients aged 28-46 years with different locations of endometriosis, diagnosed by laparoscopy before pregnancy and treated for infertility. Exclusion criteria were other forms of infertility. The study was conducted at Gudushauri National Medical Center. According to the treatment method, the patients were divided into two groups: I group – 170 pregnant women using the fertility treatment method – IVF and II group – 150 pregnant women conceived naturally after traditional treatment methods (was not specified), considered as a control. Estimated parameters include frequency of cesarean section, placenta previa cases, placenta abruption, preterm labor and pre-eclampsia.

Statistical Analysis. Descriptive statistical analyses of quantitative variables using SPSS (Statistical Social Science, version 21, Chicago, USA) were conducted. The results were considered statistically significant when the P value was less than 0.05 ($P<0.05$).

Results. The age of patients was 28-46 years with an average age of 33,25±4,39. The gestational age varies from 22 to 40 weeks of progressive pregnancy. The majority of our patients were nulliparous (68%). The overage age of pregnant women in the IVF group was 33,21±4,33 and in the group of natural pregnancy - 33,29±4,47. There was no statistically significant difference between the age between them ($P>0.05$).

After evaluation of pregnancy complications in both groups, the following results were received: the prevalence of cesarean section was significantly higher in patients after IVF -79,4% compared to naturally conceived pregnant women -38,7%, $P<0.05$; On the contrary, the rate of vaginal delivery was higher in the control group compared to IVF group: 61,3% vs. 20,6%, $P<0.05$. Preterm birth was increased in the IVF group compared to the control group: 52,0% vs. 49,4% respectively, but the difference was not significant, $P>0.05$; The abruption of the placenta was rare in both groups: 6 cases occurred in IVF patients (3,5%) and 1 case (0.7%) in patients treated with traditional methods of infertility. The difference between them was not significant, $P>0.05$; The prevalence of preeclampsia was higher in the IVF group: 54,7% compared to control 30%, $P<0.05$. Incidence of placenta previa was higher as well in the IVF group: 10,6% compared to the spontaneous pregnancy group: 4,0%, $P<0.05$.

Estimated parameters	Pregnant women after IVF (n=170)	Pregnant women conceived naturally (n=150)	P value
Cesarean Section	135 (79,4%)	58 (38,7%)	<0.05
Vaginal Delivery	35 (20,6%)	92 (61,3%)	<0.05
Preterm Birth	84 (49,4%)	78 (52,0%)	>0.05
Abruption of Placenta	6 (3,5%)	1 (0,7%)	>0.05
Preeclampsia	93 (54,7%)	45 (30%)	<0.05
Placenta Previa	18 (10,6%)	6 (4,0%)	<0.05

Discussion. Endometriosis and infertility often present together but the exact cause-effect mechanism of this association is unknown. When medical therapy is ineffective for endometriosis-related infertility, assisted reproductive technology may be required [17]. The study shows that endometriosis is an independent risk factor for mother and child morbidities. Maternal morbidity and perinatal morbidity were significantly increased by ART in addition to endometriosis [18]. Thus, estimating the risks of

pregnancy complications is essential for appropriate care of pregnant women with endometriosis using IVF treatment for infertility.

In our retrospective study, 320 pregnant women aged 28-46 years with gestational age from 22 to 40 weeks of pregnancy were included. Inclusion criteria were diagnosis of infertility and endometriosis, confirmed by laparoscopy before pregnancy. The forms of endometriosis were not specified. We have evaluated the pregnancy adverse outcome in two groups: I group – 170 pregnant women using the fertility treatment method – IVF and II group – 150 pregnant women conceived naturally.

In pregnant women with endometriosis after IVF treatment the most common pregnancy complication was caesarian section: 79,4% (n=135), both emergency and elective. The frequency of pre-eclampsia was also high in these patients: 54,7% (n=93). We observed the increased risk of preterm birth as well: 49,4% (n=84), however, the same trend was revealed in patients after treatment of endometriosis with traditional methods. In this group, preterm birth was revealed in half cases: 52,0% (n=78) and may indicate an association of this adverse outcome with endometriosis and not with ART. A relatively rare complication was placenta previa in both groups: 10,6% (n=18) and 4,0% (n=6) respectively. Only a few cases of placenta abruption were detected in both groups as well: 3,5 % (n=6) and 2% (n=4) respectively. In general, the adverse pregnancy outcome in the ART group was significantly higher compared to pregnant women conceived naturally, except for the preterm delivery and abruption of the placenta and matches with the data existing in the literature [18].

Conclusion. We concluded that IVF pregnancy in patients with endometriosis should be considered a high-risk pregnancy regarding adverse outcomes, such are: cesarean section, pre-eclampsia and preterm delivery. However, these pregnancy complications should be linked to the disease and infertility and may not be related to ART.

Our study groups were highly heterogeneous, thus future studies in homogenous groups and large cohorts are needed to confirm our findings.

References:

1. H. Dongye, Y. Tian, D. Qi, Y. Du, and L. Yan, "The Impact of Endometrioma on Embryo Quality in In Vitro Fertilization: A Retrospective Cohort Study," J Clin Med, vol. 12, no. 6, p. 12, Mar. 2023, doi: 10.3390/JCM12062416/S1.
2. H. Li et al., "Effects of Previous Laparoscopic Surgical Diagnosis of Endometriosis on Pregnancy Outcomes," Chin Med J (Engl), vol. 130, no. 4, p. 428, Feb. 2017, doi: 10.4103/0366-6999.199840.
3. A. Katole and A. Saoji, "Prevalence of Primary Infertility and its Associated Risk Factors in Urban Population of Central India: A Community-Based Cross-Sectional Study," Indian J Community Med, vol. 44, no. 4, pp. 337–341, Oct. 2019, doi: 10.4103/IJCM.IJCM_7_19.
4. P. Pirtea, E. Cicinelli, R. De Nola, D. de Ziegler, and J. M. Ayoubi, "Endometrial causes of recurrent pregnancy losses: endometriosis, adenomyosis, and chronic endometritis," FertilSteril, vol. 115, no. 3, pp. 546–560, Mar. 2021, doi: 10.1016/J.FERTNSTERT.2020.12.010.
5. G. Benagiano, I. Brosens, and D. Lippi, "The history of endometriosis," GynecolObstet Invest, vol. 78, no. 1, pp. 1–9, 2014, doi: 10.1159/000358919.
6. A. V. Borisova, S. R. D. Konnon, V. Tosto, S. Gerli, and V. E. Radzinsky, "Obstetrical complications and outcome in patients with endometriosis," J Matern Fetal Neonatal Med, vol. 35, no. 14, pp. 1–15, 2022, doi: 10.1080/14767058.2020.1793326.
7. S. Lalani et al., "Endometriosis and adverse maternal, fetal and neonatal outcomes, a systematic review and meta-analysis," Hum Reprod, vol. 33, no. 10, pp. 1854–1865, Oct. 2018, doi: 10.1093/HUMREP/DEY269.
8. G. Bonavina and H. S. Taylor, "Endometriosis-associated infertility: From pathophysiology to tailored treatment," Front Endocrinol (Lausanne), vol. 13, Oct. 2022, doi: 10.3389/FENDO.2022.1020827/FULL.
9. T. Tanbo and P. Fedorcsak, "Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options," Acta ObstetGynecolScand, vol. 96, no. 6, pp. 659–667, Jun. 2017, doi: 10.1111/AOGS.13082.

10. S. E. Bulunet al., “17β-Hydroxysteroid Dehydrogenase-2 Deficiency and Progesterone Resistance in Endometriosis,” SeminReprod Med, vol. 28, no. 1, p. 44, 2010, doi: 10.1055/S-0029-1242992.
11. S. Epelboinet al., “Endometriosis and assisted reproductive techniques independently related to mother-child morbidities: a French longitudinal national study,” Reprod Biomed Online, vol. 42, no. 3, pp. 627–633, Mar. 2021, doi: 10.1016/J.RBMO.2020.11.017.
12. A. Agarwal, A. Aponte-Mellado, B. J. Premkumar, A. Shaman, and S. Gupta, “The effects of oxidative stress on female reproduction: a review,” Reprod Biol Endocrinol, vol. 10, Jun. 2012, doi: 10.1186/1477-7827-10-49.
13. H. S. Ghaheh, A. Feizi, M. Mousavi, D. Sohrabi, L. Mesghari, and Z. Hosseini, “Risk factors of placental abruption,” J Res Med Sci, vol. 18, no. 5, p. 422, 2013, doi: 10.23946/2500-0764-2017-2-3-42-45.
14. L. Marozioet al., “Maternal age over 40 years and pregnancy outcome: a hospital-based survey,” J Matern Fetal Neonatal Med, vol. 32, no. 10, pp. 1602–1608, May 2019, doi: 10.1080/14767058.2017.1410793.
15. T. Fujii et al., “Assisted reproductive technology pregnancy complications are significantly associated with endometriosis severity before conception: a retrospective cohort study,” Reprod Biol Endocrinol, vol. 14, no. 1, Nov. 2016, doi: 10.1186/S12958-016-0209-2.
16. B. C. Tarlatzis and G. Grimbizis, “Pregnancy and child outcome after assisted reproduction techniques,” Human Reproduction, vol. 14, no. suppl_1, pp. 231–242, Sep. 1999, doi: 10.1093/HUMREP/14.SUPPL_1.231.
17. Z. Khan, “Fertility-related considerations in endometriosis,” AbdomRadiol (NY), vol. 45, no. 6, pp. 1754–1761, Jun. 2020, doi: 10.1007/S00261-019-02307-6.
18. S. Epelboin et al., “Endometriosis and assisted reproductive techniques independently related to mother-child morbidities: a French longitudinal national study,” Reprod Biomed Online, vol. 42, no. 3, pp. 627–633, Mar. 2021, doi: 10.1016/J.RBMO.2020.11.017.

РЕВАЗ СУЛУХИЯ [1,2], ЛАЛИ МЕЛИЯ [1,2], НИНО ДАВИДОВА [2,3], ЛАЛИ ПХАЛАДЗЕ [2,3]

ОСЛОЖНЕНИЯ БЕРЕМЕННОСТИ У ПАЦИЕНТОК С ЭНДОМЕТРИОЗОМ

[1]Национальный медицинский центр им. Гудушаури, Департамент акушерства и гинекологии;
[2]Государственный университет Тбилиси им. Иване Джавахишвили; [3] Институт Репродуктологии им. Жордании и Хомамаридзе

РЕЗЮМЕ

Введение: Эндометриоз является хроническим заболеванием связанное с бесплодием в 40%. При неэффективности медикаментозной терапии бесплодия, показано экстракорпоральное оплодотворение (ЭКО). Эндометриоз является независимым фактором риска заболеваемости матери и плода. Дородовое начало ухода и наблюдения за беременных являются ключевым в предотвращении тяжелых осложнений.

Цель: оценить и сравнить частоту осложнений у беременных с эндометриозом после традиционных методов лечения бесплодия и после ЭКО.

Методы: В ретроспективное исследование было включено 320 пациенток в возрасте 28-46 лет с различной локализацией эндометриоза, диагностированных при лапароскопии до беременности и получавших лечение по поводу бесплодия. Пациентки были разделены на две группы: I группа – 170 беременных с применением метода лечения бесплодия – ЭКО и II группа – 150 беременных, зачавших естественным путем после традиционных методов лечения. Осложнения беременности были оценены и статистически проанализированы.

Результаты. После лечения ЭКО наиболее частым осложнением беременности было кесарево сечение - 79,4%, как экстренное, так и плановое. Частота преэклампсии у этих пациенток также была высокая - 54,7%. Преждевременные роды составили - 49,4%, однако такая же тенденция выявлена и у пациенток IIгруппы - 52,0%. Редким осложнением было предлежание плаценты в обеих группах: 10,6% и 4,0%. Единичные случаи отслойки плаценты были выявлены в обеих

группах: 3,5 % и 2 %. В целом неблагоприятный исход беременности в I группе был значительно выше по сравнению с II группой.

Выводы. Беременность после ЭКО у пациенток с эндометриозом следует рассматривать как беременность высокого риска в отношении неблагоприятных исходов, таких как кесарево сечение, преэклампсия и преждевременные роды. Однако, эти осложнения беременности должны быть связаны с эндометриозом и бесплодием и возможно не связаны с ВРТ.

REVAZ SULUKHIA[1,2], LARISA MELIA[1,2], NINO DAVIDOVA[2,3], LALI PKHALADZE[2,3]

PREGNANCY COMPLICATIONS IN PATIENTS WITH ENDOMETRIOSIS

[1]Gudushauri National Medical Centre, Department of Obstetrics and Gynecology; [2] Ivane Javakhishvili Tbilisi State University; [3] Zhordania and Khomasuridze Institute of Reproductology

SUMMARY

Introduction: Endometriosis is a chronic disease, which causes infertility in 40%. In case of ineffective therapy, assisted reproductive technology is indicated. Endometriosis is an independent risk factor for mother and fetus morbidities. Prenatal monitoring, is essential in prevention of pregnancy-related complications.

Objective: Evaluation and comparison the frequency of pregnancy complications in women with endometriosis after traditional treatment methods of infertility and after IVF.

Methods: Retrospective study included 320 patients aged 28-46, with different locations of endometriosis, diagnosed by laparoscopy. The patients were divided into two groups: I group – 170 pregnant women using the fertility treatment method – IVF and II group – 150 pregnant women conceived naturally. Pregnancy complications were evaluated and statistically analyzed.

Results: In pregnant women with endometriosis after IVF treatment the most common pregnancy complication was caesarian section - 79.4%, both emergency and elective. The frequency of preeclampsia was also high - 54.7%. The preterm birth occurred in 49.4%, the same trend was revealed in the II group - 52, 0%. Placenta previa and placenta abruption were rare in both groups 10.6% vs. 4.0% and 3.5% vs. 2%. In general, the adverse pregnancy outcome in the ART group was
significantly higher compared to pregnant women conceived naturally except for the preterm delivery and abruption of the placenta.

Conclusions: IVF pregnancy in patients with endometriosis should be considered a high-risk pregnancy regarding adverse outcomes: cesarean section, preeclampsia and preterm delivery. However, these pregnancy complications should be linked to the endometriosis and infertility and may not to the ART.

Keywords: endometriosis, IVF, ART, spontaneous pregnancy, pregnancy complications