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Comparative effectiveness of infertility treatment using assisted reproductive technologies in patients with various forms of endometriosis and its combination with polycystic ovary syndrome

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AIM: The purpose of this study is to investigate the influence of various forms of endometriosis and its combination with PCOS on the outcome of assisted reproductive technology programs (ART) with relation to ovarian stimulation.

MATERIALS AND METHODS: During a retrospective examination, we analyzed the results of 241 ART cycles. All patients were divided into three groups: group A: endometriosis (85 ART cycles); group B: combination with PCOS (53 ART cycles), comparison group with tuboperitoneal infertility (103 ART cycles). Group A was subdivided into subgroup A1 with stage I / II endometriosis (50 cases, 58.82%) and subgroup A2 with stage III / IV endometriosis (35 cases, 41.18%). At the first stage of the study, we evaluated the anamnesis and the results of clinical and laboratory tests. During the second stage, we performed laparo- and hysteroscopy surgeries and determined the stage of endometriosis as well as the presence of concomitant pathologies. At the third stage, we performed infertility treatment using ART.

RESULTS: The highest FSH dose was employed in group A2 with the ovarian stimulation performed with GnRH-a: 2230.80 ± 614.09 IU. The minimal dose was used for group A1 (stimulation with antGnRH): 1171.43 ± 547.42 IU. The highest pregnancy rate per embryo transfer (PR) was detected in group A1 with the use of GnRH-a (50%,) higher than in the comparison group (42.72%). The minimal PR (14.29%) was found in group A2 (stimulation with antGnRH). Live Birth Rate (LBR) was higher in A1 patients stimulated with GnRH-a (40.48%), while with the use of antGnRH, all pregnancies terminated in both groups A1 and A2.

CONCLUSIONS: Our study confirmed that common forms of endometriosis are associated with a decrease in the effectiveness of infertility treatment using ART, but minimal forms of endometriosis do not affect the outcomes of ART cycles. The study revealed a negative impact of an ovarian stimulation protocol with the use of antGnRH on IVF outcomes including patients with the combination of endometriosis and PCOS. However, the small number of cases studied dictates further research to be conducted in this field.

Keywords: endometriosis; polycystic ovary syndrome; infertility; *in vitro* fertilization.

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Сравнительная эффективность лечения бесплодия методами вспомогательных репродуктивных технологий у пациенток с различными формами эндометриоза и его сочетанием с синдромом поликистозных яичников

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Цель — исследовать влияние различных форм эндометриоза и его сочетания с синдромом поликистозных яичников на исходы программ вспомогательных репродуктивных технологий в зависимости от овариальной стимуляции.

Материалы и методы. Проведено ретроспективное обследование, проанализированы исходы 241 цикла вспомогательных репродуктивных технологий. Все пациентки были разделены на три сопоставимые группы: группа А — пациентки с эндометриозом (85 циклов), группа Б — пациентки с сочетанием эндометриоза и синдрома поликистозных яичников (53 цикла), группа сравнения — пациентки с трубно-перитонеальным бесплодием (103 цикла). Дополнительно выделены: подгруппа А1 с I/II стадией эндометриоза (по ASRM) — 50 случаев (58,82 %) и подгруппа А2 с III/IV стадией эндометриоза — 35 случаев (41,18 %). На первом этапе оценивали анамнез, результаты клинико-лабораторных исследований. На втором этапе выполняли оперативное лечение в объеме лапарогистероскопии, определяли стадию эндометриоза, наличие сопутствующей патологии. На третьем этапе осуществляли терапию бесплодия методами вспомогательных репродуктивных технологий.

Результаты. Доза препаратов фолликулостимулирующего гормона была максимальной у пациенток группы А2 при проведении овариальной стимуляции с применением агонистов гонадотропин-рилизинг-гормона (2230,80 ± 614,09 МЕ) и минимальной в группе пациенток А1 при стимуляции с применением антагонистов гонадотропин-рилизинг-гормона (1171,43 ± 547,42 МЕ). Частота наступления беременности в расчете на перенос эмбрионов в группе А1, в которой стимуляцию проводили с применением агонистов гонадотропин-рилизинг-гормона, была максимальной и составила 50 %, что было выше, чем в группе сравнения, — 42,72 %. Минимальная частота наступления беременности наблюдалась в группе А2 при стимуляции с использованием антагонистов гонадотропин-рилизинг-гормона. Самая высокая частота родов отмечена при стимуляции с применением агонистов гонадотропин-рилизинг-гормона в группе А1 (40,48 %), напротив, при стимуляции с использованием антагонистов гонадотропин-рилизинг-гормона в группах А1 и А2 все беременности прервались.

Заключение. В нашем исследовании мы получили подтверждение, что распространенные формы эндометриоза сопряжены с уменьшением эффективности лечения бесплодия методами вспомогательных репродуктивных технологий, при этом минимальные формы эндометриоза не влияют на исходы циклов вспомогательных репродуктивных технологий. Выявлена тенденция отрицательного воздействия стимуляции овуляции с использованием антагонистов гонадотропин-рилизинг-гормона на исходы экстракорпорального оплодотворения, в том числе у пациенток с сочетанием эндометриоза и синдрома поликистозных яичников. Однако в связи с небольшой выборкой необходимо продолжать исследования в указанном направлении.

Ключевые слова: наружный генитальный эндометриоз; синдром поликистозных яичников; бесплодие; экстракорпоральное оплодотворение.

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BACKGROUND

Endometriosis is one of the most common diseases that is associated with infertility, is detected in 10%–15% of women of reproductive age [1], and is registered in up to 53.06% of women with infertility [2].

One of the treatment methods for such patients is assisted reproductive technology (ART). The American Society for Assisted Reproductive Technology reported a steadily increasing number of visits of patients with endometriosis year by year [3]. Thus, according to the registry in 2014, 189,347 ART cycles were performed in the USA, of which 5,271 cycles included patients with endometriosis, and in 2015, there were 214,835 and 5477 cycles, respectively. A similar trend continued in subsequent years, and in 2018, 6,636 cases of endometriosis were registered out of 275,786 ART cycles.

The European Society of Human Reproduction and Embryology (ESHRE) considers a disorder due to the development of endometriosis of the small pelvis anatomy and/or the fallopian tube function as indications for ART in patients with endometriosis-associated infertility. Moreover, in such situations, the main goal of surgical intervention should not only be the impact (ablation, excision) on endometrioid lesions but also the restoration of normal anatomical and physiological relationships of the pelvic organs, as well as its functions [4].

Expert opinions on the impact of endometriosis on the outcomes of ART cycles diverge. In recent years, more and more researchers have reported that pregnancy onset and its outcomes depend on the severity of endometriosis. Horton et al., in their meta-analysis, confirmed that endometriosis leads to a decreased number of oocyte follicles obtained by puncture and fertilization frequency. Milder forms of endometriosis most often affect fertilization (odds ratio [OR]: 0.77, 95% confidence interval [CI]: 0.63–0.93) and earlier implantation processes (OR: 0.76, 95% CI: 0.62–0.93), thereby reducing these indicators. According to ASRM, endometriosis stages, III and IV, adversely affect all stages of fertilization, cultivation, and implantation [5].

The reasons for the effect of endometriosis on fertility are widely discussed and studied but remained unclear. Endometriosis possibly negatively affects folliculogenesis through changes in oxidative stress in this category of patients. Additionally, it can be caused by immune disorders, follicle microenvironment changes, peritoneal environment, and decreased endometrial receptivity.

A direct correlation was established between the severity of endometriosis and the incidence of a combination of various gynecological pathologies. Thus, associations of gynecological diseases are four times higher in patients with infertility due to stages III–IV endometriosis, according to ASRM (AFS) [6], compared with the group of patients with stages I–II endometriosis [7].

Endometriosis and polycystic ovary syndrome (PCOS) cannot be concomitant in one patient. A hypothesis has recently emerged that endometriosis and PCOS are opposite results of variations in the development and activity of the hypothalamus–pituitary-gonadal axis [8]. However, despite ongoing discussions, evidence in the literature revealed the possibility of a combination of external genital endometriosis and PCOS in one patient. The incidence of asymptomatic endometriosis, which is detected in patients with PCOS during laparoscopic ovarian drilling, ranges from 7.7% to 16.9% [9]. Concurrently, the number of minimal forms of endometriosis (stages I and II according to the rASRM classification) prevails. Holoch et al. published data that showed that 71.5% of women with PCOS who underwent laparoscopy had endometriosis. Stage I was diagnosed in 40% (according to rASRM), stage II in 41%, stage III in 12%, and stage IV in only 7% of patients [10]. However, other authors consider this incidence as significantly overestimated and primarily attribute this to the inclusion in the study of patients with clinical manifestations of endometriosis, who initially need laparoscopy for its treatment.

A correct prediction of the efficiency of further treatment is facilitated by morphological diagnosis confirmation, which is possible only with a histological surgical material examination [11–16].

MATERIALS AND METHODS

A retrospective examination was conducted, and the outcomes of 241 ART cycles were analyzed in patients who are treated at the AVA-PETER clinic (St. Petersburg) from 2013 to 2017. Patients were examined following the order of the Ministry of Health of the Russian Federation No. 107n dated August 30, 2012 "On the procedure for the use of assisted reproductive technologies, contraindications, and restrictions to their use."

The design included three stages.

In stage 1, the anamnesis data, clinical and laboratory study results were evaluated. At stage 2, surgical treatment was performed in the scope of laparohysteroscopy, during which the stage of endometriosis was determined following the ASRM classification, as well as the presence of concomitant pathology. The diagnosis was histologically confirmed. Concomitant PCOS was defined according to the 2003 ESHRE-ASRM Rotterdam Consensus criteria (two out of three clinical or biochemical criteria, namely hyperandrogenism, ovulatory dysfunction, or multifollicular ovaries on ultrasound examination) [17]. At stage 3, infertility therapy was performed using ART methods with controlled ovarian stimulation, obtaining and fertilizing oocytes, assessing the quantity and quality of the obtained gametes and embryos, transferring embryos to the uterine cavity, and predicting the treatment outcome.

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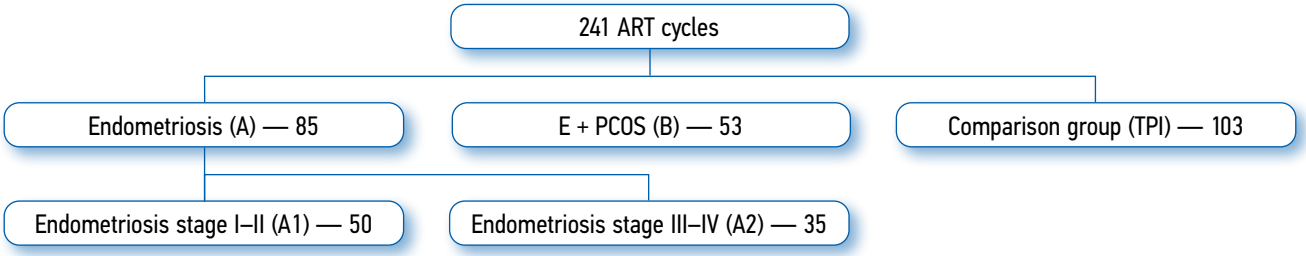

Figure. Groups of female patients. ART — assisted reproductive technologies; E — endometriosis; PCOS — polycystic ovary syndrome; TPI — tuboperitoneal infertility. A, B, A1, and A2 — study groups and subgroups

A retrospective cohort study was conducted based on the analysis of own data (Figure).

All patients were distributed into three groups, where group A included patients with endometriosis (85 ART cycles), group B included patients with a combination of endometriosis and PCOS (53 ART cycles), and the comparison group consisted of patients with tuboperitoneal infertility (103 ART cycles).

Group A was divided according to the ASRM classification into subgroups A1 with patients with stages I or II endometriosis (50 cases, 58.82%) and A2 with patients with stages III or IV endometriosis (35 cases, 41.18%).

These subgroups were also diagnosed with endometriomas. Concurrently, with increased endometriosis severity, the incidence of endometriomas increased (Table 1).

It should be noted that we were guided by the ASRM classification (AFS) as the main international tool for describing endometriosis, despite its shortcomings, namely the fact it does not consider infiltrative endometriosis [18]. In this work, an assessment following the ENZIAN classification proposed by Keckstein [19] was not performed.

In group B, 48 (90.57%) patients had stage I or II endometriosis and 5 (9.43%) had stage III or IV.

The main inclusion criteria in the study were the following:
- no current or history of malignant diseases;
- the presence of indications and the absence of contraindications following the order of the Ministry of Health of the Russian Federation No. 107n dated August 30, 2012;
- age 22–40 years;
- histologically confirmed endometriosis;
- established stage of endometriosis;
- compliance of patients with endometriosis with the criteria of the Rotterdam Consensus ESHRE-ASRM 2003;
- transfer of embryos into the uterine cavity in a "fresh" cycle;
- signed informed consent of the spouses for treatment and study participation.

Criteria for non-inclusion in the study were the following:
- contraindications for ART following the order of the Ministry of Health of the Russian Federation No. 107n dated August 30, 2012;
- obesity;
- severe pathospermia (including azoospermia) in the partner;
- uterine fibroids;
- ART with a donor ovum and/or the use of surrogacy programs.

The exclusion criteria for the study were the following:
- complication of treatment with ART methods, refusal to transfer in a "fresh" cycle (hemorrhage, inflammation, and severe ovarian hyperstimulation syndrome);
- refusal to continue treatment/participate in the program.

All couples underwent a standard examination on an outpatient basis, with the use of mandatory, special methods, and examinations for medical indications before their inclusion in the study.

The ovarian reserve was studied to predict the response of the ovaries to ovarian stimulation *in vitro* fertilization (IVF) cycles. The determination of the antral follicle count (AFC) in the ovaries and the level of anti-Müllerian hormone (AMH) in blood serum are the most applicable in clinical practice, which is associated with a significantly higher correlation with the number of primordial follicles compared to other markers [20].

AMH is mainly expressed in granulosa cells of small follicles up to 8 mm in diameter. Thus, the level of AMH corresponds to the number of antral follicles in the ovaries.

Table 1. Incidence of endometriomas

Group	Unilateral endometriomas, % (*n*)	Bilateral endometriomas, % (*n*)	Total, % (*n*)
A1 — stages I–II endometriosis (*n* = 50)	32% (16)	4% (2)	36% (18)
A2 — stages III–IV endometriosis (*n* = 35)	65.71% (23)	5.71% (2)	71.42% (25)

Table 2. General characteristics of the groups

Parameter	Endometriosis			E + PCOS (B)	TPI
	I–II (A1)	III–IV (A2)	Total (A)		
Number of cycles	50	35	85	53	103
Age, years	33.72 ± 4.49	32.29 ± 4.3	33.13 ± 4.44	31.26 ± 3.24	33.89 ± 4.32
BMI	22.54 ± 3.5	22.24 ± 4.23	22.42 ± 3.8	23.2 ± 3.91	23.14 ± 4.34
AFC	12.69 ± 4.08	7.14 ± 3.56	9.92 ± 3.82	14.75 ± 5.87	13.41 ± 5.23
AMH, pg/ml	2.16 ± 2.58	2.44 ± 2.72	2.29 ± 2.62	5.60 ± 4.65	2.69 ± 2.37

Note. E — endometriosis; PCOS — polycystic ovary syndrome; TPI — tuboperitoneal infertility; BMI — body mass index; AFC — antral follicle count; AMH — anti-Müllerian hormone.

Table 3. Characteristics of groups according to the ovarian stimulation protocol

Parameter	Endometriosis			E + PCOS (B)	TPI
	I–II (A1)	III–IV (A2)	Total (A)		
Number of cycles	50	35	85	53	103
Protocols with aGnRH, % (*n*)	84% (42)	80% (28)	82.35% (70)	39.62% (21)	72.82% (75)
Protocols with antGnRH, % (*n*)	16% (8)	20% (7)	17.65% (15)	60.38% (32)	27.18% (28)

Note. E — endometriosis; PCOS — polycystic ovary syndrome; aGnRH — gonadotropin-releasing hormone agonists; antGnRH — antagonists of gonadotropin-releasing hormone; TPI — tuboperitoneal infertility.

A positive association between AMH levels and pregnancy rates after IVF has been reported. The higher the AMH level, the more the oocytes; thus, the more embryos are obtained per cycle of ovarian stimulation, which correlates with the pregnancy rate [21, 22].

Determining the AFC, as well as the AMH levels, in assessing the ovarian reserve serves as a direct marker of the ovarian response to stimulation [23, 24]. The advantage of AFC over AMH is that the location of the ovaries, the presence of cysts (including endometriomas), and other lesions (for example, the presence of hydrosalpinxes, fibroids, polyps of the uterine cavity) can be determined with ultrasound examination of the functional reserve of the ovaries.

The AMH level was determined on days 2–3 of the menstrual cycle by enzyme-linked immunosorbent assay.

No significant differences were found in age and body mass index in the groups. A slightly higher level of AMH was noted in the group with a combination of endometriosis and PCOS (Table 2), which was since PCOS is characterized by an increased number of ovarian follicles at all stages of development. Moreover, the increased number of preantral and early antral follicles, which primarily produce AMH, is more pronounced [25].

AFC was determined using a Flex Focus 400 vaginal ultrasonograph transducer (BK Medical, Denmark) in the early follicular phase following the generally accepted method [26]. The decreased AFC level in the group of patients with endometriosis (lower values 7.14 ± 3.56 in subgroup A2) is noteworthy, which corresponds to the published data [27].

All surgical interventions were performed by laparohysteroscopic access using endoscopic equipment and instruments manufactured by KARL STORZ (Germany), Aesculap (Germany), and ERBE (Germany).

Surgical treatment of patients was performed in a scheduled manner, simultaneously in two stages. During stage 1 (laparoscopic), the internal organ condition and the endometriosis staging were assessed, a clinical diagnosis was established, and an adequate amount of surgical treatment was determined (including ovarian drilling with biopsy). At stage 2, hysteroscopy was performed.

All material removed during the surgery was subjected to pathomorphological examination for histological verification of the diagnosis.

No surgical complications were observed during the surgeries and postoperatively.

Subsequent infertility treatment by ART methods was conducted following the approved norms and rules [28].

The generally accepted protocols with gonadotropin-releasing hormone antagonists (antGnRH) and agonists (aGnRH) were observed. Patients were distributed into groups according to the stimulation protocol retrospectively, in random order (Table 3).

According to Table 3, in the group of patients with endometriosis, the vast majority of cycles were performed according to protocols with aGnRH (82.35%). A high frequency of protocols with aGnRH was also in the control group of patients with tuboperitoneal infertility (72.82%). Stimulation schemes with the use of antGnRH prevailed in group B (60.38%). The protocol was chosen based on

the expected efficiency of the cycles and the probability of complications.

Kolanska et al. found that the use of aGnRH drugs in patients with endometriosis in protocols of controlled ovarian stimulation contributes to an increased pregnancy rate (PR) per embryo transfer compared to antGnRH protocols [29]. With a comparable PR in the case of antGnRH protocols in female patients with PCOS, the risk of ovarian hyperstimulation syndrome is significantly reduced (RR: 0.53, 95% CI: 0.30–0.95) [30]. The same study showed that in the "general" group of patients, the progressive PR was lower after the use of antGnRH protocols than after long aGnRH protocols (RR: 0.89, 95% CI: 0.82–0.96, $I^2 = 0\%$), which explains the choice of such protocol in patients with tuboperitoneal infertility.

Follitropins alpha and beta, menotropins, triptorelin, and ganirelix were used to stimulate ovulation. Chorionic gonadotrophin alpha was used as a trigger for final oocyte maturation. The criteria for determining the required starting dose of follicle-stimulating hormone (FSH) are unclearly defined; thus, the dose was individually chosen, considering the history, age of patients, and indicators of ovarian reserve. Patients with a presumed ovarian hyperresponse, thus a high risk of ovarian hyperstimulation syndrome, received lower gonadotropin doses [31], while patients with a predicted hyporesponse received higher FSH preparation doses.

FSH preparations were administered starting from days 2–3 of the menstrual cycle. Follicle growth was controlled by ultrasound monitoring depending on the follicle growth dynamics. When at least two follicles reached a diameter of 17 mm, a trigger for the final maturation of oocytes was prescribed, namely recombinant chorionic gonadotrophin alpha at a dose of 6,500 IU (250 μg). Transvaginal puncture of follicles larger than 14 mm in diameter was performed under ultrasound guidance 36 h after trigger injection.

The oocytes obtained were fertilized 39–40 h after the trigger injection in IVF medium (Origio). The fertilization method was chosen following the indicators of the spermogram on the day of puncture. Embryos were cultured in individual drops of single-stage CSCM-C medium (Irvine Scientific) at a reduced oxygen content (5%) in MINCK tabletop plate incubators (COOK Medical). Fertilization was assessed 16–20 h after sperm addition in IVF or after sperm injection in intra cytoplasmic sperm injection (ICSI). Abnormally fertilized (triploids and haploids) and unfertilized oocytes were excluded. Cleavage of diploid embryos was assessed on day 3 of development. The number and homogeneity of blastomeres and the presence of fragmentation were considered (class A implied embryos with no >5% of enucleated fragments; class B implied embryos with the fragmentation of no >30% of the total size of the embryo; class C included embryos with the fragmentation of >30% of the total size of the embryo). If the transfer was performed on day 4 of development, then the degree of embryo compaction was analyzed (eM — early morula, M — morula, Mcav — cavitating morula), as well as the presence of non-incorporated cells and fragments. Day 5 embryos were scored according to Gardner.

Embryos were transferred on days 3, 4, or 5 of development, depending on the number of obtained zygotes, endometrial condition, and patient's medical history. The best embryo was chosen for transfer, and the remaining promising embryos were cryopreserved on days 5 or 6 of development using vitrification, with 1 or 2 embryos per cryotope (Kitazato).

After the transfer, progesterone preparations were prescribed to patients as maintenance therapy (dydrogesterone at 10 mg 2 times per day *per os,* micronized vaginal progesterone at 200 mg three times per day, or 90 mg of vaginal progesterone once a day).

On days 12–14 after an embryo transfer into the uterine cavity, the level of chorionic gonadotropin in the blood of patients was determined. If the level was above the threshold, an ultrasound examination of the pelvic organs was performed 10–14 days later. The criterion for the onset of clinical pregnancy includes the visualization of the gestational sac in the uterine cavity and the detection of the heartbeat.

RESEARCH RESULTS

During controlled ovarian stimulation, the FSH preparation dose was higher in all groups of patients with aGnRH protocols, and the maximum dose (2230.80 ± 614.09 IU) was required for patients with stage III–IV endometriosis. The minimum dose of FSH preparations was 1171.43 ± 547.42 IU and was recorded in the group of patients with minimal endometriosis during antGnRH stimulation.

The number of both obtained and mature oocytes (MII) in groups A1 and B were higher when stimulated with antGnRH (11.14 ± 8.93/13.47 ± 7.13 and 10.14 ± 9.06/10.81 ± 7.08, respectively). In group A2 of patients, who received stimulation with antGnRH, the number of oocytes obtained by puncture was 3.33 ± 2.07, including 3.00 ± 2.00 mature ones, and there were 9.21 ± 8.00 and 7.96 ± 6.45 oocytes with the use of aGnRH, respectively. The lowest fertilization rate (65.03 ± 32.47) was found in group A2 after aGnRH stimulation (Table 4).

The PR per embryo transfer in the group of patients with minimal endometriosis, who underwent ovarian aGnRH stimulation, amounted to 50%, which was the highest value in the study groups, and the PR was also comparable in the group with a combination of endometriosis and PCOS (42.72%).

The minimum PR (14.29%) was registered in patients in the group with stages III–IV endometriosis, in whom stimulation was performed using an antGnRH. It was identical (25%)

Table 4. Results of oocyte fertilization

Parameter	Protocol	Endometriosis		E + PCOS (B) *n* = 53	TPI
		I–II (A1) *n* = 50	III–IV (A2) *n* = 35		
Total dose of FSH, IU	aGnRH	2032.74 ± 507.86	2230.80 ± 614.09	1998.21 ± 689.55	2106.90 ± 661.83
	antGnRH	1171.43 ± 547.42	1954.17 ± 1088.63	1488.67 ± 430.12	
Number of oocytes, total	aGnRH	10.17 ± 7.99	9.21 ± 8.00	10.00 ± 6.49	9.62 ± 6.46
	antGnRH	11.14 ± 8.93	3.33 ± 2.07	13.47 ± 7.13	
MII	aGnRH	8.95 ± 7.03	7.96 ± 6.45	8.67 ± 5.47	8.26 ± 5.84
	antGnRH	10.14 ± 9.06	3.00 ± 2.00	10.81 ± 7.08	
Fertilization rate	aGnRH	79.00 ± 19.05	65.03 ± 32.47	74.8 ± 11.60	77.23 ± 17.41
	antGnRH	77.51 ± 25.94	88.89 ± 20.18	71.78 ± 8.93	

Note. E — endometriosis; PCOS — polycystic ovary syndrome; FSH — follicle-stimulating hormone; aGnRH — gonadotropin-releasing hormone agonists; antGnRH — antagonists of gonadotropin-releasing hormone; MII — mature oocytes; TPI — tuboperitoneal infertility.

Table 5. Treatment outcomes

Parameter	Protocol	Endometriosis		E + PCOS (B)	TPI
		I–II (A1)	III–IV (A2)		
PR (ET), % (*n*)	aGnRH	50.0% (21)	39.29% (11)	47.62% (10)	42.72% (44)
	antGnRH	25.0% (2)	14.29% (1)	25.0% (8)	
Frequency of termination of pregnancy (per number of pregnancies), % (*n*)	aGnRH	19.05% (4)	45.45% (5)	20.0% (2)	18.18% (8)
	antGnRH	100% (2)	100% (1)	62.5% (5)	
Birth rate (ET), % (*n*)	aGnRH	40.48% (17)	21.43% (6)	38.1% (8)	31.07% (32)
	antGnRH	0% (0)	0% (0)	9.38% (3)	

Note. PR — pregnancy rate; ET — embryo transfer into the uterine cavity; TPI — tuboperitoneal infertility.

both in patients with a combination of endometriosis and PCOS and with minimal forms of endometriosis.

The frequency of pregnancy termination in terms of the number of clinical pregnancies that occurred was higher in all groups where the antGnRH protocol was used and was highest in patients with endometriosis only. This resulted in a low birth rate (9.38%) in patients with both endometriosis and PCOS and no live birth in patients with endometriosis alone. The maximum rate of termination of pregnancy was 45.45% in groups of patients with stages III–IV endometriosis and with protocols of ovarian stimulation using aGnRH, whereas 19.05% in the group with minimal endometriosis and 20.0% in the group with a combination of endometriosis and PCOS.

Contrarily, the frequency of childbirth was significantly higher with the ratios preserved in patients whose ovarian stimulation was performed using aGnRH, as in the determination of PR; thus, the maximum rate was recorded in the group with minimal forms of endometriosis (40.48%), a similar birth rate was established in the group with a combination of endometriosis and PCOS (38.1%), and the minimum value was recorded in the group of patients with advanced forms of endometriosis (21.43%) (Table 5).

DISCUSSION

ART methods have shown their efficiency in patients with endometriosis-associated infertility. The efficiency of ART cycles is usually presented by several indicators. These include the total number of extracted follicles and oocytes during puncture, the count of mature ones, fertilization frequency, PR, and pregnancy termination frequency, and the main indicator is the frequency of childbirth with a live fetus.

Undoubtedly, the work of researchers and practitioners is aimed, on the one hand, at identifying parameters that increase the treatment efficiency, and on the other hand, at studying the effect of various manifestations of endometriosis on treatment outcomes. These aspects are often related to each other. One of the ways to improve treatment outcomes is the individualization of superovulation stimulation protocols [32, 33]. However, when implementing certain methods that are more likely to help patients overcome infertility, many problems arise, including ambiguous interpretations of the influence of various forms of endometriosis on IVF cycles outcomes.

One of the markers of successful fertilization is the number of obtained mature oocytes by a puncture. Published data

indicate that endometriosis, compared with other causes of infertility, leads to a decreased number of obtained mature oocytes [34–38]. The results of studies by Xu et al. may provide a possible explanation. Studying the ultrastructure of the oocyte cytoplasm in patients with endometriosis, the authors concluded a higher proportion of abnormal mitochondria is associated with a decreased total number of mitochondria, which ultimately reduces the potential of oocytes for final maturation, in this group [39].

In our study, the number of obtained mature oocytes by follicle puncture was the lowest in the group of patients with stages III–IV endometriosis.

We obtained data, confirming that the severity of endometriosis is inversely correlated with both the total number of oocytes obtained by puncture and the number of oocytes in phase II of meiotic division. However, significant differences are observed depending on the ovarian stimulation protocol. Thus, in subgroup A2, in which stimulation was performed using antGnRH, the number of mature oocytes was 3.00 ± 2.00 and was 7.96 ± 6.45 when stimulated with aGnRH. In the remaining groups (A1 and B), the number of both obtained and "mature" oocytes was higher in patients in cycles with antGnRH compared with patients in cycles with aGnRH.

The fertilization frequency in groups A1 and B was practically independent of the protocol of controlled ovarian stimulation. However, it was higher in group A2 when stimulated with antGnRH (88.89% vs. 65.03%).

The influence of endometriosis on PR in ART cycles has no consensus. The most common view is that any form of endometriosis reduces PR, both in spontaneous pregnancy and in the case of ART [40, 41]. This was confirmed in the work by Akande et al., who revealed a significantly lower efficiency of IVF cycles in women with endometriosis-associated infertility compared to patients with a tubal factor of infertility [42].

There is also an opposite view of this problem. Given advances in ART in overcoming infertility in patients with endometriosis, some authors believe that no significant differences in PR and birth rates among patients with various stages of endometriosis compared with women with other causes of infertility [43, 44].

As mentioned above, there is increasing evidence of an inverse relationship between the stage of endometriosis and the efficiency of ART cycles [5, 45]. Harb et al. emphasize that PR in women with "minimal" endometriosis and with tuboperitoneal infertility is comparable [45]. The same opinion is shared by other researchers [12, 16, 46–50]. In confirmation of the latter, we obtained similar results. The maximum PR was registered in the group of patients with minimal forms of endometriosis and was comparable to the PR in patients with PCOS and endometriosis since the vast majority of patients in the latter group had stage I or II endometriosis. These ratios were maintained regardless of the protocol of ovarian stimulation, but the values were higher using aGnRH (50.0%/39.29%/47.62% [A1/A2/B] vs. 25.0%/14.29%/25%, respectively]. Some authors consider the negative effect of protocols with antGnRH on endometrial susceptibility as a possible cause, which confirms the increased PR with the use of aGnRH [29].

In 1993, Balen et al. established that the pregnancy termination rate in women with cystic disease is 35.8%, which is much higher compared to women without changes in the ovaries (23.6%). However, the miscarriage rate is reduced in patients with PCOS to the level of patients with normal ovaries, using a long aGnRH protocol of ovarian stimulation (20.3%) [51]. We obtained almost identical data on pregnancy termination frequency in groups with "minimal" forms of endometriosis and with a combination of endometriosis and PCOS, where ovarian stimulation was performed using aGnRH. As in the case of PR, significant differences were found in determining the rate of pregnancy termination depending on the stimulation protocols. All pregnancy terminations in patients with endometriosis who received antGnRH should not be disregarded. An extremely small sample should be noted, which inevitably entails a large error, but this trend should be studied in more detail in subsequent works. In the subgroup of patients treated with aGnRH, the maximum frequency of terminations was recorded in the group with stages III–IV endometriosis (45.45%), and it was 19.06% and 20.0% in groups A1 and B, respectively. Based on the data on pregnancy termination frequency, the main group of positive outcomes was registered in the same patients, namely 40.48% in patients with stages I–II endometriosis and 38.1% in the group with a combination of endometriosis and PCOS.

CONCLUSIONS

We managed to confirm that common forms of endometriosis are associated with a decreased efficiency of infertility treatment using ART methods and, contrarily, minimal forms of endometriosis do not affect the outcomes of ART cycles, compared to the control group. The combination of endocrine pathologies, such as PCOS, with endometriosis, significantly affects the efficiency of infertility treatment using IVF-ICSI methods.

The tendency of the negative impact of ovulation stimulation protocols on IVF outcomes in groups with antGnRH is of particular interest. However, continuing the research in this direction is required due to the small sample size.

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