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POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

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Authors: Iwona M. Gawron, Bartosz Chrostowski, Kamil Derbisz, Robert Jach, Milosz Pietrus

DOI: 10.5603/GP.a2023.0062

Article type: Research paper

Submitted: 2023-03-22

Accepted: 2023-05-16

Published online: 2023-07-06

ORIGINAL PAPER / OBSTETRICS

Comparison of dydrogesterone plus progesterone gel with subcutaneous aqueous progesterone plus progesterone gel for luteal phase supplementation of subsequent *in vitro* cycle in women after previous cycle failure

Iwona M. Gawron[1], Bartosz Chrostowski[2], Kamil Derbisz[3], Robert Jach[1], Milosz Pietrus[4]

[1]*Department of Gynecology and Obstetrics, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland*
[2]*Centre for Reproductive Medicine ARTVIMED, Cracow, Poland*
[3]*Clinical Department of Gynecological Endocrinology and Gynecology, University Hospital in Cracow, Poland*
[4]*Clinic of Gynecological Oncology, Department of Gynecology and Obstetrics, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland*

Short title: Luteal phase support after IVF failure

Corresponding author:
Iwona M. Gawron
Department of Gynecology and Obstetrics, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland
e-mail: iwonagawron@gmail.com

ABSTRACT

Objectives: The luteal phase supplementation (LPS) of the *in vitro* fertilization (IVF) cycle is crucial to increase the chance of a live birth. There is no preferred progestogen for use in the general population. The optimal progestogen regimen in the event of prior IVF failure is unknown. The aim was to compare the live birth rate for dydrogesterone plus progesterone gel versus aqueous progesterone plus progesterone gel in LPS of the IVF cycle in women with at least one previous IVF failure.

Material and methods: A prospective randomized single-center study enrolled women with at least one previous IVF failure undergoing another IVF cycle. Women were randomly assigned in a 1:1 ratio to 2 arms depending on LPS protocol: dydrogesterone (Duphaston®) + progesterone in vaginal gel (Crinone®) vs aqueous progesterone solution in subcutaneous injection (Prolutex®) + progesterone in vaginal gel (Crinone®). All women underwent fresh embryo transfer.

Results: The live birth rate with one prior IVF failure was 26.9% for D + PG vs 21.2% for AP + PG (p = 0.54), and with at least two IVF failures: 16% for D + PG vs 31.1% for AP + PG (p = 0.16). There were no significant differences in live birth rates between protocols, regardless of the number of prior IVF failures.

Conclusions: In light of the evidence from this study that neither of the two LPS protocols is more effective in women with prior IVF failure, other factors, such as potential side effects, dosing convenience and patient preference, should be considered when choosing a treatment.

Key words: luteal phase support; *in vitro* fertilization; fresh embryo transfer; progestogens; live birth rate

INTRODUCTION

In *in vitro* fertilization (IVF) cycles the course of luteal phase is deficient due to premature luteolysis caused by supra-physiological levels of estradiol and progesterone in human chorionic gonadotropin (hCG)-induced early luteal phase, aspiration of granular cells from follicles during oocyte retrieval, and suppression of luteinizing hormone (LH) in agonist and antagonist protocols [1]. In particular, progesterone significantly reduces LH production through negative feedback mechanisms in the hypothalamus and pituitary gland. Since LH activity is crucial for the function of the corpus luteum, a significant decrease in the concentration of this gonadotropin after triggering ovulation causes relative damage to the luteal phase [2]. Furthermore, the disturbed course of the luteal phase leads to impaired development of the endometrium and asynchrony between endometrial receptivity and the maturity of the transferred embryo [3]. The above phenomena adversely affect implantation and early pregnancy development, reducing the chance of establishing and maintaining the pregnancy. The luteal phase in IVF cycles must therefore be medically assisted using progestogens or hCG, and an optional addition of gonadotropin releasing hormone (GnRH) analogues [4, 5], at least until a positive pregnancy test. Due to the increased relative risk of ovarian hyperstimulation syndrome (OHSS) associated with the use of hCG, progesterone has

become the drug of choice in the luteal phase supplementation (LPS) [6]. Much scientific research has been carried out to date to compare the efficacy and safety of progesterone preparations administered in different regimens and routes. Except for the oral administration of dydrogesterone [7], oral administration of progesterone to supplement IVF cycles is less effective compared to other routes of administration [6], *i.e.*, vaginal, rectal, subcutaneous, and intramuscular. However, no advantage of any of the above-mentioned routes of progesterone administration over the other has been identified in the systematic reviews and meta-analyzes [6]. It is worth noting that the studies conducted so far have not focused on women who are additionally burdened with factors reducing the chance of IVF success, such as previous IVF failure. Therefore, a study was designed to compare two protocols of LPS, i.e., dydrogesterone oral tablet with progesterone vaginal gel versus subcutaneous aqueous progesterone with progesterone vaginal gel in a population of women with the history of at least one IVF failure, approaching another IVF cycle. Due to the lack of a recommended administration route and dose of LPS, the addition of an oral or subcutaneous route to vaginal application in women with previous IVF failure, resulted from a cautious approach to possible issues related to progesterone bioavailability [8–11].

Objectives

Comparison of obstetric outcomes for dydrogesterone + progesterone in vaginal gel protocol (D + PG) versus progesterone in subcutaneous injection + progesterone in vaginal gel protocol (AP + PG) in LPS in IVF cycles in women with previous IVF failure.

Specific aims

1. Comparison of the rates of obtained biochemical pregnancies with the use of D + PG vs AP + PG protocols in LPS.
2. Comparison of the rates of achieved clinical pregnancies with the use of D + PG vs AP + PG protocols in LPS.
3. Comparison of the rates of achieved live births with the use of D + PG vs AP + PG protocols in LPS.

MATERIAL AND METHODS

A prospective single-center study was conducted among women undergoing government-funded IVF in the years 2015–2016. The research was approved by the Bioethics Committee of the Jagiellonian University. Inclusion criteria were: i) at least one failed IVF

cycle preceding the current cycle, ii) fresh embryo transfer (ET) strategy, iii) age 18–43 years, iv) FSH between days 2 and 4 of the cycle ≤ 10 IU/L. The exclusion criteria were: i) failure to obtain an embryo, ii) deferred ET strategy. A specialist in obstetrics and gynecology was responsible for qualification for IVF procedure, selection of ovarian stimulation protocol and qualification for transvaginal oocyte retrieval. A couple was qualified for the next consecutive IVF cycle only if all frozen embryos were used in subsequent transfers of thawed embryos. The women included in the study gave informed consent to the proposed management. Women underwent controlled ovarian hyperstimulation (COH) with a short GnRH-antagonist (cetrorelix; Cetrotide®) protocol or long GnRH-agonist (triptorelin; Gonapeptyl Daily®) protocol. The ovarian stimulation protocol, the dose and type of gonadotropins were selected individually, considering the ovarian reserve, age and weight, comorbidities and the doctor's experience [12–15]. Recombinant human chorionic gonadotropin (Ovitrelle®) was administered subcutaneously at a dose of 6,500 IU approximately 36 hours prior to oocyte pick-up to induce final oocyte maturation in all women, provided that at least 3 follicles greater than 17 mm in diameter were confirmed on transvaginal ultrasound (TVS). Women at an increased risk of OHSS, who received a trigger with 0.2 mg of triptorelin administered subcutaneously, were qualified for deferred ET [14] and were excluded from the study. Collecting oocytes by transvaginal ultrasound-guided aspiration from ovaries, laboratory embryo culture and ET were performed in accordance with current medical knowledge and appropriate guidelines [16]. *In vitro* fertilization was performed by intracytoplasmic sperm injection (ICSI) in all women. On the day of oocyte retrieval, women were randomly assigned to one of the two study arms. Random assignment to the two study arms was performed by coin toss. The first arm included women receiving oral dydrogesterone (Duphaston® 10 mg every 8 hours) combined with progesterone in vaginal gel (Crinone® 90 mg in a daily single dose) (D + PG protocol), and the second arm included women receiving progesterone in subcutaneous injection (Prolutex® 25 mg in a single dose) combined with progesterone vaginal gel (Crinone® 90 mg in a daily single dose) (AP + PG protocol). Progestogen supplementation was started within 24 hours of oocyte retrieval and continued until 12 weeks of gestation, unless spontaneous abortion occurred. ET was performed on the 5^{th} day after fertilization of the collected oocytes. The number of transferred embryos was at the discretion of the physician and patient. The pregnancy test (blood serum B-hCG detection) was performed on the 12^{th} day after ET. Treatment was discontinued if the pregnancy test was negative. In the case of a positive result, the treatment was continued and 4 weeks after ET, TVS was performed to confirm a viable pregnancy (the

presence of a fetal heartbeat in M-mode). In the absence of the fetal heartbeat at that time, appropriate diagnostic and therapeutic procedures were implemented. Blood progesterone levels were not measured in the post-oocyte retrieval course of treatment. The women whose medical data was used in the study were subjected to routine medical procedures commonly used in reference centers for infertility treatment. The study population was characterized by age, duration and the nature of infertility (primary or secondary), indications for IVF, number of previously failed IVF cycles, ovarian reserve test result expressed as Anti-Müllerian Hormone (AMH) concentration, progesterone concentration the day before oocyte aspiration, type of ovarian stimulation protocol, number of metaphase II oocytes retrieved, number of transferred embryos. Then, the percentages of biochemical pregnancies (no gestational sac on TVS and falling B-hCG concentrations), clinical pregnancies (loss of pregnancy before the fetus is viable after visualization of gestational sac in the uterine cavity) and live births (birth of a live fetus after 24 weeks of gestation) in both study arms were calculated and compared, taking into account the number of previously failed IVF cycles.

Statistical analysis

Data were analyzed according to their distribution which was confirmed with the Kolmogorov-Smirnov test. In order to compare selected variables in both subpopulations, the Mann-Whitney test was used as a non-parametric test, and the Student's t-test was used for variables with a normal distribution. Chi-square test was used to assess the categorical variable. The results were expressed as mean for continuous variable and as number of cases (N, n) and percentage (%) for categorical variable. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using StatSoft STATISTICA v 13.3 software.

RESULTS

During the study period, 250 fresh embryo transfers were performed, of which 170 were effectuated in women with at least one previous IVF failure (the study population) and another 80 in women in first-time IVF cycle. The characteristics of the study population in terms of the nature of infertility, IVF indications, stimulation protocol and progestogen regimen compared to the first-cycle IVF population are presented in Table 1, while mean values of selected variables (age, AMH and progesterone concentration, number of transferred embryos, endometrium width, duration of infertility) are presented in Table 2. Of the significant differences, in the study population of women with at least one IVF failure, the

long GnRh-agonist protocol was used more often compared to women in the first cycle of IVF (70/170 women, 41.2% vs 17/80 women, 21.3%, p = 0.002), and the short GnRH-antagonist protocol was used less frequently (100/170 women, 58.8% vs 63/80 women, 78.8%; p = 0.002). Moreover, in the study population compared to women in the first IVF cycle, the percentage of women who received the AP + PG protocol was significantly higher (78/170 women, 54.9% vs 16/80 women, 20%, p < 0.001), and the proportion of those who received the D + PG protocol was significantly lower (92/170 women, 54.1% vs 64/80 women, 80%; p < 0.001). In the study population the number of transferred embryos was also significantly higher than in the first IVF cycle (1.4 vs 1.1, p = 0.02). Mean number of metaphase II oocytes obtained in the short GnRH-antagonist protocol vs in the long GnRH-agonist protocol in the study population was 6.04 vs 6.01 (p = 0.96). The analogous values among women in the first IVF cycle also did not differ significantly and amounted to 6.23 vs 5.9 (p = 0.74). No other significant differences were found between the study population and the population in the first IVF cycle.

Of 170 women from the study population, 100 (100/170; 58.8%) had a history of one failed IVF cycle, and 70 (70/170; 41.2%) had at least two consecutive IVF failures. The characteristics of the subpopulations of women subjected to fresh ET with a history of 1 IVF failure and at least two failures compared to women in the first IVF cycle are presented in Table 3, while mean values of selected variables are presented in Table 4. The long GnRH-agonist protocol was used significantly more often in women with one IVF failure than in the subpopulation with at least two failures (43/100, 43% vs 27/70, 38.6%, p = 0.02) in which the short GnRH-antagonist protocol was used more often (43/70, 61.4% vs 57/100, 57%, p = 0.02). In women with one IVF failure, the D+PG protocol was used significantly more often than in the subpopulation with at least two failures (67/100, 67% vs 27/70, 35.7%, p < 0.001), in which the AP + PG protocol was used more often (45/70, 64.3% vs 33/100, 33%, p < 0.001). With the increasing number of failed IVF cycles, the percentage of reduced ovarian reserve as an indication for IVF increased (transfer 1: 10% vs transfer 2: 17% vs transfer ≥3: 22.9%, p = 0.02), and the percentage of idiopathic infertility decreased (transfer 1: 22.5% vs transfer 2: 17% vs transfer ≥ 3: 7.1%, p = 0.01) (Tab. 3). With the increasing number of unsuccessful IVF cycles, the number of embryos transferred (n) in subsequent cycles increased (transfer 1: n = 1.1, transfer 2: n = 1.3, transfer ≥ 3: n = 1.5; p < 0.001) (Tab. 4). The average length of time from the last thawed ET to the fresh ET in the studied IVF cycle in the subpopulation of women with one IVF failure vs in the subpopulation with more than one IVF failure did not differ significantly and equaled to 17 vs 19 weeks, respectively.

The percentage of pregnancies achieved in the study population compared to the population in the first IVF cycle in relation to LPS protocol used is presented in Table 5. The percentage of achieved pregnancies and live births did not depend on the LPS protocol used in any of the studied populations. Moreover, there were no significant differences in the rates of achieved pregnancies and live births within the subpopulation with one IVF failure vs with ≥ 2 failures depending on LPS protocol used. In women with one failed IVF cycle, the frequency of using the D + PG protocol vs AP + PG was 67% vs 33% ($p = 0.22$), in women with at least two failed IVF failures, 35.7% vs 64.3% ($p < 0.001$), and in the first IVF cycle these values were 80% vs 20% ($p < 0.001$). In the population in the first IVF cycle, there was a trend of a significantly higher percentage of live births with tubal factor than in other indications (46.7% vs 23.1%, $p = 0.06$). However, in the population with at least two failures, the percentage of live births with tubal factor was significantly lower than in the other indications (5% vs 34%, $p = 0.01$) (Tab. 6).

There were no adverse effects of the progestogens used in the studied population.

DISCUSSION

The live birth rate for IVF-ET depends on many factors, such as the cause of infertility, the type of ovarian stimulation protocol, the quality of the embryo, the woman's age, endometrial thickness and receptivity, progestogens used, and many others [17–21]. Most of these factors are difficult or even impossible to modify. Among the modifiable factors affecting the outcome of IVF-ET, the implementation of LPS is of crucial significance [6]. Although there is no doubt that LPS is essential in IVF cycles, the preferred timing of the start and end of therapy, as well as the type and route of drug administration in the general population of women undergoing IVF, have not been established [22]. In women with prior IVF failure, the possibility of implementing a more effective LPS protocol in the next cycle would be of key therapeutic importance. Our study evaluated the effectiveness of two LPS protocols, using two different routes of administration, in women with at least one IVF failure undergoing another IVF cycle. The results showed no significant differences in the rates of biochemical pregnancies, clinical pregnancies and live births between the subpopulations using the D + PG and AP + PG protocols for LPS, regardless of the number of previous IVF cycles. The obtained obstetrics results were in line with the average IVF results in the national population at that time [23]. The results of the study indicated no superiority of any of the two tested progestogen protocols in LPS of the IVF cycle in women with previous IVF failure, irrespective of the number of failed cycles. The study included women of different

age, with different diagnoses and types of infertility. Moreover, no exclusion criteria based on the woman's body mass index or comorbidities were used, allowing the two LPS protocols to be compared in real clinical practice. Similarly, the type of progestogen protocol used was not found to have a significant impact on the outcome of the first cycle of IVF. Thus, the results can be extrapolated to the general population of women undergoing IVF, i.e., women approaching the first and subsequent IVF cycles. With the increase in the number of completed IVF cycles, the frequency of using the AP + PG protocol increased in consecutive cycles due to the implementation of the study inclusion criteria. The preference of dydrogesterone for luteal supplementation over aqueous progesterone injections in the first cycle resulted from its proven non-inferior efficacy to progesterone and the convenience of oral administration [24]. It could be therefore concluded that dydrogesterone in combination with progesterone gel was no less effective than aqueous progesterone in combination with progesterone gel in supplementing the luteal phase of the IVF cycle. It is worth emphasizing that the nature of infertility (primary/secondary) and indications for IVF (idiopathic infertility, tubal factor, male factor, reduced ovarian reserve, endometriosis, anovulation) did not differ significantly between the studied subpopulations of women, both in the study population and in women in the first IVF cycle, and their impact on the results in terms of evaluating the effectiveness of progestogen protocols could be considered negligible. The more frequent use of the short GnRH-antagonist protocol than long GnRH-agonist protocol in women approaching the first cycle of IVF, compared to the study population, resulted from its recognition as the protocol of first choice in most IVF indications thanks to the lower risk of OHSS [12]. The effectiveness of both COH protocols, expressed as the number of MII oocytes retrieved [25], did not differ significantly between women in the first IVF cycle and the study population. Therefore, it could be concluded that the effect of the selected protocol on the live birth rate was insignificant. The increasing number of embryos transferred per cycle in consecutive IVF cycles resulted from the desire to increase the individual success of IVF-ET although, so far, it has not been proven that transferring more than one embryo improves the live birth rate [26]. This goal was not achieved in the study population either, which confirmed the results of previous studies. The decreasing percentage of idiopathic infertility as an indication for IVF with each successive cycle was probably caused by the effect of the number of IVF attempts made. The opposite trend was observed for reduced ovarian reserve, for which its increasing percentage among IVF indications with each subsequent IVF attempt was probably because of its significant impact limiting the couple's fertility. The chance of a live birth in the classic indication of tubal factor infertility, if

unsuccessful in the first IVF cycle, decreased significantly in subsequent cycles, which could indicate the presence of an additional hidden factor reducing fertility. In the remaining indications, there was no significant difference in the percentage of live births depending on the number of previously unsuccessful IVF cycles.

CONCLUSIONS

It could be concluded that the most important factor determining the success of the IVF cycle is the nature of the factor impairing fertility. Pharmacotherapy, including the type of LPS protocol, is of secondary importance. Considering the lack of evidence that either of the two LPS protocols of the IVF cycle is more effective in women with prior IVF failure, other considerations should be taken into account when choosing treatment, i.e., potential side effects, dosing convenience, and patient preference. It seems reasonable to give the woman a choice of the route of drug administration if a decision is made to additionally support the vaginal LPS route.

Limitations of the study

The limitations of the study are the small sample size, its single-center character and heterogeneity of indications for IVF.

Funding

The research was financed with our own resources.

Conflict of interests

The authors declare no conflict of interest.

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Table 1. Characteristics of the study population compared to the population in the first-time *in vitro* fertilization (IVF) cycle in terms of the nature of infertility, IVF indications, stimulation protocols, luteal phase supplementation protocols

Variable	First IVF cycle (1st ET transfer) (n = 80)	≥ One failed IVF (≥ 2nd ET transfers) (n = 170)	p
Primary infertility [%] (n)	73.8% (59)	74.1% (126)	0.95
Idiopathic infertility [%] (n)	27.5% (18)	12.9% (22)	0.057
Tubal factor [%] (n)	18.8% (15)	25.9% (44)	0.2
Male factor [%] (n)	46.3% (37)	50.6% (86)	0.49
Low ovarian reserve [%] (n)	10% (8)	19.4% (33)	0.058
Endometriosis [%] (n)	23.8% (19)	25.9% (44)	0.69
Ovulatory dysfunction [%] (n)	5% (4)	5.9% (10)	0.76
Short GnRh-antagonist protocol [%] (n)	78.8% (63)	58.8% (100)	0.002
Long agonist protocol [%] (n)	21.3% (17)	41.2% (70)	0.002
D + PG [%] (n)	80% (64)	54.1% (92)	< 0.001
AP + PG [%] (n)	20% (16)	45.9% (78)	< 0.001

ET — embryo transfer; D + PG — dydrogesterone + progesterone in vaginal gel; AP + PG — progesterone in subcutaneous injection + progesterone in vaginal gel

Table 2. Mean values of selected variables in the study population compared to the population in the first-time *in vitro* fertilization (IVF) cycle

Variable	First IVF cycle (1st ET transfer)	≥ One failed IVF (≥ 2nd ET transfers)	P
Mean age [years]	32.7	33.3	0.21
Mean AMH	3.5	3.45	0.82

concentration [ng/dL]			
Mean progesterone concentration [ng/dL]	0.86	0.72	0.2
Number of transferred embryos [n]	1.1	1.4	0.02
Mean endometrium thickness on the day of embryo transfer [mm]	11.1	11.1	0.94
Duration of infertility [years]	3.9	4.01	0.75

ET — embryo transfer; AMH — Anti-Müllerian Hormone

Variable	First IVF cycle (1st ET transfer)	One failed IVF cycle (2nd ET transfer)	≥ 2 failed IVF cycles (≥ 3rd ET transfer)	p
Primary infertility [%] (n)	73.8% (59)	74% (74)	74.3% (52)	0.9
Idiopathic infertility [%] (n)	22.5% (18)	17% (17)	7.1% (5)	0.01
Tubal factor [%] (n)	18.8% (15)	24% (24)	28.6% (20)	0.14
Male factor [%] (n)	46.3% (37)	49% (49)	52.9% (37)	0.4
Low ovarian reserve [%] (n)	10% (8)	17% (17)	22.9% (16)	0.02
Endometriosis [%] (n)	23.8% (19)	25% (25)	27.1% (19)	0.6
Ovulatory dysfunction [%] (n)	5% (4)	6% (6)	5.7% (4)	0.93
Short GnRh-antagonist protocol [%] (n)	78.8% (63)	57% (57)	61.4% (43)	0.02
Long agonist protocol [%] (n)	21.3% (17)	43% (43)	38.6% (27)	0.02
D + PG [%] (n)	80% (64)	67% (67)	35.7% (25)	< 0.001
P + PG [%] (n)	20% (16)	33% (33)	64.3% (45)	< 0.001

Table 3. Population characteristics in terms of the nature of infertility, indications for *in vitro* fertilization (IVF) and stimulation protocols applied in the subpopulations of women subjected to fresh embryo transfer: in the first IVF cycle (transfer 1), with a history of 1 IVF cycle failure (transfer 2), with a history of at least IVF 2 failures (transfer ≥ 3)

ET — embryo transfer; D + PG — dydrogesterone + progesterone in vaginal gel; AP + PG — progesterone in subcutaneous injection + progesterone in vaginal gel

Table 4. Mean values of selected variables in the subpopulations of women subjected to fresh embryo transfer: in the first cycle of *in vitro* fertilization (IVF) (transfer 1), with a history of 1 failure of the IVF cycle (transfer 2), with a history of at least 2 failures of the IVF cycle (transfer ≥ 3)

Variable	First IVF cycle (1st ET transfer)	One failed IVF cycle (2nd ET transfer)	≥ 2 failed IVF cycles (≥ 3rd ET transfer)	p
Mean age [years]	32.7	33.3	33.5	0.24
Mean AMH concentration [ng/dL]	3.5	3.48	3.40	0.78
Mean progesterone concentration [ng/dL]	0.86	0.76	0.66	0.2
Number of transferred embryos [n]	1.1	1.3	1.5	< 0.001
Mean endometrium thickness on the day of embryo transfer [mm]	11.1	11.1	11.1	0.99
Duration of infertility [years]	3.9	3.9	4.2	0.47

ET — embryo transfer; AMH — Anti-Müllerian Hormone

Table 5. Percentage of pregnancies achieved in the study population compared to the population in the first *in vitro* fertilization (IVF) cycle depending on the luteal phase supplementation protocol used

		Variable	**D + PG (92)**	**AP + PG (78)**	**p**
Study population (≥ 1 failed IVF cycle) (170)		Biochemical pregnancy	6.5% (6)	10.3% (8)	0.37
		Clinical pregnancy	7.6% (7)	3.8% (3)	0.29
		Biochemical and clinical pregnancy	14.1% (13)	14.1% (11)	0.99
		Live birth	23.9% (22)	26.9% (21)	0.65
		Variable	**D + PG (67)**	**AP + PG (33)**	**p**
	One failed IVF cycle (2nd ET transfer) (100)	Biochemical pregnancy	6% (4)	12.1% (4)	0.28
		Clinical pregnancy	9% (6)	6.1% (2)	0.61
		Biochemical and clinical pregnancy	14.9% (10)	18.2% (6)	0.67
		Live birth	26.9% (18)	21.2% (7)	0.54
		Variable	**D + PG (25)**	**AP + PG (45)**	**p**
	≥ 2 failed IVF cycles (≥ 3rd ET transfer) (70)	Biochemical pregnancy	8% (2)	8.9% (4)	0.89
		Clinical pregnancy	4% (1)	2.2% (1)	0.67
		Biochemical and clinical pregnancy	12% (3)	11.1% (5)	0.91
		Live birth	16% (4)	31.1% (14)	0.16
First IVF cycle (1st ET transfer) (80)		**Variable**	**D + PG (64)**	**AP + PG (16)**	**p**
		Biochemical pregnancy	6.3% (n = 4)	0 (n = 0)	0.3
		Clinical pregnancy	10.9% (n = 7)	25% (n = 4)	0.14
		Biochemical and clinical pregnancy	17.2% (n = 11)	25% (n = 4)	0.47
		Live birth	26.6% (n =	31.3% (n = 5)	0.7

		17)		

D + PG — dydrogesterone + progesterone in vaginal gel; AP + PG — progesterone in subcutaneous injection + progesterone in vaginal gel

Table 6. Live birth rate in subsequent *in vitro* fertilization (IVF) cycles depending on the cause of infertility

	IVF indication	Live birth rate (%, n)	Live birth rate (%, N-n)	p
Study population (≥ 1 failed IVF) (170)	Idiopathic infertility	40.9% (9/22)	23% (34)	0.07
	Tubal factor	18.2% (8/44)	27.8% (35)	0.19
	Male factor	24.4% (21/86)	26.2% (22)	0.75
	Low ovarian reserve	15.2% (5/33)	27.8% (38/137)	0.46
	Endometriosis	20.5% (9/44)	27% (34)	0.37
	Ovulation disorders	20% (2)	26% (41)	0.68
One failed IVF cycle (2nd ET transfer) (100)	Idiopathic infertility	41.2% (7/17)	21.7% (18/83)	0.09
	Tubal factor	29.2% (7/24)	23.7% (18)	0.61
	Male factor	22.4% (11/49)	27.5% (14/51)	0.52
	Low ovarian reserve	11.8% (2/17)	27.7% (23/83)	0.13
	Endometriosis	20 % (5/25)	26.7 % (20/75)	0.48
	Ovulation disorders	16.7% (1/6)	25.5% (24/94)	0.61
> 2 failed IVF cycles (≥3rd ET transfer) (70)	Idiopathic infertility	40% (2/5)	24.6% (16)	0.45
	Tubal factor	5% (1/20)	34% (17)	0.01
	Male factor	27% (10) 10/37	24.2% (8)	0.79
	Low ovarian reserve	18.8% (3) 3/16	27.8% (15)	0.46
	Endometriosis	21.1% (4) 4/19	27.5% (14)	0.58
	Ovulation disorders	25% (1) 1/4	25.8% (17)	0.97
First IVF cycle (1st ET transfer)	Idiopathic infertility	16.7% (3)	30.6% (19)	0.24
	Tubal factor	46.7% (7)	23.1% (15)	0.06
	Male factor	21.6% (8)	32.6% (14)	0.27
	Low ovarian	37.5% (3)	26.4% (19)	0.5

(80)	reserve			
	Endometriosis	31.6% (6)	26.2% (16)	0.64
	Ovulation disorders	50% (2)	26.3% (20)	0.3