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# Vaginal use of micronized progesterone for luteal support. A randomized study comparing Utrogestan® and Crinone® 8%

Lucie Michnova[a], Jiri Dostal[b], Milan Kudela[b,c], Petr Hamal[d], Katerina Langova[e]

**Background and Objective.** Luteal phase physiology is distorted by in vitro fertilization (IVF) cycles using gonadotropin-releasing hormone (GnRH) agonists and antagonists, Controlled ovarian hyperstimulation leads to luteal phase defect and for this reason, luteal phase support is now an integral part of IVF/ICSI-ET programs. The support is provided by hCG, progesterone or GnRH-a. This study compared the efficiency, safety and tolerance of two vaginal micronized progesterones, Utrogestan and Crinone 8%.
**Methods.** 111 women, 18-40 years old, FSH < 10 IU/L and normal uterus findings were included. The efficiency of the two preparations to provide luteal support was evaluated by the fertilization, implantation, pregnancy and take-home baby rates. The safety was compared through the results of vaginal findings and vaginal inflammation markers before and after treatment. Comparison of tolerance was made by evaluating 21 subjective patient questionnaire parameters.
**Results.** There were no significant differences between the preparations in terms of efficiency or safety though Crinone 8% was better tolerated.
**Conclusion.** The outcomes of this study suggest that a vaginal gel with micronized progesterone (Crinone 8%) is the optimal choice at this time for luteal support.

**Key words:** luteal phase support, IVF/ET, Progesterone, Utrogestan, Crinone 8%

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*[a] IVF Clinic Olomouc, Horni Lan 6, Olomouc, Czech Republic*
*[b] Department of Obstetrics and Gynecology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic*
*[c] Department of Health Care Sciences, Faculty of Humanities, Thomas Bata University in Zlin, Czech Republic*
*[d] Department of Microbiology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic*
*[e] Department of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic*
*Corresponding author: Lucie Michnova, e-mail: lucka.m@centrum.cz*

## INTRODUCTION

According to the Czech National Registry of Reproduction Health and the National Registry of Assisted Reproduction (NRAR), the need for assisted reproduction techniques (ART) is increasing. The main methods used are in vitro fertilization (IVF) and intracytoplasmic sperm injections (ICSI). There were 32245 cycles of assisted reproduction in the Czech Republic in 2013 (ref.[1]). In Belgium, Denmark, Estonia, Iceland, Norway, Slovenia, Sweden and the Czech Republic more than 3.0% of all newborns are conceived by assisted reproduction. It is estimated that there are 1.5 million cycles of AR around the world and 350 000 children are born by this method every year[2].

From the foregoing, it is thus crucial to have an optimally prepared endometrium for successful implantation of the embryo. The process starts in the proliferative phase of the menstrual cycle and continues into the luteal phase. For proper growth of the endometrium, the two basic hormones are estradiol (E) and progesterone (P). In the follicular phase of the natural cycle, the follicle stimulating hormone (FSH) stimulates the granulous cells of the Graafian follicle to produce E. Its level gradually increases and reaches a peak just before a steep rise in luteinizing hormone (LH). This triggers the ovulation process. After ovulation, the collapsed follicle and residual granulous cells form the corpus luteum. Steroid production depends on increasing levels of LH during the luteal phase[3,4]. The secretion of E and P culminates four days after ovulation. This then continues for about a week and decreases four days before the next period.

Both hormones are responsible for the proper growth and transformation of the endometrium[4]. The endometrium is the main target tissue of sex hormones and progesterone is responsible for the secretory transformation of the endometrium primed by estrogen. P affects local vasodilatation and decreases the contractility of the myometrium. The endometrial cycle depends on the ovarian cycle and corresponds to its two phases divided by ovulation. Hence the main role in the maturation of the endometrium, implantation of the embryo and conservation of the pregnancy depends on an optimal ratio of E to P (ref.[5]). During the secretory phase of the endometrium, there is a relatively short period for viable implantation, the so called implantation window[6,7].

After the impregnation, the production of P continues, due to the stimulation of the corpus luteum by human chorionic gonadotrophin (hCG) (ref.[8]). An adequate luteal function is therefore necessary not only for successful implantation of the embryo but also for maintenance of the pregnancy. The production of steroids by the corpus

luteum starts in the 5th week. It is then gradually taken over by the placenta[9]. The placenta is the only source of P and E after the 7th week of pregnancy[10].

Since the start of ART it is obvious that the luteal phase is insufficient in AR. One theory postulated that oocytes retrieval itself is responsible for luteal phase insufficiency and hence for insufficient steroid production. Later it was confirmed that the retrieval of only one follicle does not impair the luteal phase[11]. The luteal phase in stimulated cycles is different from the luteal phase in a natural cycle. It has been confirmed that the multifollicular development itself has an effect on the length of the luteal phase[12]. Stimulation after oocyte retrieval leads to the development of multiple corpora lutea and hence the levels of E and P are supraphysiological in the early luteal phase. The relative hyperestrinism suppresses hypophysal LH production and it is believed that this is possible trigger mechanism of premature luteolysis[13]. The mechanism of premature luteolysis is not known in detail but the studies point to an indirect influence of E on the corpus luteum[14,15]. The length of ovarian steroid production after controlled ovarian hyperstimulation (COH) is about two or three days shorter than in the natural cycles[4]. Premature decrease in ovarian steroid production was the reason for the introduction of luteal support into IVF/ET cycles[16,17]. Gonadotrophin-releasing hormone agonists (GnRH-a) and gonadotrophin-releasing hormone antagonists (GnRH-ant.) used in stimulation protocols emphasised the problem of a short luteal phase. For this reason, luteal support is a standard part of the treatment in IVF/ET programs[18].

The most important factor of sufficient production of endogenous P in stimulated cycles is hCG. After inducting oocytes maturation by exogenous hCG, the corpora lutea survive under its influence up to the 6th day. Rapid decrease in P levels then ensues[19]. In case of an impregnation after the ET on the 8th day, the level of endogenous hCG rises again and the corpora lutea are stimulated for production of P (ref.[18]). There is thus a 3 day interval of progesterone insufficiency and luteal support then became a fundamental part of the IVF/ICSI-ET program. This can be provided two ways. P can be delivered exogenously or corpus luteum can be stimulated to produce its own P after the retrieval of oocytes. Progesterone is routinely used for luteal support. It is possible to deliver progesterone orally, intramuscularly, subcutaneously and via the vagina, rectum, nose. The usual routes are oral, intramuscular and vaginal.

The development of the micronized technique provided better absorption of the delivered progesterone. Micronized progesterone is clear gestagen and very compatible with natural progesterone. It acts on progesterone receptors and has no androgenicity.

The target of this study was to compare the efficiency, safety and tolerance of the vaginal use of micronized P for luteal support. The women in the first group were given Utrogestan and in the second group, Crinone 8%. We also studied changes in vaginal microflora and signs of vaginal inflammation.

## PATIENTS AND METHODS

### Entry criteria and ethical aspects

The study took place in The Centre of Assisted Reproduction, University Hospital in Olomouc. Entry criteria for participation were: age 18-40years, basic value of FSH less than 10 IU/L, normal finding in the uterine cavity proven by hysterosalpingography or hysteroscopy.

According to the statistical power analysis it was necessary to randomize minimally 51 patients in each group to confirm a 15% difference in the efficiency, safety and tolerance between groups. It was expected that 16% of patients will not finish the study after the randomization. 111 patients who underwent controlled ovarian stimulation within the IVF/ICSI/ET program were included in the study. All patients fulfilled inclusion criteria and signed an informed consent approved by the Ethics board. To rule out patients with low ovarian response, the criteria for participation in the study were: E level more than 1000 pg/mL (3671 pmol/L) on the day of hCG administration and less than 5000 pg/mL (18355 pmol/L) due to increased risk of hyperstimulation syndrome OHSS.

There were 58 patients in the Utrogestan group and 53 patients in the Crinone 8% one. The patients were prospectively randomized to one of the two arms of the study according to a PC generated program.

### Controlled Ovarian Hyperstimulation (COH)

We used a long depot follicular protocol for controlled ovarian hyperstimulation with GnRH-a/rFSH (gonadotrophin- releasing hormone agonist/recombinant FSH) (Zoladex, Decapeptyl, Diphereline/Gonal F, Puregon). HCG was administered when the biggest follicle reached a diameter of 20 mm and oocyte retrieval was carried out. The embryo transfer was done after 3 days of embryo cultivation.

### Luteal support

On the day of oocyte retrieval, E levels were evaluated and the patients were randomized to the groups The patients in the first group were on Utrogestan (600 mg) - 2 capsules 3 times a day vaginally, patients in the second group on Crinone 8% (90 mg), one dose of vaginal gel daily. The micronized progesterone medication started 2 days after the oocyte retrieval and in case of positive hCG, continued up to the 10th week of pregnancy.

### Vaginal microscopy and cultivation

The cultivation and microscopic examination of the vaginal smear was carried out on the day of positive hCG test. The same day, patients answered the questionnaires. Microbiological findings were assessed by a microbiologist.

### Outcomes

The evaluation criteria were: fertilization rate (FR), implantation rate (IR), pregnancy rate (PR), take home baby rate (THBR), number of cryopreserved embryos, abortion rate, pregnancies after 12th week of pregnancy, OHSS, mode of delivery, duration of pregnancy, baby weight, multiple pregnancies, gender of babies. Further comparison

criteria were: safety, changes in vaginal microflora, signs of vaginal inflammation, evaluation of tolerance by questionnaires. Patients responded on a scale of 1 - 4 (no problems, slight, moderate, severe). Questions were focused on the route of administration, vaginal irritation, escape of medication from the vagina, sickness, vomiting, discomfort, constipation, diarrhoea, stomach-ache, headache, breast tension, joint ache, genital itching, somnolence, feeling of increased discharge, irritation of external genitals caused by discharge, feeling of urinary frequency (day and night), decreased sexual desire, dyspareunia.

**Statistical analysis**

The data are presented as median, minimal- maximal value, average and standard deviation. The data were rated through Shapiro-Wilks tests of normality. Given a skewed distribution, the means/medians were compared using a Mann-Whitney U-test. All tests were done on the level $P<0.05$ statistical significance. The IBM SPSS Statistics 22 program was used.

The patients were also compared by age. The ages were compared using a t-test.

## RESULTS

Infertility duration, infertility factor, number of previous IVF cycles, ICSI, AH, OHSS and spontaneous abortions are shown in Table 1.

**Table 1.** Demographic and treatment data for patients using Utrogestan and Crinone 8%.

| Parameter | Utrogestan | Crinone 8% | *P* |
|---|---|---|---|
| Number of patients | 58 | 53 | |
| Age | 31.7 ± 3.5 | 30.8 ± 3.2 | 0.145 |
| Infertility (years) | 4.0 ± 3.1 | 4.1 ± 2.9 | 0.538 |
| Ovarian factor | 7/58 (12.10%) | 5/53 (9.40%) | 0.848 |
| Tubal factor | 21/58 (36.2%) | 17/53 (32.1%) | |
| Male factor | 22/58 (37.9%) | 25/53 (47.2%) | |
| Endometriosis | 4/58 (6.9%) | 4/53 (7.5%) | |
| Another factors | 4/58 (6.9%) | 2/53 (3.8%) | |
| Basic FSH | 6.4±1.8 | 6.6±1.6 | 0.658 |
| Number of previous IVF/ET- 0 cycles | 42/58 (72.4%) | 35/53 (66.0%) | 0.722 |
| Number of previous IVF/ET- 1 cycles | 11/58 (19.0%) | 13/53 (24.5%) | |
| Number of previous IVF/ET- 2 cycles | 4/58 (6.9%) | 5/53 (9.4%) | |
| Number of previous IVF/ET- 3 cycles | 1/58 (1.7%) | 0/53 (0.0%) | |
| FSH for stimulation (IU) | 2265±1179 | 1978±451 | 0.138 |
| Estradiol on the day of hCG administration (pmol/L) | 10889±3645 | 11246±3383 | 0.71 |
| Progesterone on the day of hCG administration (nmol/L) | 2.7±1.5 | 2.6±1.5 | 0.732 |
| Estradiol on the day of oocytes retrieval (pmol/L) | 4206±1801 | 4574±2050 | 0.384 |
| Progesterone on the day of oocytes retrieval (nmol/L) | 49.4±22.6 | 44.7±17.8 | 0.447 |
| Number of obtained oocytes | 21.3±8.8 | 18.8±6.6 | 0.095 |
| ICSI | 48/58 (82.8%) | 44/53 (83.0%) | 1 |
| Number of oocytes with two pronuclei 2 | 10.2±5.9 | 9.3±4.8 | 0.550 |
| Assisted hatching | 49/58 (84.5%) | 42/53 (79.2%) | 0.622 |
| Cancelled before ET | 5/58 (8.6%) | 6/53 (11.3%) | 0.755 |
| Number of patients with ET | 53 | 47 | |
| Number of transferred embryos – 1 | 7/53 (13.2%) | 5/47 (10.6%) | 0.54 |
| Number of transferred embryos – 2 | 44/53 (83.0%) | 42/47 (89.4%) | |
| Number of transferred embryos – 3 | 2/53 (3.8%) | 0/47 (0%) | |
| Endometrium width ET (mm) | 11.7±2.9 | 12.0±3.5 | 0.972 |
| Estradiol on ET (pmol/L) | 5675±3289 | 5131±2361 | 0.643 |
| Progesterone on ET (nmol/L) | 227.0±134.3 | 213.4±120.5 | 0.804 |
| Number of cryopreserved embryos | 3.2±4.3 | 2.2±3.0 | 0.488 |
| Ovarian hyperstimulation syndrome 1st degree | 2/53 (3.8%) | 0/47 (0.0%) | 0.142 |
| Ovarian hyperstimulation syndrome 2nd degree | 2/53 (3.8%) | 2/47 (4.3%) | |
| Ovarian hyperstimulation syndrome 3rd degree | 4/53 (7.5%) | 0/47 (0.0%) | |
| Estradiol on the day of positive hCG (pmol/L) | 3712.0±5794.8 | 3588.1±5570.0 | 0.755 |
| Progesterone on the day of positive hCG (nmol/L) | 124.9±137.8 | 93.4±99.4 | 0.222 |

**Table 2.** Results for efficiency.

| Parameter | Utrogestan | Crinone 8% | *P* |
|---|---|---|---|
| Pregnancy based on a positive pregnancy blood test | 36/53 (67.9%) | 28/47 (59.6%) | 0.411[a] |
| Number of pregnancies by US (number of gestation sacs before proved heart beat) - singletons | 26/53 (49.1%) | 18/47 (38.3%) | 0.317[a] |
| Number of pregnancies by US (number of gestation sacs before proved heart beat) - twins | 10/53 (18.9%) | 10/47 (21.3%) | 0.806[a] |
| Vital pregnancies (US proved heart beat) | 29/53 (54.7%) | 25/47 (53.2%) | 1.000[a] |
| Vital pregnancies more than 12$^{th}$ week of gravidity | 28/53 (52.8%) | 22/47 (46.8%) | 0.689[a] |
| Vital pregnancies more than 20$^{th}$ week of gravidity | 28/53 (52.8%) | 21/47 (44.7%) | 0.431[a] |
| Births | 28/53 (52.8%) | 20/47 (42.6%) | 0.324[a] |
| Number of delivered foetuses–singletons | 19/53 (35.8%) | 11/47 (23.4%) | 0.196[a] |
| Number of delivered foetuses–twins | 9/53 (17.0%) | 9/47 (19.1%) | 0.800[a] |
| Duration of pregnancies ( gest. weeks) | 38.3±2.5 | 37.3±3.2 | 0.299[b] |
| Vaginal delivery | 18/53 (34.0%) | 7/47 (14.9%) | 0.037[a] |
| Forceps delivery | 0 | 0 | |
| VEX delivery | 1/53 (1.9%) | 1/47 (2.1%) | 1.000[a] |
| Cesarean section | 9/53 (17.0%) | 12/47 (25.5%) | 0.333[a] |
| 1$^{st}$ foetus – male | 14/53 (26.4%) | 15/47 (31.9%) | 0.660[a] |
| 1$^{st}$ foetus – female | 14/53 (26.4%) | 5/47 (10.6%) | 0.072[a] |
| 1$^{st}$ foetus birth weight | 3179.2±771.0 | 2769.5±686.8 | 0.132[b] |
| 1$^{st}$ foetus birth height | 49.3±3.1 | 47.8±4.0 | 0.192[b] |
| 2$^{nd}$ foetus – male | 2/53 (3.8%) | 3/47 (6.4%) | 0.664[a] |
| 2$^{nd}$ foetus – female | 7/53 (13.2%) | 6/53 (12.8%) | 1.000[a] |
| 2$^{nd}$ foetus birth weight | 2335.0±416.6 | 2182.2±620.7 | 0.691[b] |
| 2$^{nd}$ foetus birth height | 45.7±3.3 | 45.6±4.1 | 0.893[b] |
| Fertilization rate | 52.20% | 50.20% | 0.692[b] |
| Implantation rate | 48.10% | 41.50% | 0.390[b] |
| Pregnancy rate | 67.00% | 57.00% | 0.314[b] |
| Take home baby rate | 52.80% | 42.60% | 0.485[a] |

[a] The Fisher exact test) [b] The Mann-Whitney U-test

The groups were compared using the Mann-Whitney U-test and exact Fisher test for qualitative markers. There were no significant differences between means for any of the variables ($P$>0.05).

**Efficiency evaluation**

Efficiency, fertilization rate, implantation rate, pregnancy rate and take home baby rate were selected for evaluation in both groups. The groups were compared using the MW U-test and exact Fisher probability test.

There were no significant differences between (Table 2).

**Safety evaluation**

The safety of the two preparations was compared according to the results of vaginal smear cultivation and signs of vaginal inflammation before and after treatment. There was no statistically significant differ before and after treatment (69.8% and 68.9% resp.).

**Evaluation of tolerance**

The tolerance of the preparations was evaluated using the 21 areas in the questionnaire. Crinone 8% exhibited less subjective complaints than Utrogestan. The evaluation was carried out using a MW U-test (Table 3).

## DISCUSSION

Luteal phase insufficiency after COH is due to the supraphysiological levels of stimulating hormones. Luteal support using hCG or P is therefore an essential part of the treatment in stimulated cycles. Micronized progesterone (Utrogestan) enables better oral absorption. After oral administration, primary passage through the liver however leads to significant degradation of P. Therefore only 10% of bioactive substance remains in the circulation. Increased orally administrated doses of P causes fatigue and somnolence in most patients[4]. However increased oral doses of P do not lead to proper secretory transformation of the endometrium[20]. To overcome this setback, dydrogesterone (Duphaston) was introduced into the luteal support. This progestogene given orally has no estrogenic or androgenic effect and it ensures proper secretory transformation of the endometrium. Even if the clinical findings of the luteal support with dydrogesterone are comparable with the vaginal use of P, however dydrogesterone may cause, in some cases, non-adequate secretive transformation of endometrium[21,22].

Intramuscular administration of P enables high efficiency without the problems that may be encountered in oral administration. The usual dosage ranges between 25 – 100 mg daily. The efficiency of intramuscular P has been

**Table 3.** Evaluation of tolerance in the group with Utrogestan and in the group with Crinone 8%.

| Questions on problems connected with medication | Utrogestan | Crinone 8% | *P* |
|---|---|---|---|
| Problems with vaginal administration of a medicament | 1.2±0.6 | 1.0±0.1 | 0.023 |
| Unpleasant feelings on insertion | 1.3±0.6 | 1.1±0.3 | 0.47 |
| Vaginal discharge | 2.3±0.7 | 1.9±0.5 | 0.001 |
| Feeling of discomfort- sickness | 1.3±0.5 | 1.1±0.4 | 0.203 |
| Vomiting | 1.1±0.4 | 1.0±0.0 | 0.032 |
| Constipation | 1.3±0.8 | 1.3±0.6 | 0.546 |
| Diarrhoea | 1.3±0.7 | 1.0±0.1 | 0.022 |
| Stomach-ache | 1.3±0.6 | 1.2±0.6 | 0.154 |
| Headache | 1.3±0.6 | 1.2±0.5 | 0.368 |
| Breast tension | 1.7±0.7 | 1.9±0.7 | 0.18 |
| Joint ache | 1.1±0.5 | 1.1±0.2 | 0.803 |
| Itching | 1.4±0.6 | 1.1±0.3 | 0.028 |
| Somnolence | 1.9±0.8 | 1.6±0.7 | 0.058 |
| Unpleasant feeling in the genitals area | 1.2±0.6 | 1.3±0.5 | 0.804 |
| Increased vaginal secretion | 1.5±0.7 | 1.5±0.6 | 0.544 |
| Irritation of external genitals by discharge | 1.1±0.4 | 1.1±0.4 | 0.919 |
| Urinary frequency during the day | 1.8±0.7 | 1.6±0.6 | 0.378 |
| Urinary frequency during the night | 1.9±0.7 | 1.8±0.6 | 0.448 |
| Decreased sexual desire | 1.5±0.8 | 1.3±0.5 | 0.17 |
| Dyspareunia | 1.1±0.3 | 1.1±0.2 | 0.821 |
| Spotting or bleeding after intercourse | 1.3±0.7 | 1.4±0.8 | 0.211 |

confirmed and it is at least comparable or even better than vaginal administration[23,24]. However daily intramuscular injections are annoying. There may also be side effects like allergic reactions or sterile abscesses[25]. Eosinophilic pneumonia in an otherwise healthy patient has even been reported[26]. For these rteasons, intramuscular P is not recommended as the method of the first choice for luteal support[21].

Vaginal P enables direct transfer of P from vagina into the uterus. It bypasses liver metabolism[27]. High levels of P in the uterus and low levels in the serum were explained by the theory of a reverse flow interchangeable mechanism between the vagina and the uterus[28].

There are two available preparations of micronized P for vaginal use (Utrogestan, Crinone 8%). Utrogestan (Laboratoires Besins Iscovesco, Paris, France) is recommnded for luteal support via the vagina even though it was originally designed for oral use. The usual dose is 600-800 mg given 3 times daily. Crinone 8% gel is a jelly with micronized progesterone (Merck Serono Ltd, Feltham, UK) specifically designed for vaginal use. Vaginal administration (90 mg/day) provides several advantages and the efficiency is at least the same as the intramuscular one[23]. It is more convenient for patients and allergic reactions are rare. Comparing Utrogestan and Crinone 8%, there were no differences in efficiency though patients prefer Crinone 8% for better tolerance[29,30]. For luteal support, vaginal P is therefore the first method of choice. It is also possible to stimulate corpora lutea by the means of hCG like induction of LH peak for final maturation of the oocytes. It is however limited due to the risk of OHSS (ref.[31]). Another type of hCG (human and recombinant) can be administrated intramuscularly or subcutaneously[11]. But intramuscular hCG is preferred[11]. In 2005, GnRh was introduced as a new option for luteal support. It was expected that GnRh agonists could restore LH levels during the luteal phase and thereby ensure sufficient transformation of the endometrium[11]. In 2004 Tesarik suggested, within a program of donated oocytes, to give GnRh agonists after ICSI for 6 days. The efficiency of this method was proved by increased implantation and birth rate[32]. It was also recommended to administer P and E orally as a support of the luteal phase. The efficiency of P in luteal support has been confirmed but not E. Farhi proved that addition of E could be beneficial after the COH in long protocols with GnRH-a but a meta-analysis from 2008 showed that addition of E to P for the luteal support did not improve the results[33,34]. There is no generally accepted consensus about the length of luteal support after the COH. A study from 2002 evaluated, whether the extended luteal support in an early pregnancy had any impact on pregnancy results. The data confirmed that the luteal support could be efficient until the positivity of hCG but its later prolongation has no positive effect on abortion rate or number of deliveries[35]. The administration of P in an early pregnancy only postpones the date of abortions but does not increase the live born baby ratio[36]. Despite these facts luteal support is routinely given from day 10 up to the 12$^{th}$ week of pregnancy[24]. Micronized progesterone given orally has limited efficiency. Administration of P by the vagina is preferred.

## CONCLUSIONS

Utrogestan and Crinone 8% were compared as a means of a luteal support in the IVF/ET program in this study. There were no statistically significant differences between

the two drugs in terms of efficiency or safety. Crinone 8% was more comfortable for patients. As luteal support is an essential part of current IVF/ICSI-ET programs, the study outcomes suggest that the micronized progesterone vaginal gel is the best way.

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**Author contributions:** LM: data collecting, manuscript writing, JD: data collecting, preparation of study design, responsible for treatment at The Centre of Assisted Reproduction, MK: final approval, PH: microbiological data intepretation, KL: statistical data processing.

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