Moini *et al.*
Middle East Fertility Society Journal (2022) 27:16
https://doi.org/10.1186/s43043-022-00106-6

Middle East Fertility Society Journal

RESEARCH Open Access

Subcutaneous progesterone (Prolutex) versus vaginal (Cyclogest) for luteal phase support in IVF/ICSI cycles: a randomized controlled clinical trial

Ashraf Moini[1,2,3], Arezoo Arabipoor[1], Zahra Zolfaghari[4], Maria Sadeghi[1] and Fariba Ramezanali[1*]

Abstract

Background: To compare the safety, efficacy, and tolerability of subcutaneous vaginal progesterone suppository for luteal phase support (LPS) in assisted reproduction technology (ART) cycles in patients referred to the Royan Institute.

Methods: This randomized clinical trial was conducted from August 2016 to March 2018. The infertile patients undergoing in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) were evaluated. The controlled ovarian stimulation (COH) was performed in all of the patients with standard long GnRH agonist protocol. After ovum pickup, eligible women were randomly allocated into two groups. In group A, since oocyte retrieval day, subcutaneous injections of progesterone (50 mg) (Prolutex®) were used daily, and in group B, two vaginal suppositories (Cyclogest ®) were administrated for LPS. The clinical pregnancy and miscarriage rates and the drug's side effect were compared between two groups by appropriate statistical tests.

Results: Finally, 40 patients in each group were enrolled, and the IVF/ICSI outcomes were compared between groups. The data analysis showed that no significant differences were found between groups in terms of the demographic, infertility characteristics, and the COH outcome between groups. The chemical and clinical pregnancy rates (CPR) in group A were significantly higher than those of group B ($P=0.04$, $P=0.02$, respectively). The implantation and twin pregnancy rates in group B were significantly higher than those in group A ($P=0.009$, $P=0.02$, respectively).

Conclusion: The subcutaneous administration of progesterone 25 mg twice daily for LPS was associated with higher CPR versus vaginal progesterone, and it was safe and well-tolerated in the follow-up. In addition, it can be a suitable replacement in cases of allergic reactions to vaginal suppositories. However, further study is required to compare the cost-effectiveness of these medications.

Trial registration: The study was also registered in the Iranian Registry of Clinical Trials on February 19, 2015 (IRCT201402191141N18 at www.irct.ir, registered prospectively).

Keywords: Luteal phase support, Assisted reproduction technologies, Subcutaneous progesterone

Background

Progesterone, a reproductive hormone, has an undeniable role in support of the luteal phase, implantation, and ongoing pregnancy after assisted reproduction technology [1]. Although the pharmacokinetics and pharmacodynamics of progesterone are well-defined, there is a controversy regarding the ideal medication, the

*Correspondence: faribaramazanali@yahoo.com; fariba.ramezanali@icloud.com

[1] Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran
Full list of author information is available at the end of the article

administration method, the time of starting, and the length of continuation for luteal phase support in ART [2, 3]. One of these differences is the route of progesterone administration; nowadays, progesterone is available as an intramuscular injection, vaginal suppository or tablet, and oral capsules. Intramuscular injection is usually accompanied by local pain and local inflammatory reactions and sometimes with sterile abscesses. Patients prefer to use a vaginal type for fear of intramuscular injection [4]. Capsules or vaginal gels are usually better tolerated and have good efficacy in the endometrial secretion level. However, in some patients, the vaginal method is unacceptable or forbidden, or they have complained of vaginal discharge and have been intolerable to them [5, 6]. Currently, researchers at the Lugano Biochemical Institute in Switzerland combined progesterone with hydroxypropyl beta-cyclodextrin and introduce a new water-soluble product called Prolutex that can be administered subcutaneously [7, 8]. Sator et al. evaluated the pharmacokinetics of this drug and reported that doses of 25 and 50 mg could reach the appropriate serum levels for endometrial decidualization [9]. Lockwood and collaborators (2013) compared the effectiveness of this product with the type of vaginal gel through a randomized clinical trial and found no significant difference between the two types of medication [10]. Considering that the new product needs further investigation during a clinical trial in Iran, the present study was designed and carried out to evaluate the efficacy and tolerance of subcutaneous administration of progesterone and compare it with vaginal progesterone for luteal phase support in cycles IVF/ICSI in patients who were referred to the Royan Institute.

Materials and methods

Subjects

This randomized controlled trial was conducted on infertile patients aged 20–39 years who underwent their first IVF/ICSI and fresh embryo transfer at the Royan Institute from August 2016 to August 2017. The study protocol was approved by the Institutional Review Board and local Ethics Committee of Royan Institute, and the written informed consent was taken from all of the patients before entering the study. The study was registered in the Iranian Registry of Clinical Trials prospectively (www.irct.ir; IRCT201402191141N18).

The convenience sampling was selected for including eligible patients in the study. The patients with a serum progesterone level ≥ 1.2 ng/ml on hCG administration day, uterine factors (submucosal myoma or intramural fibroids ≥ 5 cm and multiple uterine polyps), as well as hydrosalpinx, severe male factor infertility, and moderate to severe endometriosis diagnoses, and who are candidate for preimplantation genetic detection with history of recurrent miscarriage or repeated implantation failures, and subjects with body mass index (BMI) ≥ 30 kg/m^2 were excluded from the study.

The standard long gonadotropin-releasing hormone (GnRH) agonist ovarian stimulation protocol was used for all of the study participations. Thus, the vaginal ultrasonography was performed on the 2nd or 3rd day of the menstrual cycle, and if the endometrium was less than 5 mm and no follicular cyst larger than 12 mm was observed, the patients received oral contraception pills from the 5th day of menstruation. The subcutaneous injection of 0.5 mg Buserelin (Superfact, Aventis, Frankfurt, Germany) was started daily from the 17th day of the menstrual cycle (the mid-luteal of the preceding cycle). Then, after observation of the pituitary downregulation (onset of menstrual bleeding and serum estradiol level less than 50 pg/ml), the dose of Buserelin was reduced to 0.2 mg, and ovarian stimulation was initiated the next day using 150 IU of recombinant follicle-stimulating hormone (r-FSH) (Gonal-F: Serono Laboratories Ltd., Geneva, Switzerland). From the 7th day of the cycle, vaginal ultrasound was performed every other day, and the dose of rFSH was adjusted according to the rate of ovarian response. If at least two follicles with a size of 18 mm or more were observed, the injection of GnRH agonist and gonadotropins was stopped, and two ampoules of 5000 IU of human chorionic gonadotropin (hCG, choromon, IBSA) were injected intramuscularly.

The oocytes were collected by transvaginal ultrasound-guided aspiration under sedation, 34–36 h after hCG injection. After the oocyte retrieval process, eligible women were randomly allocated into two groups: luteal phase support using daily subcutaneous injections of progesterone (Prolutex) (intervention group) in contrast and the control group using vaginal progesterone (Cylogest). The permuted block randomization was designed by the methodological advisor according to a computer-generated list. A researcher midwife in the OPU operating room carried out the patients' enrolment and assignment to intervention and control groups. The researcher who was responsible for following up the results of the patients' treatment cycle and the data analyzer was not aware of the grouping type. The ICSI or IVF was performed as the standard procedure for all patients. Forty-eight to 72 h later, two top-quality embryos were transferred.

In the experimental group (A), since ovum pickup day, a daily subcutaneous injection of progesterone (25 mg) (Prolutex®; IBSA Institute, SA Biochimique) was used, and in the control group (B), two vaginal suppositories were applied (Cyclogest ®; Actavis, Barnstaple, UK). If pregnancy has occurred, the luteal phase support was

continued until 10 weeks of pregnancy. Sixteen days after embryo transfer, as well as 6 and 10 weeks of pregnancy, possible side effects, gastrointestinal, skin, and local pain and discomfort, while using the medications were followed by the designed questionnaire and recorded. The side effects, the implantation rate, clinical pregnancy, and abortion rates were compared between two groups by appropriate statistical tests.

Statistical analysis

Due to a lack of financial resources, it was decided to conduct a pilot study with a sample size of 40 patients in each group. Upon completion of the study, the power of the study was estimated by placing the means and standard deviations of the implantation rate in two groups in the post hoc power calculator (ClinCalc software), and the analysis demonstrated that the study has 90% power with type-1 error ($\alpha = 0.05$). The normality of variables was evaluated by the Kolmogorov–Smirnov test prior to analysis. When necessary, laboratory values have been reported as mean ± standard error (SE). Baseline differences between groups were determined by the independent sample's *t*-test for normal quantitative variables, and the chi-squared test was used to compare categorical data and pregnancy outcomes between groups. Statistical analysis was performed with SPSS version 20 (SPSS, Chicago, IL, USA) with a significance level of $P < 0.05$.

Results

Totally, in this trial, one-hundred and thirty-nine patients were evaluated, forty patients have not included due to dissatisfaction with the participation in the study, twelve individuals for the risk of ovarian hyperstimulation syndrome, and seven for a poor ovarian response. Finally, eighty patients were allocated randomly to the experimental ($n = 40$) and control ($n = 40$) groups (Fig. 1).

Table 1 reveals that the patients in the two groups had no statistically significant differences in terms of primary characteristics such as age, body mass index, serum luteinizing (LH), follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH) levels, and cause and duration of infertility.

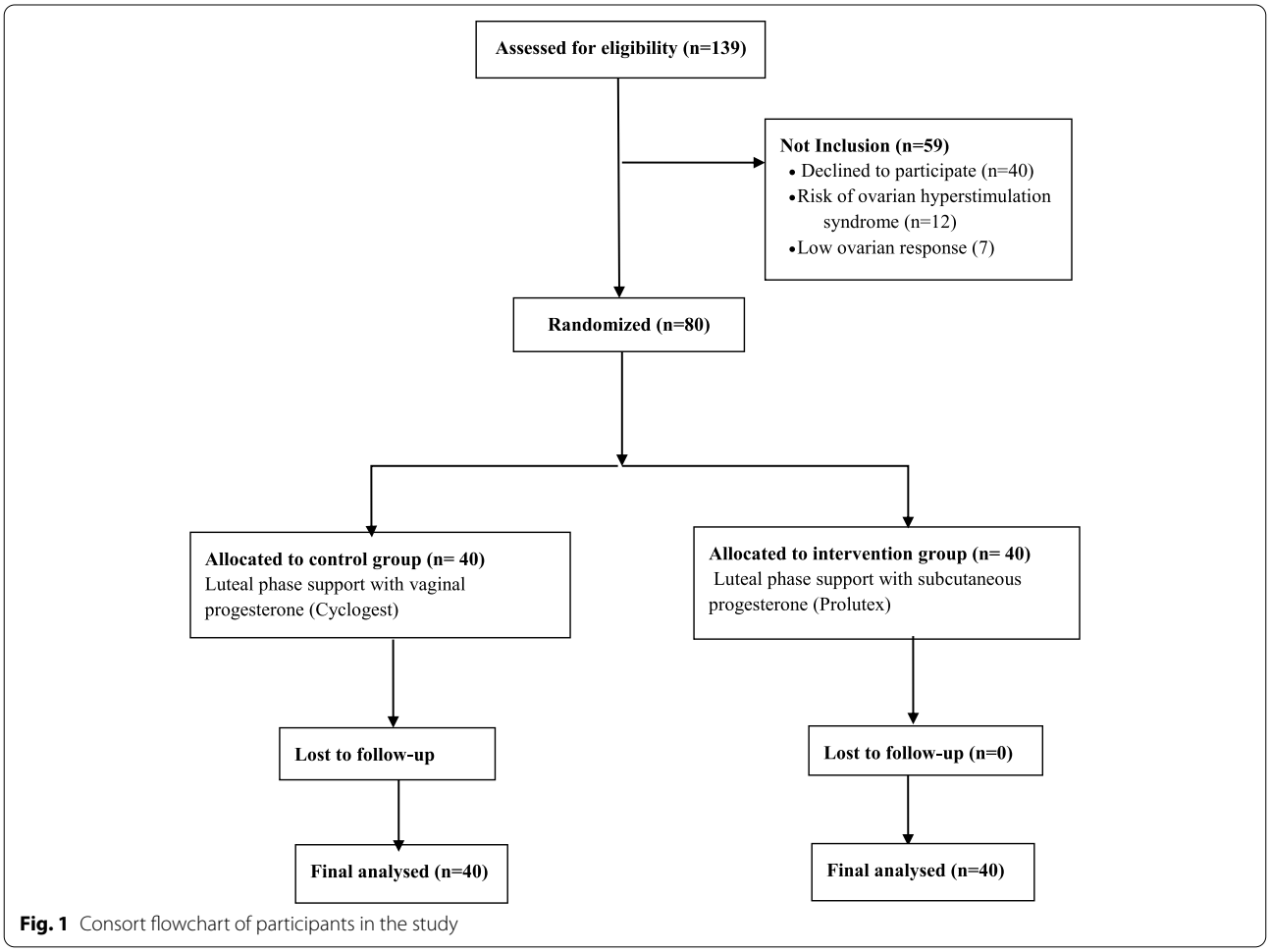

Fig. 1 Consort flowchart of participants in the study

Table 1 Comparison of the patients' baseline characteristics between two groups

Variables	Group A (Prolutex) (*n* = 40)	Group B (Cyclogest) (*n* = 40)	*p*-value
Women's age (years)	31.7 ± 4.6	32.7 ± 3.7	0.26
Body mass index (kg/m^2)	24.0 ± 3.0	25.4 ± 2.9	0.08
The serum level of AMH (ng/ml)	3.1 ± 1.8	2.4 ± 1.2	0.08
The basal level of FSH (IU/l)	6.0 ± 2.0	6.5 ± 2.7	0.08
The basal level of LH (IU/l)	4.9 ± 2.7	4.7 ± 2.3	0.76
Infertility duration (years)	5/2 ± 6/4	8/3 ± 5/4	0.98
The cause of infertility, *n* (%)			0.46
Male factor	23 (57.5)	27 (67.5)	
Unexplained factor	14 (35)	9 (22.5)	
Tubal factor	3 (7.5)	4 (10)	
Type of infertility, *n* (%)			0.75
Primary	35 (87.5)	33 (82.5)	
Secondary	5 (12.5)	7 (17.5)	

AMH, anti-Müllerian hormone; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *IU*, international unit. *P*-value less than 0.05, there was a significant difference between groups

Table 3 Comparison of the IVF/ICSI cycle outcomes between two groups

Variable	Group A (Prolutex) (*n* = 40)	Group B (Cyclogest) (*n* = 40)	*p*-value
Fertilization rate (mean ± SD)	71.7 ± 22.0	73.2 ± 25.6	0.77
Implantation rate (mean ± SD)	52.8 ± 19.8	73.0 ± 26.8	0.015*
Chemical pregnancy rate/ET	(24/40) 60.5	(15/40) 38.5	0.045*
Clinical pregnancy rate/ET, *n* (%)	(40/23) 57.5	(40/13) 32.5	0.025*
Multiple pregnancy rate, *n* (%)	2/23 (8.7)	6/13 (46.1)	0.009*
Miscarriage rate, *n* (%)	2/23 (8.7)	1/13 (7.7)	0.92

IVF/ICSI, in vitro fertilization/intracytoplasmic sperm injection; *ET*, embryo transfer. The quantitative and qualitative variables are presented as mean (standard deviation) and number (percentage), respectively.**P*-value less than 0.05, there was a significant difference between the two groups

The results of the ovarian stimulation cycle were presented in Table 2. The analysis demonstrated that the means duration of ovarian stimulation and the gonadotropins dosages, the number of retrieved oocytes, the serum progesterone level at the hCG administration day, and the day of embryo transfer, the number and quality of embryos, and endometrial thickness on hCG administration day were not significantly different between the two groups.

Table 3 shows the comparison of pregnancy outcomes between groups. The analysis indicated that the chemical and clinical pregnancy rates were significantly higher in the Prolutex group than those in the Cylogest group (60.1% vs. 38.5% and 57.5% vs. 32.5%, $P = 0.04$, $P = 0.02$, respectively). The implantation and twin pregnancy rates were significantly higher in the Cylogest group than those in the Prolutex group (73% vs. 52.8% and 46.1% vs. 8.7%, $P = 0.02$, $P = 0.009$, respectively).

In the present study, a multivariable logistic regression test was used to investigate the predictive factors of clinical pregnancy. Effective variables including age and body mass index, AMH serum level, the number of obtained MII oocytes, and the serum progesterone level changes from hCG administration day to ET day, luteal phase support type (progesterone subcutaneous injection or suppository), were included in the model. The results revealed that ultimately, the use of progesterone subcutaneous injection to support the luteal phase as well as changes in progesterone levels from the day of hCG administration day to the ET day was significantly statistical predictive factors in this study. This means that the chances of clinical pregnancy in patients who used the progesterone subcutaneous injections to the luteal phase support were 4.8 times higher than in cases who used the progesterone suppository (odds ratio: 4.8, 95%

Table 2 Comparison of the ovarian stimulation outcomes between two groups

Variables	Group A (Prolutex) (*n* = 40)	Group B (Cyclogest) (*n* = 40)	*p*-value
Number of used gonadotropins (rFSH) ampoules	21.7 ± 5.9	22.6 ± 5.7	0.45
Duration of ovulation stimulation (day)	10.8 ± 2.3	11.3 ± 1.8	0.24
Total number of retrieved oocytes	8.7 ± 4.6	9.1 ± 3.9	0.69
Number of MII oocytes	7.1 ± 3.6	8.0 ± 3.6	0.27
The serum level of progesterone on hCG day (ng/ml)	0.78 ± 0.47	0.74 ± 0.50	0.44
The serum level of progesterone on ET day (ng/ml)	55.7 ± 8.1	55.0 ± 9.8	0.93
The number of transferred embryos	2.0 ± 0.5	2.0 ± 0.6	0.68
Endometrial thickness (mm)	5.1 ± 8/9	4.1 ± 7.9	0.88

rFSH, recombinant follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *ET*, embryo transfer. The data are presented as mean (± standard deviation). *P*-value less than 0.05, there was a significant difference between groups

confidence interval (CI): 1.4–16.6, $P=0.01$). Also, for every 10 ng/ml increase in serum progesterone levels from hCG administration day to ET day, the chance of clinical pregnancy increases by 20% (odds ratio: 1.2, CI 95%: 1.07–1.3, $P=0.002$).

Assessing the questionnaire of the side effects showed that two patients in the Prolutex group complained of difficulty in using the medication due to pain in the injection site as well as four complaining patients in the Cylogest group due to spotting, discharge, and pulling out of the suppositories. Ultimately, the patient satisfaction in both groups was more than 90%.

Discussion

Recently, the introduction of subcutaneous progesterone injections to support the luteal phase in ART cycles expands the range of treatment options, especially for those women who are dissatisfied with vaginal formulation or who cannot tolerate this procedure. The results of the present study showed that the effectiveness of progesterone subcutaneous ampoules was comparable with vaginal suppositories, such that the clinical pregnancy rate in the group using subcutaneous injection of progesterone was significantly higher than that of in the vaginal group.

Doblinger et al. [11] combined data from two clinical trials into a meta-analysis and reported that there are no statistically significant or clinically significant differences exist between subcutaneous and vaginal progesterone for LPS. In their study, in addition to the similar efficacy of subcutaneous progesterone injections compared to the vaginal type on the likelihood of live birth, it was found that only female age and ovarian response were both independent predictor factors for the probability of live birth, and the type of progesterone used to LPS did not change a patient's chances of having a live birth.

The clinical pregnancy rates in two RCTs were 27.4% in Lockwood et al. [10], 41.6% in Baker et al. [8] studies, and recently, Hibshi et al. [12], in a retrospective study, reported 26.3% in the Prolutex group; nonetheless, three studies demonstrated non-inferiority of subcutaneous to vaginal progesterone. In our study, the clinical pregnancy rate (57.5%) in the Prolutex group was significantly higher than the rates reported in the previous studies. This inconsistency is reassuring given that different results could be obtained in different patient populations. The difference between the present study and previous studies can be due to the difference in the dose of subcutaneous injections of progesterone. The eligible patients in the present study were normal women who underwent the first therapeutic IVF/ICSI cycles, and the LPS with 50 mg of subcutaneous progesterone ampoule daily was compared with 400 mg of vaginal suppositories twice daily. It seems that the better clinical pregnancy outcomes in the group receiving progesterone subcutaneous ampoules could be due to the fact that the dose of progesterone ampules in the present study was twice as much as in the previous two clinical trials. In addition, the subcutaneous injection of progesterone (Prolutex) dissolved in water has more rapid absorption, and peak serum progesterone was achieved 3 to 4 times faster than intramuscular injection [13].

So far, only two clinical trial studies have been conducted in this area, although a large number of trials initiated by researchers have been recorded on the clinicaltrial.gov site. It is expected that the use of subcutaneous progesterone in various clinical scenarios including frozen embryo transfer cycles and oocyte donation is a complementary therapy to be studied in early pregnancy.

Since Levine et al. [14], and later Yanushpolsky et al. [15], confirmed that patients prefer vaginal progesterone to intramuscular injections, this is clearly related to the pain and difficulty associated with intramuscular injection, even when the injection is given by a nurse. At present, the ART cycle relies almost entirely on subcutaneous injections of agonist, antagonist, and gonadotropin ampules, and many women feel comfortable performing this subcutaneous injection [16]. Also, some women refuse to insert the suppository into the vagina due to cultural and religious beliefs, especially when pregnancy has been confirmed, and many patients suffer from gel or suppository leaks, and they are concerned about the complete absorption of the drug. In addition, vaginal manipulation when the environment is not clean enough could increase the risk of reproductive tract infections as a cause of abortion [17] and premature birth,[18] if not treated immediately. Therefore, this new product (subcutaneous injection of progesterone) may be a patient-friendly alternative treatment in particular for patients who have a cultural, personal, or medical ban on using vaginal progesterone [16]. However, more research is required to compare the cost-effectiveness of this drug with other LPS treatment options.

In the present study, multivariable logistic regression demonstrated that the route of progesterone administration and the changes in serum progesterone levels from the day of hCG administration day to the ET day were the significant predictors for clinical pregnancy in our study population. It means that every 10 ng/ml increase in serum progesterone levels from hCG administration day to ET day elevates the chance of clinical pregnancy by 20%. Most of the previous studies have reported the negative role of the primary rising of serum progesterone levels to more than 1.5 ng/ml on hCG administration day in fresh ET cycles [19–21]. In the present study, we excluded patients with a serum progesterone

level ≥ 1.5 ng/ml on ovum pickup day; therefore, the changes in the serum progesterone level between the puncture to ET days were evaluated. Since these findings were the secondary outcome of our study for the first time, more studies are needed for discussion in this field.

Conclusions

On the basis of present results, the daily administration of 50 mg subcutaneous progesterone for LPS is associated with more clinical pregnancies than 800 mg daily vaginal suppositories, and it can be a safe and suitable alternative option in cases of allergic reactions to vaginal suppositories.

Abbreviations

LPS: Luteal phase support; ART: Assisted reproduction technologies; IVF: In vitro fertilization; ICSI: Intracytoplasmic sperm injection; COH: Controlled ovarian stimulation; CPR: Clinical pregnancy rate; GnRH: Gonadotropin-releasing hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; AMH: Anti-Müllerian hormone; hCG: Human chorionic gonadotropin; SD: Standard deviation.

Acknowledgements

We would like to express our appreciation to the participants and our colleagues at the Royan Institute (Miss Azar Yahyaei and Miss Zahra Chekini) and the collaborators in the Shafayab Gostar Company for their assistance in this research. The subcutaneous progesterone ampoules (Prolutex) have been granted by the Shafayab Gostar company representative of the IBSA Institute Biochimique S.A., in Iran.

Authors' contributions

AM and FR: conducted the design of the study and drafting and revising the manuscript. AM, FR, and AA: participated in the conception of the study, interpretation of data, and drafting and revising the manuscript. MS: contributed to the data acquisition and drafting and revising the manuscript. ZZ: performed the data analysis and revising the manuscript. The authors read and approved the final manuscript.

Funding

The study did not have any funding support.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

The Institutional Review Boards and the Ethics Committees of the Royan Institute approved this study (ethics code: EC/93/1102). The eligible patients signed written informed consent forms prior to participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran. [2]Department of Gynecology and Obstetrics, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran. [3]Breast Disease Research Center (BDRC), Tehran University of Medical Sciences, Tehran, Iran. [4]Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran.

Received: 15 December 2021 Accepted: 27 May 2022
Published online: 27 June 2022

References

1. Van der Linden M, Buckingham K, Farquhar C, Kremer J, Metwally M (2012) Luteal phase support in assisted reproduction cycles. Hum reprod update 18(5):473
2. Di Guardo F, Midassi H, Racca A, Tournaye H, De Vos M, Blockeel C (2020) Luteal phase support in IVF: comparison between evidence-based medicine and real-life practices. Front Endocrinol 11:500
3. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015;7(7):1-222. Art. No.: CD009154. https://doi.org/10.1002/14651858.CD009154.pub3.
4. Check JH (2009) Luteal phase support in assisted reproductive technology treatment: focus on Endometrin(R) (progesterone) vaginal insert. Ther Clin Risk Manag 5(4):403–407 (Epub 2009/09/16)
5. Tomic V, Tomic J, Klaic DZ (2011) Oral micronized progesterone combined with vaginal progesterone gel for luteal support. Gynecol Endocrinol 27(12):1010–1013
6. Silverberg KM, Vaughn TC, Hansard LJ, Burger NZ, Minter T (2012) Vaginal (Crinone 8%) gel vs. intramuscular progesterone in oil for luteal phase support in in vitro fertilization: a large prospective trial. Fertil Steril. 97(2):344–8
7. de Ziegler D, Sator M, Binelli D, Leuratti C, Cometti B, Bourgain C et al (2013) A randomized trial comparing the endometrial effects of daily subcutaneous administration of 25 mg and 50 mg progesterone in aqueous preparation. Fertil Steril 100(3):860–866
8. Baker VL, Jones CA, Doody K, Foulk R, Yee B, Adamson GD et al (2014) A randomized, controlled trial comparing the efficacy and safety of aqueous subcutaneous progesterone with vaginal progesterone for luteal phase support of in vitro fertilization. Hum Reprod 29(10):2212–2220
9. Sator M, Radicioni M, Cometti B, Loprete L, Leuratti C, Schmidl D et al (2013) Pharmacokinetics and safety profile of a novel progesterone aqueous formulation administered by the s.c. route. Gynecol Endocrinol. 29(3):205–8
10. Lockwood G, Griesinger G, Cometti B, De Placido G, Alviggi C, Ranieri A et al (2014) Subcutaneous progesterone versus vaginal progesterone gel for luteal phase support in in vitro fertilization: a noninferiority randomized controlled study. Fertil Steril 101(1):1129 (e3)
11. Doblinger J, Cometti B, Trevisan S, Griesinger G (2016) Subcutaneous progesterone is effective and safe for luteal phase support in IVF: an individual patient data meta-analysis of the phase III trials. PLoS ONE 11(3):e0151388
12. Hibshi A, Aldriweesh A, Saeed B, Coskun S, Awartani K (2020) Subcutaneous progesterone (Prolutex)® for luteal phase support in cycles of in vitro fertilization–embryo transfer-a retrospective cohort study. Clin Obstet Gynecol 6:1–5
13. Sator M, Radicioni M, Cometti B, Loprete L, Leuratti C, Schmidl D et al (2013) Pharmacokinetics and safety profile of a novel progesterone aqueous formulation administered by the sc route. Gynecol Endocrinol 29(3):205–208
14. Levine H (2000) Luteal support in IVF using the novel vaginal progesterone gel Crinone 8%: results of an open-label trial in 1184 women from 16 US centers. Fertil Steril 74(4):836–837
15. Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M (2010) Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization–embryo transfer cycles: a prospective randomized study. Fertil Steril 94(7):2596–2599
16. Engmann L, Benadiva C (2012) Agonist trigger: what is the best approach? Agonist trigger with aggressive luteal support. Fertil Steril 97(3):531–533
17. Donders GG, Van Bulck B, Caudron J, Londers L, Vereecken A, Spitz B (2000) Relationship of bacterial vaginosis and mycoplasmas to the risk of spontaneous abortion. Am J Obstet Gynecol 183(2):431–437

18. Flynn CA, Helwig AL, Meurer LN (1999) Bacterial vaginosis in pregnancy and the risk of prematurity. J Fam Pract 48(11):885–892
19. Elgindy EA (2011) Progesterone level and progesterone/estradiol ratio on the day of hCG administration: detrimental cutoff levels and new treatment strategy. Fertil Steril 95(5):1639–1644
20. Bosch E, Labarta E, Crespo J, Simon C, Remohi J, Jenkins J et al (2010) Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. Hum Reprod 25(8):2092–2100
21. Venetis C, Kolibianakis E, Bosdou J, Tarlatzis B (2013) Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles. Hum Reprod Update 19(5):433–457

Publisher's Note