RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.2021-12
Cyprus J Med Sci 2022;7(6):806-811

A Comparison of the Effects of Early and Late Ovarian Stimulation on Reproductive Outcomes in Patients with Polycystic Ovary Syndrome

Nurettin Türktekin[1], Ramazan Özyurt[1], Arzu Yurci[2]

[1]In Vitro Fertilization Center, İstanbul, Turkey
[2]Memorial Kayseri Hospital, Unit of In Vitro Fertilization Center, Kayseri, Turkey

Abstract

BACKGROUND/AIMS: Data on the effect of onset time of gonadotropins for ovarian stimulation on in vitro fertilization (IVF) outcomes are limited. This study was planned to compare the effects of early and late-onset ovarian stimulation on gonadotropin dose, ongoing pregnancy and live birth rates in women with polycystic ovary syndrome (PCOS).

MATERIALS AND METHODS: The data of 432 patients who underwent IVF/intracytoplasmic sperm injection for PCOS-induced infertility/subfertility were reviewed retrospectively. Among them, 304 were included in this study. They were divided into two groups according to the timing of their ovarian stimulation (2nd & 5th days of the menstrual cycle).

RESULTS: The total oocyte count, the number of fertilized oocytes, and the number of grade 1 or 2 embryos were significantly higher in those subjects receiving ovarian stimulation on the 2nd day of the menstrual cycle. Those patients who received ovarian stimulation on day 2 had a higher total gonadotropin dose and a longer gonadotropin administration time. Although the number of total oocytes was higher in those patients starting treatment on the 2nd day, treatment started on day 5 (shorter treatment) provided better fertilization.

CONCLUSION: In women with infertile PCOS, ovarian stimulation started on the 2nd day of the cycle provided more favorable IVF results in terms of total oocytes and fertilized oocytes, while the total gonadotropin dose was found to be higher. Fertilization and oocyte quality were better in the stimulations started on the 5th day.

Keywords: Polycystic ovary syndrome, infertility, in vitro fertilization, early or late stimulation

INTRODUCTION

Polycystic ovary syndrome (PCOS), which is characterized by polycystic ovary morphology, ovulatory dysfunction and hyperandrogenism, has been reported to affect up to 10% of reproductive-age women.[1] It is also one of the leading causes of anovulatory infertility.[2] In vitro fertilization (IVF) protocols have been reported to be successful in achieving clinical pregnancy in women with PCOS.[3] In this protocol, one or more mature egg cells are taken from the woman's ovaries and fertilized in a special environment outside the body with sperm taken from the male. After the procedure, this fertilized egg is placed in the uterus or frozen and stored for future use. IVF is a repeatable procedure with satisfactory results, applied in many infertility cases caused by men or women.[4]

Controlled ovarian hyper-stimulation is used to prevent the development of multiple follicles and the associated risk of premature luteinization,

To cite this article: Türktekin N, Özyurt R, Yurci A. A Comparison of the Effects of Early and Late Ovarian Stimulation on Reproductive Outcomes in Patients with Polycystic Ovary Syndrome. Cyprus J Med Sci 2022;7(6):806-811.

ORCID IDs of the authors: N.T. 0000-0001-8167-3124; R.Ö. 0000-0001-6822-2222; A.Y. 0000-0003-4808-9019.

Address for Correspondence: Arzu Yurci
E-mail: arzuyurci@yahoo.com
ORCID ID: orcid.org/0000-0003-4808-9019

Received: 31.07.2020
Accepted: 17.01.2021

as well as ovarian hyper-stimulation syndrome (OHSS).[5] The purpose of controlled ovarian hyper-stimulation is to support the production of oocytes of good quality, and it is frequently initiated in the early stages of the menstrual cycle.[6] Recombinant follicle-stimulating hormone (rFSH) is also usually administered on the 2nd or 3rd day of the menstrual cycle. However, such early administration may not only lead to OHSS but could also cause the development of multiple low-quality oocytes.[7] On the other hand, late administration of rFSH may limit the number of oocytes which are required for fertilization.

Data concerning the impact of the timing of ovarian stimulation on IVF outcomes are very limited. This study aimed to compare early (2nd day of the menstrual cycle) and later (5th day of the menstrual cycle) ovarian stimulation in terms of oocyte quality, total gonadotropin dose and also the rates of pregnancy, ongoing pregnancy and live birth.

MATERIALS AND METHODS

The data of 432 patients with PCOS (aged between 18-37 years) who had undergone IVF due to infertility at the gynecology department of a tertiary healthcare institute, between January 2012 and January 2020, were obtained from institutional digital records. The diagnosis of PCOS was based on the diagnostic criteria revised by the Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group.[8]

Among the 432 patients, 128 were excluded (pregnant women, smokers, women in early menopause, breastfeeding women, women with diagnosed hypertension, diabetes mellitus, and adrenal gland disorder). The final group of 304 women with PCOS was divided into two groups, according to the timing of ovarian stimulation, as follows: Ovarian stimulation on the 2nd day of the menstrual cycle (group 1) and ovarian stimulation on the 5th day of the menstrual cycle (group 2). All procedures performed in this study involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and within the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Clinical Research Ethic Committee of Erciyes University (approval number: 2011-KAEK-80). Informed consent was obtained from all individual participants included in this study.

The patients' FSH, estradiol and baseline ultrasonography analyses were performed on the 2nd and 3rd days of menstruation. Initial gonadotropin dose was determined according to their body mass index, antral follicle counts and serum anti-mullerian hormone (AMH) levels. Before initiating gonadotropins, we confirmed the absence of >20 mm follicles and evaluated baseline estradiol and progesterone levels (confirming, E2 <40 pg/mL, progesterone <1 ng/mL). All patients were treated with flexible daily gonadotropin releasing hormone (GnRH) protocols for controlled ovarian stimulation. The initiation of GnRH antagonists (Cetrotide, Merck-Serono) was performed after the determination of ≥14 mm follicle size and/or ≥400 pg/mL serum E_2 levels on the fifth day of treatment. Ovulation was triggered with choriogonadotropin alfa 250 mch (Ovitrelle, Merck-Serono) when at least two leading follicles were ≥18 mm. Oocytes were collected 35 or 36 hours after triggering. Oocytes were fertilized by the microinjection method and embryo transfer was performed 5 days later. One or two blastocyst embryo transfer was performed at the stage of top quality or good quality embryos according to Gardner and Schoolcraft blastocyst grading system. Luteal phase support with progesterone gel was continued until a pregnancy test was performed. The patients underwent pregnancy testing via blood samples (beta-hCG) 12 days after transfer and were scheduled for USG evaluation 15 days later for the identification of the fetal heart-beat.

Biochemical pregnancy was established when the pregnancy test result was positive with >20 mIU/mL HCG levels on the 12th day after embryo transfer. Clinical pregnancy was defined as the presence of fetal cardiac activity on vaginal ultrasonography.

The differences between the two groups with respect to total oocyte count, MII oocyte count, fertilization, biochemical and clinical pregnancy rates were the primary outcome measures of this study. The total dose of gonadotropin used was the secondary outcome measure.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were used to assess normal distribution. According to the distribution characteristics, continuous data are given as mean ± standard deviation or median (minimum-maximum). Categorical variables are described with frequency (and percentage). The comparison of normally distributed variables was performed with the independent samples t-test; whereas non-normally distributed variables were analyzed with the Mann-Whitney U test. The comparison of groups in terms of categorical variables was carried out with chi-square tests. Multiple logistic regression analysis (forward conditional method) was performed to determine significant factors effective on pregnancy and live birth. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

A total of 304 women with PCOS who underwent IVF at our institute were analyzed (mean age: 28.60±4.80 years). Among these, 161 received ovarian stimulation on the 2nd day of the menstrual cycle and

Table 1. Summary of the patients' characteristics with regard to starting day

	Starting day			
	2nd day (n=161)	5th day (n=143)	Total (n=304)	p
Age, years	28.88±4.82	28.28±4.77	28.60±4.80	0.276
Duration of infertility, years	6 (1-22)	5 (1-24)	6 (1-24)	0.094
BMI, kg/m^2	27.02±2.21	26.77±1.94	26.90 ±2.09	0.242
E_2 (day 2), pg/mL	35 (8-97)	36 (6-93)	36 (6-97)	0.458
Progesterone (day 2), ng/mL	0.2 (0.01-0.8)	0.1 (0.01-0.7)	0.17 (0.01-0.8)	0.009
AMH, ng/mL	5.9 (4.6-8.2)	5.1 (4.0-7.1)	5.4 (4.0-8.2)	<0.001

AMH: anti-müllerian hormone, BMI: body mass index, E_2: estradiol. Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to normality of distribution.

143 received ovarian stimulation on the 5th day of the menstrual cycle. The progesterone concentration measured on the second menstrual day was significantly higher in those subjects receiving ovarian stimulation on the 2nd day of the menstrual cycle compared to those receiving ovarian stimulation on the 5th day of the cycle [0.2 (0.01-0.8) vs. 0.1 (0.01-0.7), p=0.009]. Recipients of ovarian stimulation on the 2nd day of the menstrual cycle had higher E_2 and progesterone concentrations on the day of ovulation compared to those receiving ovarian stimulation on the 5th day of the menstrual cycle (p<0.001, for each). Additionally, anti-mullerian hormone (AMH) values were significantly higher in the recipients of ovarian stimulation on the 2nd day (p<0.001) (Table 1).

As shown in Table 2, those patients who received ovarian stimulation on day 2 had a higher total gonadotropin dose and a longer gonadotropin administration time compared to those receiving ovarian stimulation on the 5th day of the cycle. When the two groups were compared, we found that the total oocyte count [28 (12-66) vs. 21 (11-37), p<0.001], the number of fertilized oocytes [14 (4-45) vs. 13 (6-26), p=0.041], and the number of grade 1-2 embryos [21 (7-55) vs. 17 (10-35), p=0.001] were significantly higher in those subjects receiving ovarian stimulation on the 2nd day of the menstrual cycle (longer treatment). It was also noted that those subjects starting ovarian stimulation on the 2nd day of the menstrual cycle were more likely to undergo thaw cycles; whereas those starting ovarian stimulation on the 5th day of the menstrual cycle were more likely to undergo fresh cycles. Both groups were similar in terms of clinical pregnancy, ongoing pregnancy and live birth rates (Figure 1).

During multiple logistic regression analysis, we found that early hCG administration was associated with a higher frequency of clinical pregnancy rates (p=0.004). Other variables included in the model, such as 2nd day E_2 (p=0.053), 2nd day progesterone (p=0.230), total gonadotropin dose (p=0.642), stimulation day (p=0.785), days with gonadotropin (p=0.785), hCG day E_2 (p=0.388), total oocyte number (p=0.822), M_2 (p=0.179), PN (p=0.109), type of procedure (p=0.870) and embryo day (p=0.113) were found to be non-significant (Table 3).

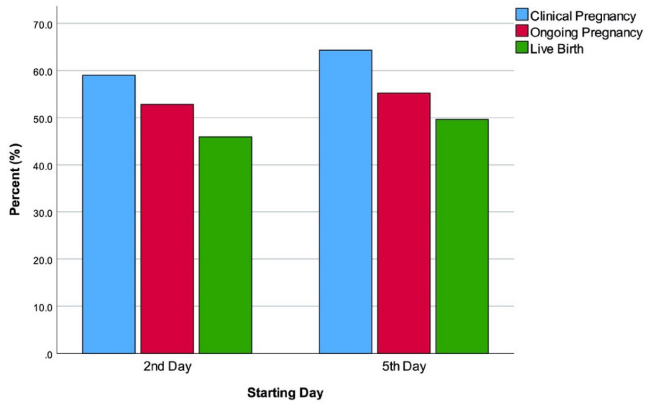

Figure 1. Pregnancy and live birth rates with regard to starting day.

Table 2. Comparison of the characteristics of the groups according to the onset day of ovarian stimulation.

	Starting day			
	2nd day (n=161)	5th day (n=143)	Total (n=304)	p
Total GND dose	2,700 (1,000-4,500)	1,600 (800-3,375)	2,000 (800-4,500)	<0.001
Days with GND	10 (8-13)	8 (8-10)	9 (8-13)	<0.001
E_2 (hCG day), pg/mL	3,300 (1,000-12,470)	2,890 (1,016-7,577)	3,000 (1,000-12,470)	<0.001
Progesterone (hCG day), ng/mL	1.2 (0.09-4)	0.9 (0.1-2.5)	1.09 (0.09-4)	<0.001
Total oocyte count, (n)	28 (12-66)	21 (11-37)	24 (11-66)	<0.001
M^2 embryos, (n)	21 (7-55)	17 (10-35)	18 (7-55)	0.001
PN, (n)	14 (4-45)	13 (6-26)	13 (4-45)	0.041
Embryo day				
2 & 3	70 (43.48%)	51 (35.66%)	121 (39.80%)	0.165
5 & 6	91 (56.52%)	92 (64.34%)	183 (60.20%)	
Procedure				
Thaw cycle, (n)	118 (73.29%)	55 (38.46%)	173 (56.91%)	<0.001
Fresh cycle, (n)	43 (26.71%)	88 (61.54%)	131 (43.09%)	
Clinical pregnancy, (n)	95 (59.01%)	92 (64.34%)	187 (61.51%)	0.340
Ongoing pregnancy, (n)	85 (52.80%)	79 (55.24%)	164 (53.95%)	0.669
Live birth, (n)	74 (45.96%)	71 (49.65%)	145 (47.70%)	0.521

E_2: estradiol, GND: gonadotropin, hCG: human chorionic gonadotropin. Data are given as median (minimum-maximum) for continuous variables, and as frequency (percentage) for categorical variables.

Table 3. Factors affecting clinical pregnancy rates during logistic regression analysis

	β coefficient	Standard error	Wald	p	Exp (β)	95% confidence interval for β	
hCG day	-0.606	0.211	8.240	0.004	0.546	0.361	0.825
(Constant)	1.168	0.273	18.301	<0.001	3.215	-	-

Dependent variable: Clinical pregnancy; Nagelkerke R^2=0.038. hCG: human chorionic gonadotropin.

DISCUSSION

This study compared IVF outcomes in subjects receiving ovarian stimulation on the 2nd day or the 5th day of the menstrual cycle. Our findings showed that the total oocyte count, the number of grade 1-2 embryos, and the number of fertilized oocytes were higher in those subjects receiving earlier ovarian stimulation than in those receiving ovarian stimulation later in the cycle; however, this advantage of earlier ovarian stimulation did not translate into an increased frequency of clinical pregnancies or live births. We also determined that the number of days with gonadotropin and total gonadotropin dose were lower in those subjects receiving earlier ovarian stimulation compared to those receiving later ovarian stimulation. These results show that shorter treatment has similar pregnancy results compared to longer treatment, with advantages of less drug exposure and lower cost. The logistic regression model revealed that earlier hCG administration was independently associated with higher clinical pregnancy rates.

IVF has been reported to be successful in about 50% of cases, with significant success particularly in those younger than 35 years of age.[9] It is also well-known that IVF is frequently utilized in the treatment of PCOS-related infertility, which is one of the most common causes of female infertility.[10,11] Although earlier practice with IVF was based on the spontaneous cycle of women, later studies showed that it was possible to obtain a higher number of oocytes by inducing ovulation through the administration of gonadotropins during the menstrual cycle.[12,13] To date, several protocols for achieving controlled ovarian hyper-stimulation in patients undergoing IVF have been introduced.[7,14] Although some of these protocols may provide more favorable pregnancy outcomes depending on the underlying cause of infertility and the hormonal status of the subject, none of the various protocols have demonstrated universal superiority.[15-17]

Recombinant FSH (rFSH) is a commonly utilized agent in controlled ovarian hyper-stimulation of patients undergoing IVF.[7,18,19] Current practice is based on administering rFSH earlier in the cycle, on the 2nd or 3rd day.[17,18] However, earlier administration of rFSH may be associated with OHSS development and may increase healthcare costs. However, data concerning IVF outcomes in subjects receiving ovarian hyper-stimulation later in the menstrual cycle are limited. To the best of our knowledge, there are no directly comparable studies in the literature. Only a few studies have evaluated the role of ovarian stimulation timing on IVF-related characteristics. For instance, in a recent study including patients who were to receive gonadotoxic therapy, Von Wolff et al.[20] reported that ovarian stimulation after day 5 of the menstrual cycle was associated with an increased number of oocytes compared to ovarian stimulation between the 1st and 5th days of the menstrual cycle. Studies conducted on patients requiring urgent cancer treatment have also shown that "random start" ovarian stimulation is comparable to conventional stimulation protocols with regard to the yield of mature oocytes and their developmental potential into embryos.[21,22] Taking into account the data derived from studies investigating random ovarian stimulation, we hypothesize that ovarian stimulation in the later stages of the menstrual cycle would perform similar to ovarian stimulation in the early stages of the menstrual cycle in terms of IVF outcomes in women with PCOS. This is a critical result as shorter treatment would result in lower exposure to gonadotropins and would lower the cost of treatment.

We must also mention the fact that women with PCOS are often considered to have a higher propensity for OHSS.[23] Fischer et al.[24] reported that when FSH dosage was calculated sparingly (low-dose stimulation), women with PCOS had no significant increase in the frequency of OHSS. Other studies have also identified a reduced risk of OHSS in PCOS with the use of various treatments; including metformin,[25] lower GnRH dose,[26] GnRH antagonists,[27] and the "*coasting*" method.[28] Therefore, the higher total gonadotropin dose and longer treatment with earlier stimulation may represent a risk for OHSS. However, there is no unanimous opinion on this topic and considering the deviations between studies, it seems apparent that there is a yet-to-be-elucidated dynamic hormonal balance/imbalance which is at play during the development of OHSS, especially considering its unquestionable relationship with the hCG trigger.[26] It has been reported that AMH-based ovarian stimulation protocols significantly reduce the risk of OHSS, the dose of rFSH used, and the duration of stimulation.[29] Therefore, in determining the initial rFSH dose, we use patient age, previous starting doses as well as a serum AMH measurement. We prefer AMH mostly to assess ovarian reserve in poor responders, premature ovarian aging or in cases of endometrioma/endometriosis. However, we use AMH values to determine the starting dose of rFSH to minimize the risk of OHSS due to PCOS.

In this study, clinical pregnancy rates were similar between the groups, and overall, 61.5% of the cases had clinical pregnancy and 47.7% of them had live birth. When the previous studies were examined, it was seen that the reported frequencies are heterogeneous. Although there were studies in which similar results were published with our study,[30-32] lower frequencies were also reported.[33-35] In particular, the results of studies in which the cumulatively pregnancy and live birth rates of several IVF trials were published were higher than our study, while single IVF trial results were lower. The difference in participant characteristics between the studies may have affected these results. The relatively younger ages of the subjects in our study may be one of the reasons for this situation. Additionally, in a meta-analysis, it was reported that the frequency of live births after IVF in PCOS cases was higher than in infertility cases caused by other reasons (odds ratio: 1.29, 95% confidence interval: 1.24-1.34).[36] The fact that all of the participants in our study were PCOS cases may be one of the reasons for better results compared to infertility cases caused by other reasons.

This is the first study investigating the timing of ovarian stimulation on IVF and pregnancy outcomes in women with PCOS. Our findings show that early ovarian stimulation provides higher total oocyte and fertilized oocytes compared to late ovarian stimulation in PCOS women. We also found that the later start of ovarian stimulation was associated with a shorter length of ovarian stimulation and lower total gonadotropin dose. Although a detailed cost-effect analysis was not performed, given the lower amount of gonadotropins used in subjects receiving fifth day ovarian stimulation (shorter treatment), we speculate that later ovarian stimulation may reduce treatment costs for infertility in women with PCOS. Another critical finding of this study was that the day of hCG administration was independently associated with clinical pregnancy rates. Nevertheless, there were no significant differences between those subjects receiving earlier or later ovarian stimulation with respect to clinical pregnancy rates and live birth rates.

Another controversial issue regarding IVF outcomes in PCOS or non-PCOS patients undergoing FET or fresh cycle is basal or pre-transfer

serum progesterone levels. We found a significant difference in serum progesterone levels between the second and fifth day groups (1.2 ng/mL vs 0.9 ng/mL). However, changes in progesterone levels did not cause a difference between the groups in terms of clinical pregnancy and live birth rates. The results of other studies on the relationship between serum progesterone levels and reproductive outcome in FET cycles are heterogeneous. While there are some studies showing that pre-transfer serum progesterone concentration affects live birth rates,[37] there are other studies reporting that progesterone levels do not affect IVF outcome.[38] As we showed in the logistic regression analysis, the difference in progesterone levels on the 2nd day and ovulation day did not cause any significant changes in the reproductive outcome parameters. Consistent with our results, it has been reported that hCG day progesterone values measured in fresh cycles do not have a significant effect on subsequent FET results in PCOS patients.[38]

Study Limitations

The important limitations of our study are that it was conducted in a single center and it had a retrospective design. Due to this study design, some variables which may have affected the results could not be evaluated retrospectively. An important limitation of our study was the inhomogeneous distribution of fresh and FET cycles among the groups. The high thaw cycle rates in the early stimulation group with the high fresh cycle rate in the late stimulation group may be due to the heterogeneity of the groups and the freeze all criteria. In both groups, OHSS risk, preimplantation genetic screening, fluid accumulation in the endometrium, weak endometrium and social indications were accepted as criteria for freeze-all. The fact that the groups could not be determined randomly may explain the difference in fresh and thaw cycle rates to some extent.

CONCLUSION

In conclusion, ovarian stimulation on the 2nd day of the menstrual cycle appears to provide more favorable IVF outcomes in terms of the total oocyte count, the number of grade 1-2 embryos and the number of fertilized oocytes when compared to ovarian stimulation on the 5th day of the cycle. However, the total gonadotropin dose was lower in those patients receiving ovarian stimulation on the 5th day of the menstrual cycle. In terms of the ultimate goals of IVF, the results of the two groups were similar.

MAIN POINTS

- In PCOS women with infertility, ovarian stimulation starting on the 2nd day of the menstrual cycle appears to provide more favorable IVF outcomes in terms of the total oocyte count and the number of fertilized oocytes.
- In PCOS women with infertility, the total gonadotropin dose is lower in those recipients of ovarian stimulation on the 5th day of the menstrual cycle.
- In PCOS women with infertility, fertilization and oocyte quality were better in those starting treatment on the 5th day.

ETHICS

Ethics Committee Approval: This study was approved by the Clinical Research Ethic Committee of Erciyes University (approval number: 2011-KAEK-80).

Informed Consent: Informed consent was obtained from all individual participants included in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.T., R.Ö., A.Y., Design: N.T., R.Ö., A.Y., Supervision: N.T., R.Ö., Resource: A.Y., Materials: A.Y., Data Collection and/or Processing: R.Ö., A.Y., Analysis and/or Interpretation: R.Ö., A.Y., Literature Search: A.Y., Writing: N.T., R.Ö., A.Y., Critical Review: N.T., R.Ö., A.Y.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

REFERENCES

1. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016; 106(1): 6-15.
2. Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: a review. J Assist Reprod Genet. 2017; 34(2): 167-77.
3. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016; 22(6): 687-708.
4. Choe J, Archer JS, Shanks AL. In vitro fertilization. [Internet]. StatPearls; 2020.
5. Kurzawa R, Ciepiela P, Baczkowski T, Safranow K, Brelik P. Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study. J Assist Reprod Genet. 2008; 25(8): 365-74.
6. Grisendi V, La Marca A. Individualization of controlled ovarian stimulation in vitro fertilization using ovarian reserve markers. Minerva Ginecol. 2017; 69(3): 250-8.
7. Maher JY, Christianson MS. Controlled ovarian stimulation and triggers in in vitro fertilization: protocol personalization key to optimize outcomes. Minerva Endocrinol. 2018; 43(1): 37-49.
8. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19(1): 41-7.
9. Eskew AM, Jungheim ES. A History of Developments to Improve in vitro Fertilization. Mo Med. 2017; 114(3): 156-9.
10. Yang W, Yang R, Yang S, Li J, Tu B, Gao C, et al. Infertile polycystic ovary syndrome patients undergoing in vitro fertilization with the gonadotropin-releasing hormone-antagonist protocol: role of hyperandrogenism. Gynecol Endocrinol 2018; 34(8): 715-8.
11. Spritzer PM, Motta AB, Sir-Petermann T, Diamanti-Kandarakis E. Novel strategies in the management of polycystic ovary syndrome. Minerva Endocrinol. 2015; 40(3): 195-212.
12. Legro RS. Practices in in vitro fertilization. Semin Reprod Med. 2015; 33(2): 61-2.
13. Reichman D, Rosenwaks Z. The difficult in vitro fertilization patient: an individualized approach. Semin Reprod Med. 2015; 33(2): 153-8.
14. Alper MM, Fauser BC. Ovarian stimulation protocols for IVF: is more better than less? Reprod Biomed Online. 2017; 34(4): 345-53.

15. Romar R, Funahashi H, Coy P. In vitro fertilization in pigs: New molecules and protocols to consider in the forthcoming years. Theriogenology. 2016; 85(1): 125-34.

16. Wang P, Zhao J, Jin C, Yu R, Lin J, Zhu R, et al. Comparision of in vitro maturation applied in PCOS and non-PCOS patients undergo stimulated and unstimulated protocols. Zhonghua Fu Chan Ke Za Zhi. 2014; 49(12): 903-8.

17. Paulson RJ. Introduction: Contemporary approaches to alternative ovarian stimulation strategies for in vitro fertilization. Fertil Steril. 2017; 108(4): 555-7.

18. Howie R, Kay V. Controlled ovarian stimulation for in-vitro fertilization. Br J Hosp Med (Lond). 2018; 79(4): 194-9.

19. Zech NH, Zech M, Baldauf S, Comploj G, Murtinger M, Spitzer D, et al. Ovarian stimulation in ART - Unwinding pressing issues. Minerva Ginecol. 2015; 67(2): 127-47.

20. Von Wolff M, Capp E, Jauckus J, Strowitzki T, Germeyer A; FertiPROTEKT study group. Timing of ovarian stimulation in patients prior to gonadotoxic therapy: an analysis of 684 stimulations. Eur J Obstet Gynecol Reprod Biol. 2016; 199: 146-9.

21. Danis RB, Pereira N, Elias RT. Random Start Ovarian Stimulation for Oocyte or Embryo Cryopreservation in Women Desiring Fertility Preservation Prior to Gonadotoxic Cancer Therapy. Curr Pharm Biotechnol. 2017; 18(8): 609-13.

22. Cakmak H, Rosen MP. Random-start ovarian stimulation in patients with cancer. Curr Opin Obstet Gynecol. 2015; 27(3): 215-21.

23. Thakre N, Homburg R. A review of IVF in PCOS patients at risk of ovarian hyperstimulation syndrome. Expert Rev Endocrinol Metab. 2019; 14(5): 315-9.

24. Fischer D, Reisenbüchler C, Rösner S, Haussmann J, Wimberger P, Goeckenjan M. Avoiding OHSS: Controlled Ovarian Low-Dose Stimulation in Women with PCOS. Geburtshilfe Frauenheilkd. 2016; 76(6): 718-26.

25. Palomba S, Falbo A, Carrillo L, Villani MT, Orio F, Russo T, et al. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil Steril. 2011; 96(6): 1384-90 e4.

26. El Tokhy O, Kopeika J, El-Toukhy T. An update on the prevention of ovarian hyperstimulation syndrome. Womens Health (Lond). 2016; 12(5): 496-503.

27. Lin H, Li Y, Li L, Wang W, Yang D, Zhang Q. Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs. PLoS One. 2014; 9(3): e91796.

28. Ohata Y, Harada T, Ito M, Yoshida S, Iwabe T, Terakawa N. Coasting may reduce the severity of the ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome. Gynecol Obstet Invest. 2000; 50(3): 186-8.

29. Cui L, Lin Y, Lin J, Wang F. AMH-based ovarian stimulation versus conventional ovarian stimulation for IVF/ICSI: a systematic review and meta-analysis. Arch Gynecol Obstet. 2020; 301: 913-22.

30. Chen R, Chen S, Liu M, He H, Xu H, Liu H, et al. Pregnancy outcomes of PCOS overweight/obese patients after controlled ovarian stimulation with the GnRH antagonist protocol and frozen embryo transfer. Reprod Biol Endocrinol. 2018; 16(1): 36.

31. Bezirganoglu N, Seckin K, Baser E, Karsli M, Yeral M, Cicek M. Isolated polycystic morphology: Does it affect the IVF treatment outcomes? J Obstet Gynaecol. 2015; 35(3): 272-4.

32. Li HW, Lee VC, Lau EY, Yeung WS, Ho PC, Ng EH. Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. J Assist Reprod Genet. 2014; 31(2): 205-11.

33. Chen ZJ, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med. 2016; 375: 523-33.

34. Swanton A, Storey L, Mcveigh E, Child T. IVF outcome in women with PCOS, PCO and normal ovarian morphology. Eur J Obstet Gynecol Reprod Biol. 2010; 149(1): 68-71.

35. Kuivasaari-Pirinen P, Hippeläinen M, Hakkarainen H, Randell K, Heinonen S. Cumulative baby take-home rate among women with PCOS treated by IVF. Gynecol Endocrinol. 2010; 26(8): 582-9.

36. Sha T, Wang X, Cheng W, Yan Y. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. Reprod Biomed Online. 2019; 39(2): 281-93.

37. González-Foruria I, Gaggiotti-Marre S, Álvarez M, Martínez F, García S, Rodríguez I, et al. Factors associated with serum progesterone concentrations the day before cryopreserved embryo transfer in artificial cycles. Reprod Biomed Online. 2020; 40(6): 797-80.

38. Pouya K, Şükür YE, İsrafilova G, Özmen B, Sönmezer M, Berker B, et al. hCG day progesterone level has no impact on the frozen thawed embryo transfer cycle outcome. J Gynecol Obstet Hum Reprod. 2021; 50(6): 102120.