**Reproductive Medicine;** *Endocrinology and Infertility*

# Does Baseline Serum Androgen Levels Have an Impact on Ovulation Induction Cycle Outcomes by Using Clomifene Citrate among Infertile Women with Polycystic Ovary Syndrome? A Retrospective Cohort Study

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**ABSTRACT**

**OBJECTIVE:** Hyperandrogenism is one of the diagnostic criteria for polycystic ovary syndrome. Women with polycystic ovary syndrome suffer from infertility due to anovulation. Hyperandrogenism results in follicular arrest at the antral stage during folliculogenesis. baseline intrinsic hyperandrogenism affects the success of ovulation induction or not. The relationship between baseline serum androgen levels and ovulation induction cycle outcomes by using clomifene citrate among infertile women with polycystic ovary syndrome has not been investigated thoroughly.

**STUDY DESIGN:** Ovulation induction cycle outcomes of 35 infertile women diagnosed with polycystic ovary syndrome according to Rotterdam criteria who have received 50-100 mg/day clomifene citrate have been evaluated retrospectively. Menstrual cycle day 2-5 serum levels for gonadotropins, androgens, metabolic parameters, and ovulation induction cycle outcomes have been compared between women who have and have not achieved clinical pregnancy following treatment.

**RESULTS:** Serum basal follicular stimulating hormone, LH, E2, fasting cholesterol, glucose, and HOMA-IR levels were comparable between these two groups of patients. Unlike other serum androgens, baseline serum-free testosterone level is significantly lower for patients who have achieved clinical pregnancy following ovulation induction with clomifene citrate. The baseline serum cut-off level for free testosterone to predict clinical pregnancy was 1.94 pg/ml with 75% sensitivity and 67% specificity rates.

**CONCLUSION:** Lower or higher levels of androgenic milieu within the ovaries result in defective folliculogenesis and ovulation failure. Increased serum levels of free testosterone which is a proxy for ovarian androgen production might be a detrimental factor for clinical pregnancy rates of women with polycystic ovary syndrome by impairing proper folliculogenesis.

**Keywords:** Androgen, Eycle outcome, Infertility, Polycystic ovary syndrome, Testosterone

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## Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent (8-13%) endocrinological disease among reproductive-age women (1). Reproductive, metabolic, and psychological disturbances can be seen in women with PCOS based on the severity of the disease. Psychological features include anxiety, depression, and body image; reproductive features include irregular menstrual cycles, hirsutism, infertility, and pregnancy complications; and metabolic features include insulin resistance (IR), metabolic syndrome, impaired glucose tolerance,

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type 2 diabetes, and increased risk for cardiovascular diseases (2). Two out of three of the Rotterdam PCOS diagnostic criteria including clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound are necessary to establish the diagnosis of the syndrome. The components of the diagnostic criteria still remain controversial while ethnic differences and variations in clinical features during the life course of women result in a diagnostic challenge. Despite obesity, IR, and increased serum anti-mullerian hormone (AMH) levels being frequent signs of the syndrome; these signs are not included in the diagnostic criteria. Four different phenotypes of the syndrome have been defined based on the presence of three diagnostic criteria of the Rotterdam consensus. The prevalence of phenotypes is variable based on ethnic groups. According to the metabolic syndrome risk assessment the prevalence was lowest in phenotype D regarding hyperandrogenemia, insulin resistance, and worse cardiometabolic profile unlike phenotypes A, B, and C (3). Infertility is a common problem for PCOS patients due to disturbances of folliculogenesis and ovulation. Optimization of glucose tolerance, body weight, blood pressure, smoking, alcohol, diet, exercise, sleep quality, mental integrity, and sexual health before initiating treatment strategies for infertility is needed to improve reproductive and obstetric outcomes (4). Lifestyle modifications, ovulation induction agents like letrozole, metformin, clomiphene citrate, gonadotropins, laparoscopic ovarian drilling, and in vitro fertilization and embryo transfer (IVF-ET) are stepwise treatment modalities of infertility in PCOS. Clinical and/or biochemical hyperandrogenism is seen in all phenotypes of PCOS except phenotype D. It is not clear whether baseline intrinsic hyperandrogenism affects the success of ovulation induction or not. In this study, we investigated the relationship between baseline serum androgen levels and ovulation induction cycle outcomes by using clomifene citrate among infertile women with PCOS diagnosis based on the Rotterdam criteria.

## Material and Method

This retrospective cohort study has been performed with the evaluation of ovulation induction cycle outcomes by using clomifene citrate and intrauterine insemination among 21-39 years old women with a PCOS diagnosis according to the Rotterdam criteria between 2020-2021. The institutional ethics committee of our hospital approved the conduction of this study on 09/12/2020 with an approval number of E1-20-1171. Informed consent has been taken from all participants who have been included in the study.

Ovulation induction cycle outcomes were extracted from the patient files. Women with a body mass index level of >=30 $kg/m^2$, confirmed insulin resistance, a history of recently used hormonal contraceptives, previous abdominal surgery, endometriosis, tubal factor infertility, male factor infertility, systemic diseases, and missing cycle outcome records were excluded. Among 64 patients with PCOS, 29 of them have been excluded due to the abovementioned criteria and 35 remaining patients have been included in the study.

The demographic properties of the participants have been recorded. Menstrual cycle day 2-5 serum levels for follicular stimulating hormone (FSH), LH, E2, androstenedione, DHEAS, total testosterone, free testosterone, SHBG, FAI (free androgen index), and antral follicle count as a surrogate marker for ovarian reserve have been detected. The insulin resistance situation of the patients has been evaluated with 75 grams oral glucose tolerance test and HOMA-IR. Ovulation induction of the patients has been performed by using oral 50-100 mg clomifene citrate (CC) tablets starting on 3-5. days of spontaneous or induced menstruation. Patients were scheduled to evaluate follicular growth on 11. day of the menstrual cycle. When at least one follicle >18 mm has been detected on transvaginal ultrasonography ovulation has been triggered by using recombinant hCG (Ovitrelle, Merck Serono, Türkiye) and intrauterine insemination procedure has been performed after 36 hours of following ovulation trigger. Luteal phase support has not been utilized. Cycles with >=3 preovulatory follicles and/or CC resistance have been excluded due to the cancellation of the treatment cycle. CC utilization dose, ovulation induction cycle parameters like number of >10 mm dominant follicles, number of >=18 mm preovulatory follicle, and clinical pregnancy rates have been recorded.

Statistical analyses have been performed with SPSS version 22. The distribution for normality of the evaluated clinical and laboratory parameters has been tested by using the Kolmogorov-Smirnov test. Independent Samples t-test has been used to analyze normally distributed variables. Nonparametric variables and variables without normal distribution have been compared by using the Mann-Whitney U test. Correlations have been measured with the Pearson test for parametric and/or normally distributed variables and with the Spearman test for nonparametric variables and/or variables without normal distribution respectively. The chi-square test and Fisher's exact test have been utilized for the comparison of categorical variables. P values lower than 0.05 has been considered statistically significant.

## Results

Patient characteristics and cycle outcomes of 35 PCOS patients who have and have not achieved clinical pregnancy following ovulation induction with clomifene citrate plus intrauterine insemination have been presented in table I. Serum basal FSH, LH, E2, fasting cholesterol, glucose, and HOMA-IR levels were comparable between these two groups of patients. Baseline serum-free testosterone level is significantly lower for patients who have achieved clinical pregnancy following ovulation induction with CC. The receiver operating characteristic (ROC) curve test has been utilized to investigate

***Table I:*** *Patient characteristics and cycle outcomes of polycystic ovary syndrome patients who have and have not achieved clinical pregnancy following ovulation induction with clomifene citrate plus intrauterine insemination*

| Parameter (mean±SD) | Patients who achieved clinical pregnancy (mean±SD) n=15 | Patients who have not achieved clinical pregnancy (mean±SD) n=20 | *p* |
|---|---|---|---|
| Age (years) | 25.6±4.2 | 26.3±3.9 | 0.61¶¶ |
| Body mass index (ratio) | 27.8±4.6 | 28.6±5.4 | 0.62¶¶ |
| Infertility duration (years) | 2.6±0.8 | 2.7±1.2 | 0.98¶¶ |
| Day 3 Follicular stimulating hormone (mIU/mL) | 6.6±0.9 | 6.7±1.4 | 0.79¶¶ |
| LH (mIU/mL) | 5.4±3.1 | 5.2±2.7 | 0.75¶¶ |
| E2 (pg/mL) | 35.1±12.5 | 38.2±10.9 | 0.44¶¶ |
| Ovulation induction cycle number (n) | 1.2±0.7 | 1.4±0.5 | 0.11¶¶ |
| Day 21 progesterone (ng/mL) | 3.2±4.5 | 2.9±4.1 | 0.96¶¶ |
| Total testosterone (ng/dL) | 32.7±11.3 | 36.7±9.6 | 0.15¶¶ |
| Free testosterone (pg/mL) | 1.88±0.58 | 2.65±1.25 | 0.036¶¶ |
| Sex hormone-binding globulin (nmol/L) | 30.9±12.9 | 40.9±28.0 | 0.66¶¶ |
| Free androgen index | 4.1±2.0 | 5.0±4.1 | 0.73¶¶ |
| 17-OH-Progesterone (ng/dL) | 42.9±22.7 | 49.3±28.2 | 0.54 |
| Androstenedione (ng/mL) | 13.2±32.6 | 49.0±89.4 | 0.14¶¶ |
| Dehydroepiandrosterone sulfate (microgram/dL) | 207.6±81.5 | 237.9±91.7 | 0.42¶¶ |
| Antimullerian hormone (ng/dL) | 6.3±3.1 | 5.4±2.3 | 0.45¶¶ |
| Total cholesterol (mg/dL) | 169.6±27.2 | 171.5±35.4 | 0.93¶¶ |
| Low-density lipoprotein (mg/dL) | 96.4±18.6 | 99.9±29.2 | 0.69¶¶ |
| High-density lipoprotein (mg/dL) | 50.7±15.5 | 48.6±12.2 | 0.65¶¶ |
| Triglyceride (mg/dL) | 113.8±45.4 | 120.4±74.2 | 0.76¶¶ |
| Fasting glucose (mg/dL | 89.4±9.6 | 88.7±9.9 | 0.65¶¶ |
| Fasting insulin mLU/L | 12.6±4.6 | 13.2±5.8 | 0.88¶¶ |
| HOMA-IR | 2.5±0.8 | 3.9±6.5 | 0.67¶¶ |
| HbA1C (%) | 5.2±0.2 | 5.3±0.2 | 0.23¶¶ |
| Maximum follicle diameter on hCG day (mm) | 18.9±1.0 | 18.3±1.9 | 0.20¶¶ |
| Rate of 2 >17 mm follicles (%) | 6.7% | 10% | 0.61¶¶ |

*¶: Mann Whitney U test, ¶¶: Independent samples t test. ¶¶¶: Fisher's exact test. *p<0.05*

the association between baseline serum-free testosterone level and clinical pregnancy achievement (Figure 1) (AUC: 0.71; 95% CI: 0.53-0.88) (*p*=0.03). The baseline serum cut-off level for free testosterone to predict clinical pregnancy was 1.94 with 75% sensitivity and 67% specificity rates. Despite baseline serum androstenedione levels being found to be lower for patients who have achieved clinical pregnancy than those who have not, this result was statistically insignificant due to wide confidence interval values of the measured serum androstenedione levels (13.2±32.6 vs. 49.0±89.4 respectively, *p*=0.14). When we compared clinical pregnancy rates according to intrauterine insemination timing; 25% of 4 patients and 45.2% of 31 patients achieved clinical pregnancy 24 hours and 36 hours following ovulation trigger respectively (*p*=0.61). A statistically insignificant positive relationship has been found between hCG day maximum follicle diameter and achievement of clinical pregnancy based on ROC curve analysis (AUC: 0.62; 95% CI: 0.43-0.81) (*p*=0.22).

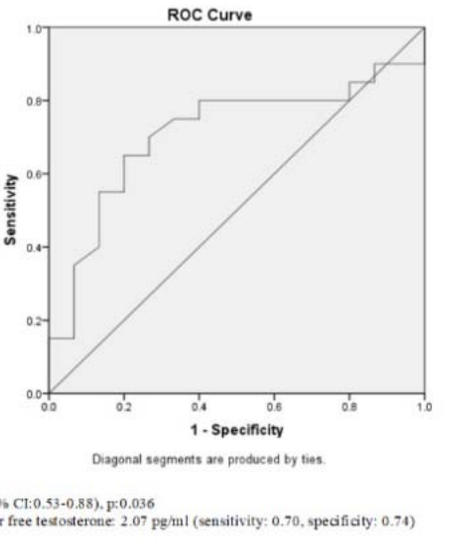


***Figure 1:*** *Receiver operating characteristic curve demonstrating the negative correlation between serum-free testosterone level and clinical pregnancy achievement following ovulation induction with clomifene citrate plus intrauterine insemination*

## Discussion

Polycystic ovary syndrome is characterized by anovulation, oligo/amenorrhea, and biochemical/clinic hyperandrogenism. Insulin resistance, arrest of folliculogenesis in the antral follicle stage, and hypersecretion of androgens from the adrenal gland are the main causes of hyperandrogenism in PCOS patients. Despite the establishment of 50-70% ovulation rates and 30-40 pregnancy rates by utilization of oral ovulation induction agents, persistence for ovulation and/or failure to get pregnant following oral ovulation induction agents remains a challenging clinical issue for clinicians and patients. The utilization of oral antidiabetic drugs, alone or combined with oral ovulation induction agents has been demonstrated to increase ovulation rates. However, the correction of hyperandrogenism by using combined hormonal contraceptives for suppression of ovarian hypersecretion of androgens before ovulation induction treatment has not been investigated thoroughly. Similarly, to the best of our knowledge, clinical studies investigating the effects of baseline hyperandrogenism on ovulation induction cycle outcomes are lacking. In a retrospective study, Sun et al. evaluated the association of basal total testosterone (T) levels and ovarian response or pregnancy outcomes in on-PCOS women undergoing in vitro fertilization (IVF) cycles (5). They concluded that basal total T levels were found to be positively correlated with ovarian reserve function, the number of follicles >14 mm on human chorionic gonadotrophin (HCG) day. Total gonadotropin dose except for pregnancy outcome for non-PCOS patients. Patients with lower ovarian reserve markers have been found to have lower levels of basal T (<20 ng/dl) which have necessitated the utilization of higher FSH dosage during controlled ovarian hyperstimulation (5).

During the follicular phase of the normal menstrual cycle, androgens are both precursors for ovarian estrogen synthesis and stimulators for augmenting FSH receptor expression on granulosa cells on small antral follicles via androgen receptors. Increasing granulosa cell proliferation, reduction of apoptosis of follicles, and stimulation of steroidogenic enzymes in mature granulosa cells are other significant effects of androgen actions in ovarian physiology (6). Ovarian androgen deficiency results in defective folliculogenesis concomitant with decreased estrogen synthesis. Animal studies have revealed that insufficient androgen activity in females causes infertility which is a frequent clinical situation in women with diminished ovarian reserve (DOR). Clinical useful effects of androgen supplementation in women with DOR have been demonstrated in low-quality studies.

In a meta-analysis including eight studies, despite having no effect on retrieved oocyte numbers, DHEA supplementation (75 mg daily in one or three divided doses for 3 to 4 months) has been seen to slightly improve clinical pregnancy rates in DOR undergoing assisted reproductive technique procedures (7). Contrarily, in another randomized clinical trial, despite AR and FSH receptor expression is increased in granulosa cells following DHEA utilization, no significant effect on clinical pregnancy rate has been seen in women with DOR (8). It remains unknown whether a subgroup of DOR patients might have needed androgen supplementation for proper folliculogenesis or not. From another aspect of view, future studies are needed about the potential detrimental or protective effects of androgen supplementation on physiological follicle depletion (9).

Both androgen deprivation and androgen excess can cause defects in folliculogenesis and ovulation processes. It seems evident that balanced levels of androgen activity in the ovary are crucial for reproductive health in women. The clinical effects of high intraovarian androgen levels on healthy follicle development and pregnancy achievement have not been investigated thoroughly. PCOS is characterized by hyperandrogenism of both the intraovarian milieu and systemic circulatory system which results in anovulation and infertility. Follicular recruitment to the preantral and antral stages is increased but progression to the preovulatory stage and ovulation is defective in women with PCOS. Tonic increased pulse frequency of the GnRH and LH secretion leads to increased testosterone production from the overstimulated theca cell population resulting in a hyperandrogenic milieu. In-utero exposure to high androgen levels has been blamed to induce future PCOS establishment in the offspring which is characterized by increased LH tone and hyperplastic follicles secreting high amounts of androgens (10). Selective estrogen receptor modulators, aromatase inhibitors, and gonadotropins are utilized to stimulate ovaries by increasing endogenous and exogenous gonadotropin discharge to achieve ovulation in infertile women with PCOS. Whether intraovarian increased androgen levels affect the folliculogenesis, ovulation, and achievement of clinical pregnancy or not is unknown. In our study, we have demonstrated that increased serum-free testosterone level, which can be a proxy for intraovarian androgen level, is significantly associated with decreased clinical pregnancy rate. Defects in folliculogenesis, ovulation, fertilization, embryo quality, and implantation theoretically might be affected by already increased ovarian androgen production even at the beginning of the ovulation induction treatment cycle. Combined oral contraceptive (COC) pills are prescribed to women with PCOS to decrease ovarian androgen production and to increase SHBG levels which result in the normalization of biochemical hyperandrogenism. In a randomized controlled trial, Legro et al. demonstrated that COC usage for 4 months before ovulation induction with CC plus timed intercourse for four months has not been found to be superior to lifestyle modification to lose weight in terms of correction of metabolic parameters and ovulation rates (11). Recently, in a prospective cohort study, Chen et al. evaluated the effects of antiandrogenic pretreatment using 3 months COCs before ovulation induction with letrozole in infertile patients with polycystic

ovary syndrome (PCOS) with hyperandrogenism. They concluded that COC pretreatment was not superior to directly performed letrozole-induced ovulation therapy in improving ovulation and pregnancy results in women with PCOS (12). Song et al. have assessed the effects of pretreatment with COC on cycle outcomes in women with PCOS who underwent in vitro fertilization and embryo transfer (IVF-ET) treatment. Pretreatment with COC in women with PCOS before IVF-ET has been found to have an adverse effect on clinical outcomes in terms of increased miscarriage rates and decreased cumulative pregnancy rates, especially with a GnRH antagonist protocol (13). Contrarily, Ozmen, et al. have retrospectively investigated the effects of oral contraceptive pill (OCP) pretreatment on cycle outcomes in patients with PCOS undergoing IVF-ET treatment with GnRH antagonist protocol and they emphasized that OCP pretreatment was found to have no beneficial or adverse effects on IVF-ET cycle outcomes (14). Another randomized controlled study evaluating the IVF-ET treatment cycle outcomes of women with PCOS has revealed that ongoing pregnancy rates of COC pretreatment+GnRH agonist and COC pretreatment+GnRH antagonist protocols were similar (15). In most of these studies, patient groups have not been categorized based on baseline serum androgen levels which might be a potential predictive parameter to detect women with PCOS who would have benefitted from the COC pretreatment before ovulation induction. In our study, since we have not administered COCs before ovulation induction treatment we only observed a significantly decreased clinical pregnancy rate in women with baseline high serum-free testosterone levels. Well-controlled future studies are needed to delineate the effects of short/ long-term treatment with COCs before ovarian stimulation on ovulation induction cycle outcomes of women with PCOS according to the presence or absence of baseline hyperandrogenism.

## Conclusion

Ovarian androgen production should be at a physiologically normal level to support folliculogenesis and ovulation processes properly. Lower or higher levels of androgenic milieu within the ovaries result in defective folliculogenesis and ovulation failure. Increased serum levels of free testosterone might be a detrimental factor for the clinical pregnancy rates of women with PCOS. However, due to the low number of studies regarding this issue, whether a baseline hyperandrogenic state before ovulation induction cycles have a detrimental effect on cycle outcomes is not clear. Similarly, clinical effects for the treatment of hyperandrogenism by using COCs before ovulation induction should also be investigated thoroughly.

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*Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request. The datasets and code used and/or analyzed during the current study are available from the corresponding author upon reasonable request.*
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## References

1. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2016;31(12):2841-55. Doi: 10.1093/humrep/dew218. PMID: 27664216.
2. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90(4):1929-35. Doi: 10.1210/jc.2004-1045. PMID: 15623819.
3. Spritzer PM. Polycystic ovary syndrome: reviewing diagnosis and management of metabolic disturbances. Arq Bras Endocrinol Metabol. 2014;58(02):182-7. Doi: 10.1590/0004-2730000003051. PMID: 24830595.
4. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Polycystic-Ovary-Syndrome
5. Sun B, Wang F, Sun J, Yu W, Sun Y. J Basal serum testosterone levels correlate with ovarian response but do not predict pregnancy outcome in non-PCOS women undergoing IVF. Assist Reprod Genet. 2014;31(7):829-35. Doi: 10.1007/s10815-014-0246-8. PMID: 24849376, PMCID: PMC4096887.
6. Astapova O, Minor BMN, Hammes SR. Physiological and pathological androgen actions in the ovary. Endocrinology. 2019;160(5):1166-74. Doi: 10.1210/en.2019-00101. PMID: 30912811, PMCID: PMC6937455.
7. Li J, Yuan H, Chen Y, Wu H, Wu H, Li L. A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection. Int J Gynaecol Obstet. 2015;131(3):240-5. Doi: 10.1016/j.ijgo.2015.06.028. PMID: 26421833.
8. Hu Q, Hong L, Nie M, Wang Q, Fang Y, Dai Y, et al. The

effect of dehydroepiandrosterone supplementation on ovarian response is associated with androgen receptor in diminished ovarian reserve women. J Ovarian Res. 2017;10(1):32. Doi: 10.1186/s13048-017-0326-3. PMID: 28472976, PMCID: PMC5418866.

9. Walters KA, Rodriguez Paris V, Aflatounian A, Handelsman DJ. Androgens and ovarian function: translation from basic discovery research to clinical impact. J Endocrinol. 2019;242(2):R23-R50. Doi: 10.1530/JOE-19-0096. PMID: 31125975.
10. Abbott DH, Barnett DK, Bruns CM, Dumesic DA. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? Hum Reprod Update. 2005;11(4):357-74. Doi: 10.1093/humupd/dmi013. PMID: 15941725.
11. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, et al. Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2015;100(11):4048-58.Doi: 10.1210/jc.2015-2778. PMID: 26401593, PMCID: PMC4702450.
12. Chen Z, Tan J, Wang H, Zheng B, Liu J, Hao G. A Randomized cohort study: is it worth the time to receive antiandrogenic pretreatment before ovulation induction for women with polycystic ovary syndrome? Front Endocrinol (Lausanne). 2022;13:813188. Doi: 10.3389/fendo.2022.813188. eCollection 2022. PMID: 35282449, PMCID: PMC8907996.
13. Song SY, Yang JB, Song MS, Oh HY, Lee GW, Lee M. Effect of pretreatment with combined oral contraceptives on outcomes of assisted reproductive technology for women with polycystic ovary syndrome: a meta-analysis. Arch Gynecol Obstet. 2019;300(3):737-50. Doi: 10.1007/s00404-019-05210-z. PMID: 31172307
14. Ozmen B, Sükür YE, Seval MM, Ateş C, Atabekoğlu CS, Sönmezer M. Dual suppression with oral contraceptive pills in GnRH antagonist cycles for patients with polycystic ovary syndrome undergoing intracytoplasmic sperm injection. Eur J Obstet Gynecol Reprod Biol. 2014;183:137-40. Doi: 10.1016/j.ejogrb.2014.10.033. PMID: 25461367
15. Haydardedeoglu B, Kilicdag EB, Parlakgumus AH, Zeyneloglu HB. IVF/ICSI outcomes of the OCP plus GnRH agonist protocol versus the OCP plus GnRH antagonist fixed protocol in women with PCOS: a randomized trial. Arch Gynecol Obstet. 2012;286(3):763-9. Doi: 10.1007/s00404-012-2348-9. PMID: 22569710