Brief Communication

The significance of anthropometric and endocrine parameters in ovulation induction with clomiphene citrate in women with polycystic ovary syndrome

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ABSTRACT

Objectives: To investigate factors associated with the response to ovarian stimulation in patients with polycystic ovary syndrome.

Methods: The records of patients with polycystic ovary syndrome and infertility who underwent ovulation induction with clomiphene citrate were reviwed between January 2011 and December 2014 in Etlik Zübeyde Hanim Women's Health Training and Research Hospital Ankara, Turkey. The anthropometric and endocrine factors of patients who were resistant to treatment at a dose of 150 mg/day (n=84) were compared with those who responded with growth of at least one graaffian follicle at a dose of 50 mg/day (n=342).

Results: Of the parameters examined, body mass index, luteinizing hormone level, and luteinizing hormone/follicle stimulating hormone ratio were significantly higher in the clomiphene citrate-resistant group compared with the responsive group.

Conclusion: Reproductive treatment in patients with polycystic ovary syndrome show different outcomes. Significantly higher body mass index, luteinizing hormone level, and luteinizing hormone/follicle stimulating hormone ratio observed in clomiphene citrate resistant group can be a possible explanation for this impedance.

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Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility.[1] Despite its identification in 1935 and high frequency, PCOS remains controversial after 8 decades.[2] Studies of the prevalence of PCOS within the same populations give different prevalences according to the 1990 National Institute of Health criteria (NIH), 2004 Rotterdam criteria, and Androgen Excess-PCOS Society criteria.[3] In practice, the course of PCOS has a spectrum of metabolic and reproductive outcomes, paralleling its diagnostic criteria. Clomiphene citrate (CC) is a selective oestrogen receptor modulator that is recommended as the first-line medication for inducing ovulation in women with PCOS.[4] Clomiphene citrate leads to ovulation in 78-85% of the cases.[5,6] At respective doses of 50 and 100 mg/day, 52% and 22% of the patients responded to treatment by developing a dominant follicle.[6] This study examined why 15-22% of PCOS patients do not respond to CC. We considered that if we could eliminate the factors causing CC resistance, we could reduce the need for second-line therapies such as gonadotropin stimulation and the associated increased risk of ovarian hyperstimulation. The present study aimed to gather initial data toward this end. Thus, we compared the anthropometric and endocrine parameters of PCOS patients at the beginning of ovulation induction in CC-responsive and -resistant groups.

Methods. This study was conducted at the Etlik Zübeyde Hanim Women's Health Training and Research Hospital, Ankara, Turkey after the approval by the Institutional Review Board. The study enrolled PCOS patients (according to the Rotterdam 2004 criteria) who were admitted to the Infertility Department and underwent ovulation induction treatment with CC between January 2011 and December 2014. The electronic medical records of the patients were used to obtain their demographic characteristics, anthropometric measurements, hormone profile, tubal patency, and ovarian response to stimulation. The study excluded patients with systemic disease (diabetes mellitus, hypertension, thyroid dysfunction, and liver disease), gynecologic pathologies (such as, benign ovarian cysts and uterine anomalies), coincidental tubal and male factor infertility, and cycle cancelations due to the risk of ovarian hyperstimulation. During the study period, 84 women with PCOS who were resistant to CC treatment at a dose of 150 mg/day and met the inclusion criteria formed the study group. From the PCOS patients responsive to CC at a dose of 50 mg/day, 342 patients were randomly assigned as the control group. According to our departmental protocols, after obtaining a detailed gynecologic and obstetric history of the infertile couple, a bimanual pelvic examination of the woman is performed. In the early follicular phase of the cycle, the antral follicular count and endometrial echogenicity are evaluated using transvaginal ultrasound (TVUSG; Mindray DC-T6; Shenzhen, China), and venous blood is taken to measure the follicle-stimulating hormone (FSH; IU/L),

luteinizing hormone (LH; IU/L), oestradiol (pg/mL), prolactin (ng/mL), and thyroid-stimulating hormone (TSH; µIU/mL) levels. After menstruation (up to day 12 of the cycle), hysterosalpingography is performed to evaluate the uterine cavity and tubal patency. In addition, a urologist evaluates the male partner's semen. The women with PCOS scheduled for ovulation induction with CC were re-evaluated on the third day of menstruation to confirm that the largest follicular diameter was smaller than 10 mm and that endometrial echogenicity was less than 5 mm. Initially, they were given CC at dose of 50-100 mg/day for 5 days. The dose was adjusted accord BMI; kg/m^2 and the response in the previous cycle. At 6-8 day of stimulation and following 2-3 day intervals, the women were evaluated with TVUSG. When the leading follicle reached a diameter of 18-20 mm, 250 µg of choriogonadotropin alpha (HCG; Ovitrelle; Merck Serono, Istanbul, Turkey) was administered subcutaneously. The TVUSG was used to examine the follicle for signs of ovulation 36 hours after administering the HCG, and intrauterine insemination was performed if appropriate. In women who were unresponsive to CC at a dose of 100 mg/day, CC at a dose of 150 mg/day was used in the next cycle. PCOS patients who were anovulatory following CC administration of 150 mg/day were deemed CC resistant.

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 11. Data were shown as the mean ± SD or median (range), as applicable. For the analysis, the chi square test was used. A *p*-value less than 0.05 was accepted as significant.

Results. In the CC-resistant group, the mean patient age (27.1 ± 4.4 years), duration of marriage (4.7 ± 3.6 years), and duration of infertility (3.2 ± 2.8 years). In this group, 65.5% (n=55) of the women had primary infertility. The mean BMI of the women in this group was 26.8 ± 3.2 kg/m^2. In the group that responded to CC at a dose of 50 mg/day, the mean age (26.4 ± 3.6 years), duration of marriage (4.5 ± 3.9 years), and duration of infertility (2.6 ± 1.8 years). In this group, 69.3% (n=237) of the women had primary infertility, and the mean BMI was 24.3 ± 3.1 kg/m^2. Of the parameters examined, only BMI was differed, being significantly higher in the CC-resistant group (p<0.001), (**Table 1**). In the basal hormone profile, the luteinizing hormone level was significantly (p<0.001) higher in the CC-resistant (9.6 ± 6.4 IU/L) compared with the CC-responsive group (6.8 ± 4.5 IU/L). The LH/FSH ratio was also significantly higher (p=0.01) in the CC-resistant (1.4 ± 1.2) compared with the CC-responsive group (1.0 ± 1.1) (**Table 2**).

Table 1 - Demographic characteristics of the clomiphene citrate-resistant and clomiphene citrate-responsive women with polycystic ovary syndrome.

Characteristics	CC resistant (n=84)	CC responsive (n=342)	*P*-value
Age (years)	27.1 ± 4.4	26.4 ± 3.6	0.12
Duration of marriage (years)	4.7 ± 3.6	4.5 ± 3.9	0.65
Duration of infertility (years)	3.2 ± 2.8	2.6 ± 1.8	0.06
Type of infertility			0.25
Primary infertility, n (%)	55 (65.5)	237 (69.3)	
Secondary infertility, n (%)	29 (34.5)	105 (30.7)	
Body mass index (kg/m^2)	26.8 ± 3.2	24.3 ± 3.1	<0.001

CC - clomiphene citrate, *P*-value <0.05 was considered significant

Table 2 - Basal hormone profiles of the clomiphene citrate-resistant and clomiphene citrate-responsive women with polycystic ovary syndrome.

Characteristics	CC resistant (n=84)	CC responsive (n=342)	*P*-value
FSH (IU/L)	6.3 ± 1.8	6.6 ± 1.9	0.19
LH(IU/L)	9.6 ± 6.4	6.8 ± 4.5	<0.001
LH/FSH	1.4 ± 1.2	1.0 ± 1.1	0.01
Oestradiol (pg/mL)	40.2 ± 17.7	41.7 ± 19.1	0.50

FSH - follicle stimulating hormone, LH - luteinizing hormone, *p*-values <0.05 were considered significant.

Discussion. This study evaluated possible factors responsible for the difference in the ovulation induction response to CC in women with PCOS. We observed significant differences in the LH level, LH/FSH ratio, and BMI between the CC-resistant and CC-responsive women with PCOS. Folliculogenesis and ovulation require a balanced relationship of FSH and LH. In an unstimulated cycle, this relationship results in monofollicular growth and ovulation. The superiority of human menopausal gonadotropin to pure FSH in patients with hypogonadotropic hypogonadism suggests that LH is essential for normal folliculogenesis.[7] In addition, in patients with a poor ovarian reserve, a higher FSH/LH ratio was found to be related to a lower mature oocyte count.[8] These 2 examples demonstrate the necessity of keeping LH at detectable levels. By contrast, very high LH levels are reported to result in menstrual irregularities, anovulation, infertility, and a higher first trimester abortion risk.[9] According to the LH ceiling hypothesis, every follicle has a threshold for LH, and higher LH levels result in follicular atresia and degeneration.[10] Supporting this hypothesis is the observation that ovarian drilling induces ovulation via a decrease in LH secretion in women with PCOS.[11]

In PCOS, increased thecal cell hyperplasia (and consequently androgen levels) caused by high LH levels suppresses granulosa cells, which in turn arrests follicular growth at the mid-antral level. Our CC-resistant patients had significantly higher LH levels than did their CC-responsive counterparts, who experienced arrest of follicular growth at the mid-antral level. Willis et al[12] reported that the small antral follicles (4 mm in diameter) of women with PCOS secrete the same amount of progesterone as do mid-antral follicles (9.5-10 mm diameter) of women without PCOS. It is possible that one of the reasons for CC resistance is premature luteinization of the growing follicle. In our clinic, we did not monitor the progesterone levels of women receiving CC stimulation. The retrospective design is one of the study limitations. Franks et al[13] reported that high insulin levels acted synergistically with LH on granulosa cells in women with PCOS. Similar to their finding, insulin resistance and hyperinsulinemia have been demonstrated in anovulatory, but not in ovulatory, women with PCOS.[14-17] In our study, a significantly lower follicular response was observed in women with PCOS with a higher BMI, who likely also have insulin resistance due to obesity. Another limitation of our study is that we could not demonstrate this association using the fasting glucose and concomitant insulin levels. Obesity increases the volume of distribution of drugs, which increases the amount of drug required for the equivalent action at the target organ.[18] Obesity also decreases sex hormone-binding globulin levels, which increases the levels of free oestradiol and testosterone.[19] Fatty tissue converts testosterone into oestriol, which is a much less potent oestrogen than oestradiol. All of these factors associated with obesity negatively influence ovulation induction treatment.

In conclusion, the difference in the response to CC induction in the women with PCOS could be due to the differences in the LH level, LH/FSH ratio, and BMI. Our results suggest that losing weight before the start of ovulation induction treatment could increase the chance of pregnancy in women with PCOS. This might prevent the need for stimulation with gonadotropins and the associated higher risk of ovarian hyperstimulation.

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Clinical Practice Guidelines

Clinical Practice Guidelines must include a short abstract. There should be an Introduction section addressing the objective in producing the guideline, what the guideline is about and who will benefit from the guideline. It should describe the population, conditions, health care setting and clinical management/diagnostic test. Authors should adequately describe the methods used to collect and analyze evidence, recommendations and validation. If it is adapted, authors should include the source, how, and why it is adapted? The guidelines should include not more than 50 references, 2-4 illustrations/tables, and an algorithm.