

Short Term Alterations of Hormone Profile Following Oocyte Pick-Up in Women with Polycystic Ovarian Syndrome to Assess the Effect of Multiple Needle Entries Into the Ovarian Cortex and Stroma

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ABSTRACT

OBJECTIVE: Some hormonal alterations after ovarian diathermy have been proposed in previous studies. Based on this data, we aimed to analyze some hormone profile changes following oocyte pick-up in women with polycystic ovarian syndrome.

STUDY DESIGNS: A total of 50 women with polycystic ovarian syndrome underwent ovarian stimulation for IVF cycle with an indication of anovulatory infertility. Some hormone profiles with the insulin resistance were assessed before and after oocyte pick-up to (early in the morning before starting stimulation and repeated 1 month later from oocyte pick-up day) assess whether high number of needle entries into the ovarian cortex and stroma result in similar effect with the diathermy.

RESULTS: Comparison of some variables revealed significantly decreased HOMA-IR and serum total testosterone concentrations after intervention. Correlation analyses showed significant correlations between number of needle entries, change in HOMA-IR, baseline total testosterone level and change in AMH level.

CONCLUSION: Our data showed significant metabolic and hormonal alterations following oocyte pick up consistent with the effect of ovarian diathermy in women with polycystic ovarian syndrome.

Keywords: Ovarian puncture, Polycystic ovarian syndrome, Diathermy, Testosterone, Insulin resistance
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Introduction

Ovarian diathermy was introduced as a treatment option for anovulatory patients with polycystic ovarian syndrome (PCOS) (1,2). While there is no data regarding the exact mechanism of this approach, it is well known that ovarian damage by any method result in similar endocrinological alterations (3). Several articles have been published about the

endocrine consequences of these procedures. Some theories have been proposed for the exact mechanism of this procedure including reduced size of ovary to allow gonadotrophins to act more effectively and increased blood flow to the ovaries (4-6).

Whatever the exact mechanism, studies are consistent about some endocrine alterations secondary to these procedures such as less (free) androgens, lower luteinizing hormone (LH) levels and lower anti-Mullerian hormone (AMH) production (7,8). And secondary to these endocrine alterations, an increased ovarian responsiveness to FSH has been proposed (7).

There is also an argument that the mechanical manipulation/movement of the ovaries itself may be the main cause of this effect rather than the diathermy. Therefore, a recent study showed significantly decreased LH concentrations just after mechanical movement of the ovaries by an ultrasound probe in PCOS patients, a neuronal pathway from the ovaries communicating to the hypothalamic-pituitary system was proposed to be the most reasonable explanation (9).

Based on this data, we aimed to analyze some hormone profile changes following oocyte pick-up that result in both mechanical movement and injury of the ovary in women with PCOS.

Material and Method

This study has been approved by the ethics committee of

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Zeynep Kamil Women and Children's Health Training and Research Hospital, Istanbul, Turkey. An informed consent was obtained from each participant. This prospective, single-center cohort study was performed on the infertile women who underwent assisted reproductive technologies treatment in IVF clinic of Zeynep Kamil Women and Children's Health Training and Research Hospital, Istanbul, Turkey between July 2016 to November 2016. Seventy-four women recruited for baseline metabolic and hormone analyses, fifty cases without embryo implantation were included in the final analyses. All participants underwent ICSI cycles with antagonist protocol in the ART center.

Demographic features and medical information regarding menstrual cycles, obstetric and gynecological history, and previous medication and/or disease were collected from the medical records. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters squared). The waist to hip ratio (W/H) was calculated from dividing the waist circumference by the hip circumference. PCOS was diagnosed according to the Rotterdam criteria with the existence of at least two of the following three features: 1) oligo- or amenorrhea; 2) clinical or biochemical hyperandrogenism; or 3) polycystic ovarian morphology on pelvic ultrasound, after exclusion of other causes of hyperandrogenism, thyroid disorders, hyperprolactinemia.

Inclusion criteria were normal serum prolactin levels and without hormone treatment (oral contraceptives, progestin etc.) within 3 months. The patient ages ranged from 20 to 39 years. In all patients assisted reproductive techniques were indicated for anovulatory infertility.

Exclusion criteria were previous ovarian surgery, oral contraceptive or metformin use within the last 3 months, mechanical or male subfertility and co-existing endocrine diseases (diabetes mellitus, estrogen-dependent tumors, thyroid disease, Cushing's syndrome or congenital adrenal hyperplasia).

Follicle monitorization was performed by two dimensional sonographic measurements of growing follicles and calculating the mean value at each visit. Antagonist protocol was used in all cases; on the second day of the menstrual cycle, ampules of rFSH (Gonal-F, Merck-Serono, Geneva, Switzerland) 75-150 IU, depending on patient's response, were administered and follicular growth was monitored using transvaginal sonography. The dosage of rFSH was adjusted from day 5 of stimulation according to the ovarian response.

Antagonist (Cetrorelix, Merck-Serono, Geneva, Switzerland) 0.25 mg/day was administered when the follicular size was 12 mm. After the follicular size reached 18 mm, rhCG 250 µg was administered, and follicular puncture was performed after 34–36 hours by 17-gauge double-lumen needle (Cook Ireland Ltd., Limerick, Ireland). Endocrine measurements were performed early in the morning before starting stimulation and repeated 1 month later from oocyte pick-up day in women who did not conceive in the first attempt.

Endocrine measurements

Serum total testosterone levels were measured by immunoassay method (Advia Centaur XP, Siemens, Erlangen, Germany). Glucose and insulin levels were measured using the enzyme-linked immunosorbent assay (ELISA) method. IR was calculated by homeostasis model of assessment (HOMA) according to fasting blood glucose and insulin levels [HOMA-IR= fasting glucose level (mg/dL) × fasting insulin level (mIU/mL) / 405]. Change in AMH, testosterone and HOMA-IR levels were calculated by formula: the level before OPU-the level after OPU

Primary outcome

Some metabolic and endocrine alterations secondary to oocyte pick up.

Statistical analysis

Data were analyzed using SPSS 15.0 for Windows. Paired samples *t* test was used to compare continuous variables within the groups. Wilcoxon signed rank test was used to compare non-normally distributed continuous variables within the groups before and after intervention. Correlation analyses were used to show correlations between variables. *p* value < 0.05 was accepted to be statistically significant.

Results

Some clinical and demographic characteristics of whole study population were summarized in table 1.

Table 1: Summary of some clinical and demographic characteristics of whole study population

| | Mean | Std. Deviation | Minimum | Maximum |
|------------------------------------|--------|----------------|---------|---------|
| Age (Years) | 28.5 | 3.6 | 23 | 36 |
| Duration of infertility (Years) | 5.8 | 3.3 | 1 | 14 |
| Day 3 FSH (mIU/mL) | 4.9 | 1.3 | 3.30 | 8.18 |
| Day 3 Estradiol (pg/mL) | 41.3 | 14.6 | 25.7 | 76.00 |
| Fasting glucose before OPU (mg/dL) | 95.8 | 26.9 | 68 | 267 |
| Serum insulin before OPU (uU/mL) | 10.9 | 6.9 | 3 | 34.3 |
| Fasting glucose after OPU (mg/dL) | 89.8 | 7.1 | 72 | 110 |
| Serum insulin after OPU (uU/mL) | 8.4 | 3.1 | 2 | 15.5 |
| Gonadotropin starting dose (U) | 148.5 | 10.6 | 75.0 | 150 |
| Total gonadotropin dose (U) | 1431.1 | 328.2 | 525.0 | 2400 |
| Duration of stimulation (Days) | 9.6 | 2.03 | 7 | 16 |
| Estradiol at trigger day (pg/mL) | 2033.9 | 907.1 | 558 | 4117.0 |
| Number of needle entries | 18.8 | 9.4 | 8 | 45 |
| Total oocyte number | 9.6 | 3.8 | 6 | 24 |

Comparison of some variables before and after oocyte pick-up was shown in table 2 indicating significantly decreased HOMA-IR and serum total testosterone concentrations after intervention. Correlation analyses revealed significant correlations between the number of needle entries, change in HOMA-IR, total testosterone concentration, baseline total testosterone level and the change in AMH level (Table 3).

Discussion

In our study, we aimed to assess some endocrine changes after oocyte pick-up procedure in women with PCOS. Our hypothesis was based on the endocrine changes after ovarian diathermy and the data coming from the study by Hendriks et al., which proposed the mechanical movement/manipulation of the ovaries to be the main confounder for the ovarian response to diathermy procedure (9). Morphological changes in the ovary was claimed to be the underlying mechanism of responses to ovarian drilling (10). During oocyte pick up procedure, both follicular destruction, stromal injury and mechanical manipulation of ovary occur with the needle entry, therefore it is expected to see similar responses to this procedure. In a previous randomized study, ultrasound-guided transvaginal ovarian needle drilling was shown to have similar effect on endocrine profile in women with PCOS, no difference was observed between groups with ovarian diathermy and ovarian needle drilling in terms of rate of regular menses, hirsutism, acne, regular ovulation, pregnancy, serum LH, FSH, FSH/LH ratio and testosterone levels (11). Spontaneous ovulation is the main goal for this intervention, therefore some endocrine changes in the AMH, testosterone, free androgen index, and LH were studied and shown to be associated with ovulatory response after unilateral or bilateral diathermy in women with polycystic ovary syndrome (12). In their study,

authors showed the value of testosterone achieved in the 1st month after the diathermy as one of the strongest and consistent determinant of ovulation response. Based on this data, we assessed hormone profiles at 1st month after oocyte pick up procedure and our data showed significantly decreased testosterone levels. According to the pathophysiological point of view, a disorder in folliculogenesis was shown to be associated with increased production of androgens and AMH by the antral follicles in women with PCOS. And diathermy was proposed to decrease in these antral follicles which lead to folliculogenesis and ovulation (13). In our data, there were decreased AMH levels after procedure but the difference did not reach statistical significance. And degree of decrement in AMH levels were significantly correlated with number of needle entries and degree of decrement in serum testosterone levels. Although there is no consensus on this issue, another study pointed the possible beneficial effect of androgen-producing stroma destruction as the critical effect of procedure (14). In majority of the cases with multiple follicle development, needle is needed to be inserted all through the stroma in order reach the follicles located at the upper site of the ovary. These invasive interventions were thought to result in similar effect with the diathermy that lead to metabolic alterations.

Some variables were introduced that affect the treatment success of diathermy including the amount of thermal energy (15), number of punctures, power used, and duration of each punctures (16). Higher number of punctures with higher doses of thermal energy resulted in the reductions of free androgen index and testosterone (17). It seems that higher degree of tissue destruction result in better results in this procedure. Generally, it is expected to see higher amount of destruction in cases with multiple follicle development by multiple needle entries.

Table 2: Comparison of some variables before and after oocyte pick-up indicating significantly decreased HOMA-IR and serum total testosterone concentrations after intervention

| | Before | After | p value |
|--------------------------|-----------|-----------|-----------------------------------|
| HOMA-IR | 2.7±0.6 | 1.8±0.7 | <0.05 |
| T (nmol/L) | 1.04±1.3 | 0.4±0.013 | <0.05 (Wilcoxon signed rank test) |
| W/H ratio | 0.85±0.07 | 0.86±0.08 | NS |
| AMH (pg/dL) | 7.35±4.9 | 5.8±3.1 | NS (Wilcoxon signed rank test) |
| BMI (kg/m ²) | 26.6±4.4 | 26.9±4.5 | NS |

T: Testosterone, W/H: Waist/hip ratio, BMI: Body mass index

Table 3: Correlation analyses revealed significant correlations between number of needle entries, change in HOMA-IR, total testosterone concentration, baseline total testosterone level and change in AMH level

| | No of needle entries | Change in HOMA-IR | Change in T | Baseline T |
|---------------|----------------------|-------------------|-------------|------------|
| Change in AMH | r | 0.502 | -0.109 | 0.742 |
| | p | 0.009 | 0.589 | 0.000 |
| | n | 50 | 50 | 50 |

T: Testosterone, r: correlation coefficient, p: p value

Laparoscopic ovarian drilling was thought to result in favorable intra-ovarian and systemic endocrinal milieu. Some systemic endocrinal changes were shown such as decreased plasma LH and in its pulsations, increased FSH, decreased LH: FSH ratio, a temporary fall in inhibin B, increased sex hormone binding globulin and a constant fall in androgens, free androgen index and Ferriman-Gallwey score (18,19).

Drilling results in the decrease of AMH level that lead to the consideration of higher rate of ovulation in women with greater decline in AMH concentrations (20). We see an insignificant decline in AMH levels after the procedure.

Insulin resistance (IR) is frequently seen in women with polycystic ovarian syndrome and was shown to play a significant role in the pathogenesis of this syndrome (21). Hyperinsulinemia causes disordered folliculogenesis and steroidogenesis that result in oligo/anovulation. BMI and free androgen index were some other confounders for successful outcome after laparoscopic ovarian drilling (22). A multivariate regression model including these three parameters to determine which of the three closely related factors (HOMA index, BMI and free androgen index) is the independent predictor of ovulation after laparoscopic ovarian drilling showed HOMA-IR index to be the most important confounder for the ovulation after laparoscopic ovarian drilling (23). In addition to the decreased total testosterone levels, our data revealed significantly decreased HOMA-IR levels after oocyte pick-up procedure.

Consistent with our result, ovarian electrocautery was shown to result in amelioration of insulin resistance in PCOS (24), however some studies have demonstrated no impact of laparoscopic ovarian drilling on metabolic parameters (25, 26). Additionally, insulin sensitivity and serum glucose levels and lipoprotein profiles remained unchanged in some studies (27). All these studies were conducted on very small number of women so it is expected not to observe significant difference of insulin resistance before and after intervention.

In addition to the tissue destruction by mechanical needle insertion, pathophysiological mechanisms may also include the consequences of inflammatory responses to multiple needle entries supported by the previous data showed deleterious effect of chronic inflammation on the ovarian reserve (28). There are some studies published in the literature that showed elevated serum testosterone levels and insulin resistance following ovarian stimulation (29,30). Therefore, endocrine alterations shown in our study may not be linked to suprphysiologic endocrine milieu secondary to ovarian hyperstimulation.

This is the first study in the literature which showed the effect of needle drilling in PCOS patient underwent ovarian hyperstimulation, although, we do not have the data regarding spontaneous ovulation, both decreased HOMA-IR level and testosterone concentrations in our study, as significant predic-

tors, indicated possibility for following ovulatory cycles and better responses in next cycles.

Our data showed significant metabolic and hormonal alterations following oocyte pick up consistent with the effect of ovarian diathermy in women with PCOS. A spontaneous pregnancies or favorable ART outcomes may be expected in selected cases; further investigations are needed to clarify this issue.

✉ : *The authors reported no conflict of interest.*

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