Original Article

Evaluation of relationship between serum levels of anti-müllerian hormone, androgen, and insulin resistant with retrieval oocytes in overweight patients with polycystic ovary syndrome

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Abstract

Background: This study aimed to find a correlation between increased body mass index (BMI), insulin resistance (IR), hyperandrogenism, and anti-mullerian hormone (AMH) serum levels with the number of follicles retrieved in polycystic ovary syndrome (PCOS) patients.

Materials and Methods: The descriptive study was taken on 80 women with average ages of 20-35 years at Alzahra Hospital of Tabriz-Iran who referred for *in vitro* fertilization. Patients were divided into four groups and serum levels of AMH, testosterone and IR were evaluated at the puncture time.

Results: The mean number of follicle retrieved was higher in PCOS ($P < 0.05$) group than non-PCOS patients. There was a negative significant correlation of follicle number with BMI ($r = -0.26$, $P < 0.05$). The ratio of follicle numbers in PCOS/overweight group decreased in comparison to PCOS/normal weight group (-30%, $P < 0.05$) while the follicle numbers in non-PCOS/overweight patients decreased in comparison with non-PCOS/normal weight (-26%, $P > 0.05$). There was a significant negative association between BMI with AMH ($r = -0.59$, $P < 0.05$), BMI with the follicle numbers ($r = -0.2$, $P < 0.05$) and a positive association BMI with -IR ($r = 0.3$, $P < 0.05$), but there wasn't a significant correlation between BMI with testosterone ($r = 0.1$, $P < 0.5$).

Conclusion: Our finding provides that increasing BMI with direct effect on AMH levels and IR can affect the number of follicles, which are retrieved in these patients.

Key Words: Anti-mullerian hormone, insulin resistance, follicles retrieved, polycystic ovary syndrome, testosterone

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder and its prevalence is estimated 5-10%, but the prevalence rates depend on exact diagnosis of the disease and the ethnically of the studied population.[1,2]

Based on the Rotterdam criteria, PCOS is diagnosed based on at least two of the three following criteria: Hyperandrogenism, ovulatory dysfunction (oligoovulation and anovulation) and the presence of 12 or more follicles with 2-9 mm in diameters.[3] The pathogenesis of PCOS isn't understood and maybe multiple mechanisms involve in it. PCOS is also associated with hyperandrogenemia, hyperinsulinemia, insulin resistance (IR), diabetes, hirsutism, and obesity.[4]

Previous studies showed that 30-70% PCOS patients are overweight or obese. Therefore, PCOS is associated with metabolic alterations that may be exacerbated by obesity.[5] Obesity may increase metabolism disorders of sex-steroid hormones, risk menstrual dysfunction, and miscarriage rates.[6] Studies show PCOS associates with disorders of ovulation and metabolic that these feature of PCOS overlap with obesity disorders.[7,8]

On the other hand, overweight/obesity has an important role in development of the hyperandrogenic and hyperinsulinemic.[6] Studies show both obese patients and even PCOS patients with normal body mass index (BMI) may have IR and hyperinsulinemia. However, hyperinsulinemia has a positive correlation with degrees of hyperandrogenism.[9] Hyperinsulinemia and IR are features of the PCOS that may be considered as an involved second element in folliculogenesis.[10] During developing follicles, insulin receptors express on granulosa and theca cells of primary follicles. Indeed, insulin increases transitional primordial follicles to primary stage. Therefore, increased levels of insulin in PCOS patients may play a significant role in folliculogenesis disorders.[11]

Hyperandrogenemia is one of the genuine endocrine features of PCOS, which has a positive correlation with increased adipose tissue.[12] Indeed obesity persuades production and secretion of androgens.[13] Androgens up-regulate follicular stimulating hormone (FSH) receptors expression in preantral follicles. Therefore, they stimulate early stages of follicle growth and increase the number of antral follicles.[14]

One of the involved hormones in ovulation induction is anti-mullerian hormone (AMH). AMH induce inhibition of follicular recruitment and decrease sensitivity of follicles to FSH.[15] Furthermore in PCOS patients, AMH causes inhibition of the dominant follicle selection and therefore, increases the number of antral follicles. Studies showed that AMH is one of the powerful predictors of the number of oocyte retrieved during *in vitro* fertilization (IVF) and may predict pregnancy outcome.[15]

During assisted reproductive treatment (ART), predictor of ovarian response to controlled ovarian hyperstimulation (COH) is often difficult because it depends on various factors such as BMI, ovarian reserve, AMH levels, and metabolic factors.[16]

Based on several reports, the effects of BMI on the outcome of IVF are different. It may lengthen the duration of ovarian stimulation, decrease E_2 production, the number of follicles retrieved and may increase the cycle cancellation rate.[17] Increased BMI also affects the levels of androgen and insulin production, which involve in folliculogenesis disorders.[18] On the other hand, obesity decreases AMH level, which is the best predictor of the number of oocyte retrieved during a COH cycle.[19]

Therefore, our aim was to find a correlation or association between increased BMI, IR, hyperandrogenism, AMH serum levels with the number of follicles retrieved in PCOS patients.

MATERIALS AND METHODS

The descriptive study was taken on 80 women with average ages of 20-35 years who referred to Alzahra hospital of Tabriz-Iran for IVF. Our study was approved by Ethics Committee of Tabriz University of Medical Sciences. Consent forms were obtained from all participants. During the study, the patients didn't use any medication that may interfere with normal function of the hypothalamic-pituitary for 3 months before sample collection. The patients were classified according to World Health Organization Criteria of BMI and the Rotterdam criteria of PCOS to four groups. BMI was calculated by dividing weight per squared height (kg/m^2). BMI 18.5-24.9 was considered as normal weight and BMI 25-29.9 as overweight. We selected normal groups among patients with tubal and/or male disorders or volunteers of oocyte donation with normal ovaries. All patients were divided into the following four groups:
Group A: PCOS with overweight (20 subjects)
Group B: PCOS with normal weight (19 subjects)
Group C: Non-PCOS with overweight (18 subjects)
Group D: Non-PCOS with normal weight (20 subjects).

We excluded patients with following features; a history of menstrual disorders as cycle length either was

fewer 25 days or more 35 days and patients with other potential endocrine disorders or neoplastic causes of hyperandrogenemia such as androgen-secreting tumors (serum testosterone above 0.6 ng/mL), congenital adrenal hyperplasia, and Cushing's syndrome.

Patients were treated daily with gonadotropin releasing hormone antagonist, long down-regulation protocol consisting of triptorelin (Decapeptyl; Ferring, Malmo, Sweden) 3 mg intramuscular in order to pituitary down-regulation at mid-luteal of the previous cycle. Then, recombinant FSH (Gonal-F; Serono, Geneva, Switzerland) was added until the follicles reached a mean diameter of 17 mm afterward, 250 μg of recombinant human chorionic gonadotropin (hCG) (Ovidrel, Serono, Switzerland) was administrated subcutaneously 36 h before transvaginal oocyte retrieval.

Before the operation, blood samples were collected and centrifuged for subsequent biochemical analyses. Then, serums were stored at −80°C until total testosterone, AMH, insulin and glucose assays.

Serum AMH levels were measured using the enzyme-linked immunosorbent assay (ELISA) Kit (Beckman Coulter Immunotech, Villepinte, France), which had the lowest detection limit of 0.053 ng/ml. Serum insulin levels were determined by ELISA method using the commercial kit (Insulin: Monobind Inc., lake Forest, CA, USA) with an automated enzyme immunoassat (EIA) analyzer. Serum glucose levels were measured by glucose oxidase method on a Roche Modular clinical chemistry analyzer. IR value was measured using the homeostasis model assessment (HOMA) and was calculated using the following formula:

Fasting plasma glucose (mmol/L) * Fasting serum insulin (μmol/L)/22.5.

$$\frac{\text{Fasting plasma glucose (mmol / l)} \times \text{Times fasting serum insulin (mU / l)}}{22.5}$$

Total testosterone levels were measured using the ELISA method (testosterone: Monobind Inc., Lake Forest, CA, USA).

Statistical analysis

All statistical procedures were run using the SPSS 16 software (SPSS Inc., Chicago, IL) and $P < 0.05$ was considered statistically significant. Normality of distribution was evaluated with the one-sample Kolmogorov-Smirnoff test. Comparisons of means were performed with one-way ANOVA and general linear model multi-variance with *post hoc* analysis for pairwise comparisons. Correlations were evaluated with calculation of the Spearman coefficient and independent relationships were assessed by means of multiple regression analysis.

RESULTS

All four groups were comparable in terms of the baseline characteristics, including age, BMI, serum AMH, and testosterone levels and finally HOMA-IR. The continuous variables showed that there was a normal distribution and it was confirmed by the use of the Kolmogorov Smirnoff test. Data are presented as mean ± SD multiple regression analysis was used to examine the relationship of follicle number with obesity, AMH, testosterone, and HOMA-IR levels.

The data for all patients groups are illustrated in Table 1.

We observed that the follicle numbers were significantly higher ($P < 0.05$) in the PCOS patients in comparison with the non-PCOS patients [Table 1]. In addition, among the factors investigated, HOMA-IR and serum levels of AMH were significantly higher ($P < 0.05$) in PCOS subjects in comparison to non-PCOS subjects. Spearman correlation results in the total groups showed a negative significant correlation of follicle number with BMI ($r = -0.26$, $P < 0.05$). Correspondingly, a negative significantly correlation of AMH with age ($r = -0.3$, $P < 0.05$) was found. When the correlation was carried out within the groups, a significant correlation of follicle number with BMI and AMH didn't showed.

Since, the follicle numbers were different in four groups, the ratio of AMH against follicles and corresponding of BMI against follicles was estimated.

The ratio of follicle numbers in PCOS/overweight group were decreased in comparison to PCOS/normal weight group (−30%, $P > 0.05$) whiles the follicle numbers in PCOS/normal weight group were increased in comparison with non-PCOS/normal weight (49%, $P < 0.05$). The ratio of follicle numbers in non-PCOS/overweight patients were decreased in comparison with non-PCOS/normal weight (−26%, $P > 0.05$) while it was increased in PCOS/overweight group in comparison with non-PCOS/overweight (43%, $P < 0.05$).

The correlation between BMI with follicle number, AMH, testosterone and HOMA-IR is shown in Figure 1. When all studied patients were included, there was a negative correlation between BMI and

Table 1: Clinical and biochemical characteristics of patients

	PCOS/overweight	PCOS/normal weight	Non-PCOS/overweight	Non-PCOS/normal weight
Subjects number	20	19	18	20
Age (years)	29±4.9	28.16±4.1	28.1±2.3	28.9±4.2
BMI (kg/m^2)	28.4±2.7	23±1.9	28.1±2.1	22.5±2
AMH (ng/ml)	2.7±1.5[a]	3.9±1.3[c,d]	2.6±2.1	2.8±1.8
Testosterone (ng/ml)	1.9±0.4	2±0.7	1.7±0.4	1.2±0.5
Insulin (μmol/L)	24.7±9.6[a,b]	11.6±2.5	19.6±1.8[e]	13.7±2.7
HOMA-IR	7.3±1.4[a,b]	5.8±0.9[c,d]	2.5±1.1	2.3±0.4
No. Follicle	12.7±3[a,b]	17.2±4.2[c,d]	7.2±1.2	9.1±2

Values are referred as mean±SD, [a]Difference significant at the 0.05 level between PCOS/overweight and PCOS/normal weight, [b]Difference significant at the 0.05 level between PCOS/overweight and non-PCOS/overweight, [c]Difference significant at the 0.05 level between PCOS/normal weight and non-PCOS/normal weight, [d]Difference significant at the 0.05 level between PCOS/normal weight and non-PCOS/overweight, [e]Difference significant at the 0.05 level between non-PCOS/normal weight and Non-PCOS/overweight, PCOS: Polycystic ovary syndrome, BMI: Body mass index, AMH: Anti-mullerian hormone, HOMA-IR: Homeostasis model assessment-insulin resistance

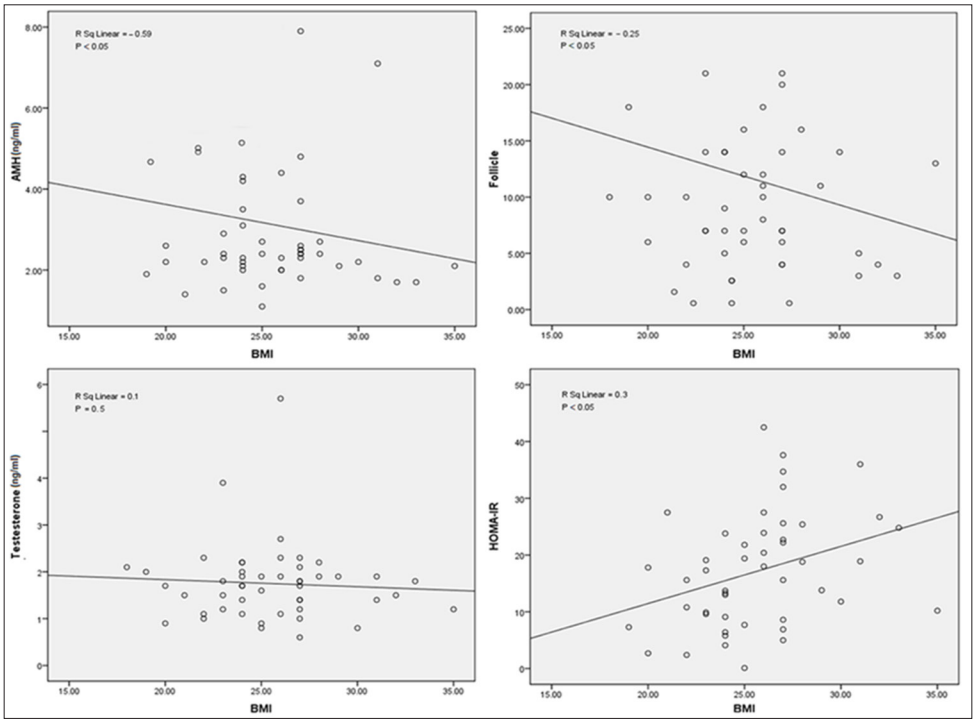

Figure 1: Increased body mass index and its association with anti-mullerian hormone, follicle number, testosterone and homeostasis model assessment-insulin resistance in total group

AMH also there was a positive association between BMI and HOMA-IR.

DISCUSSION

The overlapping features of PCOS and obesity affect these patients also obesity may because more complex PCOS features; therefore, obesity difficult to determine IVF protocol outcomes.

Approximately, half of PCOS patients are overweight or obese, which has a crucial role in the development of the hyperandrogenemia and hyperinsulinemia. Studies showed that compared with normal weight patients, obese patients are stimulated poorly during ovulation induction with IVF process.[6] Furthermore, obesity may increase miscarriage rates and negatively impact on implantations.[17] However, several reports indicate that increased BMI doesn't adversely affect ovulation induction.[20,21] However, obesity may affect on the average number of follicles retrieved during IVF process and its mechanism is not clear. It is likely that obesity can influence on interaction of adiponectins with granulosa cells.[22] Adiponectines, which are secreted from white adipose tissue, decrease in obese women and they interact with their receptors on granulosa cells so, they modify enzymes of steroid synthetic pathways and decrease aromatase activity in these cells.[23] Therefore, it is expected that with increasing BMI and modified enzyme activity in granulosa cells, steroid hormone levels can be changed.

Based on evidence, serum AMH levels correspond to the number of antral follicles. Therefore, it is a powerful means for predicting ovarian response to COH.[24] Our results showed circulation AMH level was significantly higher in the PCOS patients and this finding was confirmed the previous researches.[25] Furthermore, we found that PCOS patients with high AMH levels had a higher number of follicle retrieved. Therefore, AMH levels associate with a number of small antral follicles because AMH secretes from granulosa cells of pre-antral and antral follicles.

Recent reports indicate a negative correlation between BMI and serum AMH levels.[8] Our results showed, when all patients were included, there was a significant negative association between BMI with AMH ($r = -0.59$, $P < 0.05$), BMI with the follicle numbers ($r = -0.2$, $P < 0.05$) and a positive association between BMI with HOMI-IR ($r = 0.3$, $P < 0.05$), but there wasn't a significant correlation between BMI with testosterone ($r = 0.1$, $P > 0.05$) [Figure 1]. When we assessed the correlation of BMI with each variable within the groups, we didn't find statistically significant association. However, this problem may be due to the low number of subjects in each group.

Other research shows that AMH levels in obese patients (BMI ≥ 30) were 65% lower compared to non-obese women (BMI ≤ 30).[19] Our study showed AMH levels in PCOS patients with overweight (BMI = 25-29.9) were 24% lower compared to normal weight PCOS individuals. It indicates that serum levels of AMH reflect the severity of PCOS and its levels are negatively affected by increased BMI.[26] However, our findings in connection with decreased AMH levels with increased BMI do support the previous research. Furthermore, factors such as sample size, age, basal FSH levels and obesity phenotype may be affect the decrease of AMH levels in PCOS patients with overweight.[27]

Furthermore, our study showed that serum testosterone levels weren't significantly increased in PCOS patients with overweight in compared to PCOS women with normal weight [Table 1].

However, according to the previous study, it can be express that PCOS individuals with higher BMI (BMI ≥ 30) have a significant increase of testosterone levels compared to PCOS patients with normal weight.[28] It should be noted that the increase in testosterone levels commensurate with the severity of PCOS and increased BMI.[28]

Based on evidence, androgens act directly through androgen receptors on granulosa cells and appear to have an important role in encouragement of early follicle growth. In addition, androgen receptors express at the preantral and antral stages of follicles and decreases following in pre-ovulatory follicles.[29] Studies showed that androgens have an indirect effect on promoting follicular expression of FSH and insulin growth factor 1 expression in small antral follicles.[30]

It can be stated that testosterone has an effect on the early stages of follicular growth and following ovulation, its value decreases so, it may decrease at the time of puncture. Our results showed that there wasn't a significant relationship between increased BMI and testosterone levels in the each group of individuals during puncture.

Furthermore, studies show both obese and non-obese PCOS patients may have insulin resistant that it correlates strongly with the degree of hyperandrogenism. On the other hand, IR levels in women can have an impact on the outcome of ART.[31] Some studies show increased IR levels relatively stimulate follicle recruitment and development, which it may increase the number of follicles retrieved.[32,33]

A number of researchers have expressed that PCOS patients with IR compared with controls had a greater total number of follicles during the early stages of FSH stimulation at ART protocol.[11] Therefore, they suggested using of insulin doses may improve follicular recruitment during IVF in patients who resistant to COH process.[33]

Our results showed there was a significant positive relationship between increased BMI and IR ($r = 0.34$, $P < 0.05$) [Figure 1]. IR levels in PCOS patients with overweight increased 20% ($P > 0.05$) compared with PCOS patients with normal weight although, this value was not statistically significant, but its levels were imperative. Furthermore, there was a negative correlation to HOMA-IR with the number of follicle retrieved ($r = -0.18$, $P < 0.05$). Therefore, increased BMI has a positive effect on IR levels in PCOS patients but IR doesn't have a significant relationship on the number of follicles retrieved. It can be suggested that insulin has an effect on the early stages of follicular growth.

However, one of our study limitations was low sample size that limited our aptitude to evaluate separately BMI increasing with the number of retrieval oocyte per each groups. In this study, we didn't evaluate pregnancy rates because a successful pregnancy results from suitable interactions of physiological processes in both men and women and some of the participants had male disorders too. Furthermore,

studies showed that increasing age may contribute in quantity of retrieval oocyte, but the majority of the participants in this study were aged 20 until 35 years.

CONCLUSION

PCOS is a disease that causes abnormality in folliculogenesis. Therefore, it increases the number of follicles retrieved at these patients. The number of follicles retrieved is controlled by several hormonal and metabolic factors including AMH, testosterone, insulin and obesity. Among the factors investigated the number of follicles was significantly reduced in PCOS/overweight group compared to PCOS/normal weight. Therefore, increased BMI has a negative effect on the number of follicles. Our study indicates that there is a significant negative correlation between BMI and serum AMH and the effect of BMI on the follicles retrieved are completely evident. On the other hand, there is a significant positive association between BMI and HOMA-IR, but IR doesn't have a positive effect on the follicles retrieved.

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