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Impact of insulin resistance and obesity on intracytoplasmic sperm injection outcomes in young women with polycystic ovary syndrome

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ABSTRACT

OBJECTIVE: To examine effects of body mass index (BMI) and insulin resistance (IR) on the *in vitro* fertilization (IVF) outcomes in women with polycystic ovary syndrome (PCOS).

METHODS: A total of 106 women with PCOS who underwent intracytoplasmic sperm injection were investigated. The patients were stratified into groups according to their BMI [healthy weight: BMI <25 kg/m^2 (n=51), overweight: ≤25–29.9 kg/m^2 (n=27), and obese: ≥30 kg/m^2 (n=28)]. Secondly, the patients were classified based on the presence of IR (IR was considered to be present if homeostatic model assessment-IR was >2.5). The main outcome measures were reproductive and IVF outcomes with respect to BMI and IR.

RESULTS: The basal hormonal evaluations, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH, estradiol, testosterone, DHEAS, AMH, and antral follicle counts, were similar between the groups of BMI and IR. The number of retrieved oocytes, MII oocytes, embryo counts, and fertilization and pregnancy rates were similar between lean and overweight/obese PCOS with and without IR. Even though pregnancy and delivery rates per started cycle and embryo transfer were higher in healthy-weight women with PCOS than in overweight/obese patients, it did not reach statistical significance.

CONCLUSION: Reproductive outcomes in women with PCOS according to BMI and IR were similar. Neither BMI nor IR had an independent effect on ovarian response and IVF success in young women with PCOS.

Keywords: polycystic ovary syndrome, obesity, adiposity, insulin resistance, IVF, ICSI.

Polycystic ovary syndrome (PCOS) is a complex and multifactorial syndrome related to adiposity, hyperinsulinemia, and metabolic dysfunction [1]. The ESHRE/ASRM consensus (2003) define PCOS using the following criteria; oligo and or anovulation, clinical and/or biochemical signs of hyperandrogenism, presence of ≥12 follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 ml). The presence of at least two of the defining criteria is required for diagnosis as PCOS. In addition, known disorders that mimic PCOS, such as congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome, should be excluded [2].

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Almost 73% patients suffer from anovulatory infertility because of PCOS and 35% of the patients with PCOS are obese [3, 4]. Weight and body mass are important parameters for the maintenance of normal reproductive functions [5]. The adipose tissue plays an important role in the pathogenesis of PCOS. There is a close correlation between adiposity and symptom severity, such as menstrual irregularities, hyperandrogenism, and infertility; insulin resistance (IR); and dyslipidemia [6]. However, existing studies linking obesity and PCOS to outcomes of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment are limited and controversial [7–9].

Controlled ovarian stimulation and IVF outcomes are adversely affected and miscarriages are higher in PCOS women than in normal women [8]. These adverse outcomes may partially be attributed to increased luteinizing hormone (LH), intrafollicular, and androgen levels; increased follicular degeneration; and hyperandrogenemia [7]. However, besides hyperandrogenism, the independent effect of adiposity and IR on reproductive outcomes in women with PCOS is unclear [9]. Almost 70% women with PCOS have decreased sensitivity to insulin because of increased weight. IR in PCOS is related to increased aromatase activity, androgen synthesis, and impaired progesterone synthesis in cultured granulosa cells [10]. Moreover, the independent role of IR in IVF outcomes is less defined in the literature [11].

The results of prior studies are varied [9–11]. The differences in the literature may be attributed to different body mass index (BMI) classification, chronological ages, different stimulation protocols, and IVF indications. The chronological age of the patient was the main factor in IVF success, but prior studies did not exclude patients aged >35 years [12]. Therefore, this study was planned on women with PCOS who underwent IVF, including women aged <35 years with anovulatory dysfunction or tubal factor infertility, and the same controlled ovarian hyperstimulation (COH) protocol. This retrospective cohort investigated the role of obesity and IR on ICSI success in women with PCOS.

MATERIALS AND METHODS

Women with PCOS who underwent an ICSI procedure in Kocaeli University between May 2010 and September 2011 were retrospectively recruited. The ICSI outcomes were compared with regard to the presence of obesity and IR in women with PCOS. The Local Ethics Committee approved the study.

Patient Selection

Only patients with PCOS who met the criteria of the recent ESHRE/ASRM Consensus (2003) and underwent ovarian stimulation using the flexible multi-dose GnRH-antagonist protocol were included [2]. Inclusion was limited to women aged >35 years to minimize the influence of age on ovarian response. Exclusion criteria were male factor infertility, medical disorders (chronic hypertension, diabetes mellitus, and renal disorders), and endometriosis that negatively affects pregnancy outcome. Of the 125 women, only 106 women with PCOS, aged <35 years, with anovulatory dysfunction and the tubal factor, and without male factor infertility and endometriosis were included in the study.

Basal Evaluation

Data on patients' characteristic features and BMI variables were collected from the files. Weight and height were taken at the time of oocyte retrieval. Day 3 hormonal evaluations of follicle-stimulating hormone (FSH), LH, and estradiol levels were recorded. Thyroid-stimulating hormone (TSH), prolactine, and anti-Mullerian hormone levels were also recorded in the files. The total dose of gonadotropins, duration of stimulation, number of follicles, retrieved oocytes, and number of embryos were recorded. Visualization of a gestational sac was defined as clinical pregnancy. Patients with enlarged ovaries (5–10 cm); abdominal tenderness; and who have complained of nausea, vomiting, and diarrhea

Table 1. Baseline characteristics of the patients

Characteristics	Healthy weight ≤25 (kg/m²) (n=51)	Overweight 25–29.9 (kg/m²) (n=27)	Obese ≥30 (kg/m²) (n=28)	p
Age (y)	29.5±1.7	29.6±1.8	29.5±1.8	0.9
Duration of infertility (y)	5.9±3.3	5.1±4	7.1±2.8	0.2
Antral follicle count	21±11.7	22.2±10.9	21.9±11.4	0.9
Day 3 FSH (IU/ml)	6.8±2.5	6.5±1.4	6.1±2.2	0.52
Day 3 LH (IU/ml)	8.3±6.8	7.5±5.1	6.1±3.6	0.35
LH/FSH	1.4±1.6	1.1±0.6	1.0±0.6	0.37
AMH (ng/ml)	3.7±2.9	5.3±3.7	3.3±2.8	0.3
TSH (μU/ml)	1.9±1.1	2.0±1.5	2.3±1.5	0.52
PRL (ng/ml)	18.3±15.1	15.3±7.3	10.7±4.8	0.06
HOMA –IR	1.7± 1.5	2±2.1	2.4±0.5	0.01

Values are n, mean±standard deviation. FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E2: Estradiole; TSH: Thyroid stimulating hormone; PRL: Prolactine; AMH: Anti-mullerian hormone; HOMA-IR: Homeostatic model assessment of insulin resistance.

were defined as mild ovarian hyperstimulation syndrome.

BMI and homeostatic model assessment of IR (HOMA-IR) classification

First, patients were stratified into the following three subgroups according to BMI: healthy weight (BMI <25 kg/m²), overweight (BMI=25–29.9 kg/m²), and obese (BMI ≥30 kg/m²) [13]. Second, patients were classified according to the presence of IR. IR was defined if HOMA-IR > 2.5. The HOMA-IR formula [HOMA-IR = fasting insulin (mIU/ml)×fasting glucose (mg/dl)/18)/22.5] was used for calculating IR [14].

Main Outcome Measures

The main outcome measures were reproductive and ICSI outcomes in women with PCOS with respect to BMI and IR.

Data Analysis

The statistical analysis of data was performed using the Statistical Package for Social Sciences for Windows (SPSS, Chicago, IL, USA). Results were reported as mean, standard deviation, and percentages. Descriptive statistics for nominal data was expressed in absolute numbers and percentages. The chi square test was used for comparing different variables. The ANOVA parametric method or Kruskal–Wallis non-parametric tests were applied. Tukey's test was applied as post-hoc multiple comparisons. Statistical significance was considered at $p<0.05$. Logistic and linear regression analyses was used for examining factors associated with ICSI outcomes.

RESULTS

A total of 106 women with PCOS were included in the study. The mean age of the women was 29.7±1.8 (range 27–34) years. Fifty-one, 27, and 28 women were included in the healthy-weight, overweight, and obese groups, respectively. Table 1 represents basal characteristics of women with PCOS with respect to BMI. Age and day 3 FSH, day 3 LH, LH/FSH, prolactin, and TSH levels were similar in the three groups. The duration of infertility was longer in obese women with PCOS than in overweight and healthy-weight women with PCOS, but these differences did not reach statistical significance (5.9±3.3 vs 5.1±4 vs 7.1±2.8; p=0.2). The HOMA-IR index was significantly higher in obese women than in overweight and healthy-weight

TABLE 2. Results of ovarian stimulation and ICSI outcome in each group according to BMI

	Healthy weigt ≤25 (kg/m^2) (n=51)	Overweight 25–29.9 (kg/m^2) (n=27)	Obese ≥30 (kg/m^2) (n=28)	p
Total gonadotrophin dose (IU)	1769±1048	2595±2336	2259±915	0.18
Duration of induction	8.03±2.1	9.3±1.8	8.8±3.5	0.18
Peak E2 levels on hCG day (pg/ml)	1782±1124	2005±1006	1501±1265	0.48
Number of retrieved oocytes	14.7±2.7	15±3	13.7±2.3	0.19
Number of MII oocytes	13.5±2.6	13.4±2.9	12.1±1.9	0.06
Number of embryos	11.3±2.5	11.6±2.4	10.3±1.5	0.08
Ovarian hyperstimulation (OHSS)	3 (5.8)	1 (3.7)	1 (3.5)	0.86
Cycle cancellation	0	0	0	1

ICSI: Intracytoplasmic sperm injektion; BMI: Body mass index; E_2: Estradiole; hCG: Human chorionic gonadotropin; OHSS: Ovarian hyperstimulation syndrome; MII: Metaphase II.

TABLE 3. Fertilization–implantation rates, pregnancy, biochemical pregnancy, miscarriage, and delivery rates relative to BMI

	Healthy weight women with PCOS (n=51)	Overweight women with PCOS (n=27)	Obese women with PCOS (n=28)	p
Fertilization rate	84.2±68	86±6	85.3±6	0.19
Implantation rate	40.1±47.9	37.03±47.2	30.3±45.8	0.67
Number of pregnancies/cycle	24/51 (47.05)	12/27 (32.4)	10/28 (35.7)	0.95
Number of pregnancies/transferred embryo	24/54 (44.4)	12/31(38.7)	10/29 (34.4)	0.95
Number of biochemical pregnancies/cycle	1/51 (1.9)	1/27 (3.7)	1/28 (3.5)	0.39
Number of biochemical pregnancies/transferred embryo	1/54 (1.8)	1/31 (3.2)	1/29 (3.4)	0.44
Number of miscarriages/cycle	2/51(3.9)	1/27 (3.7)	2/28 (7.1)	0.95
Number of miscarriages/transferred embryo	2/54 (3.1)	1/31 (3.2)	2/29(6.8)	0.96
Number of deliveries/cycle	21/51(41.1)	10/27 (37)	7/28 (25)	0.63
Number of deliveries/transferred embryo	21/54 (38.8)	10/31 (32.2)	7/29 (24.1)	0.62

BMI: Body mass index; PCOS: Polycystic ovary syndrome.

women with PCOS (1.7±1.5 vs 2±2.1 vs 2.4±0.5; p=0.01).

Total dose of gonadotrophin, duration of ovulation induction, estradiol levels on human chorionic gonadotropin day , number of retrieved oocytes, metaphase II (MII) oocytes, and embryos were similar in women with PCOS with regard to BMI. Table 2 shows the the details of comparison. When the number of patients with ovarian hyperstimulation syndrome was compared between the groups , no statistical significant difference was detected [n=3 (5.8%), n=1 (3.7%), and n=1 (3.5%), respectively; p=0.86]. No cycle cancelation was detected in either of the groups.

Table 4. Basal characteristics and IVF outcomes relative to insulin resistance

	PCOS without IR	PCOS with IR	p	Overweight/obese PCOS without IR n=41	Overweight/obese PCOS with IR n=14	p
Age	29.8±1.7	29.1±2.0	0.17	29.8±1.7	29.8±2.1	0.31
BMI	25.3±4.9	31.0±5.4	0.00	29.8±3.3	32.3±2.4	0.03
HOMA-IR	1.7±0.4	3.6±2.3	0.00	1.8±0.4	3.7±2.4	0.00
FSH	6.8±2.4	5.9±2.7	0.17	6.8±2.2	5.8±1.8	0.12
LH	7.7±5.6	7.7±6.6	0.93	7.3±5.0	6.3±4.7	0.54
LH/FSH	1.2±1.2	1.1±0.9	0.76	1.1±0.7	1.0±0.7	0.89
E^2	49.6±32.2	46.1±23.9	0.70	45.7±16.6	49.8±23.9	0.51
Testosterone	42.6±20.9	37.1±17.7	0.51	45.5±24.0	40.9±15.0	0.64
DHEA-S	207±104	237±93	0.43	215±138.0	237±93	0.67
AMH	3.7±3.2	3.8±2.6	0.97	3.9±3.5	4.0±2.7	0.94
Prolactin	14.1±10.5	13.9±11.1	0.94	13.0±6.3	11.0±6.0	0.36
TSH	1.9±1.3	2.8±1.5	0.02	1.6±1.3	2.9±1.5	0.003
AFC	21.6±10.5	24.5±10.6	0.37	20.9±10.7	24.4±11.4	0.40
Total oocyte retrieved	10.2±8.1	7.8±4.5	0.35	10.2±9.2	7.8±4.5	0.43
MII oocyte	7.3±6.3	5.2±3.3	0.29	7.5±7.4	5.2±3.3	0.38
Embryo count	3.3±3.1	3.1±2.2	0.84	2.7±2.6	3.1±2.2	0.71
Fertilization ratio	61.9±28.4	65±34.6	0.76	57.1±29.2	65.0±34.6	0.56
Pregnancy rate	47.7%	43.75%	0.857	34.1 %	42.8%	0.693

IVF: Invitro fertilization; PCOS: Polycystic ovary syndrome; IR: Insülin resistance; BMI: Body mass index; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; E^2: Estradiol; DHEA-S: Dehydroepiandrosterone sulfate; AMH: Anti-Mullerian hormone; AFC: Antral Follicle Count; MII: Metaphase II.

Table 3 shows ICSI outcomes in women with PCOS according to their BMI. The number of pregnancies, biochemical pregnancies, miscarriages, and deliveries per transferred embryo and per started cycle was similar (p>0.05). Even though pregnancy and delivery rates per started cycle and embryo transfer were higher in healthy-weight women with PC OS than in overweight/obese women with PCOS, the differences did not reach statistical significance level. Biochemical pregnancy and miscarriage rates per started cycle and embryo transfer were higher in obese women with PCOS, but without statistical significance.

Table 4 presents reproductive and ICSI outcomes in women with PCOS according to IR. Women with PCOS with IR and obese women with PCOS and IR had significantly increased BMI, HOMA-IR, and TSH levels. However, age; day 3 FSH, LH, LH/FSH, prolactin, and AMH levels; and antral follicle count (AFC) were similar (p>0.05). The total oocyte retrieved, mature oocytes, embryo counts, and fertilization and pregnancy rates were also similar in the groups with and without IR (p>0.05). Although total oocyte retrieved, MII oocytes, and pregnancy rates declined in the group with IR, this declination did not reach statistical significance.

The associated factors of ovarian response and pregnancy rates were evaluated by regression analysis. IR, overweight/obesity, chronological age, AMH levels, and AFC were independent variables for pregnancy rates. HOMA-IR, BMI, age, AMH, and AFC were independent variables for an ovarian response. None of the factors predict pregnancy rates and ovarian response, independently (p>0.05).

DISCUSSION

The independent effect of BMI and IR on IVF success in women with PCOS is controversial. Despite the large number of studies on the effect of obesity on IVF outcomes in women with PCOS [6–12, 15–22], the impact of IR with or without obesity on IVF outcomes in those with PCOS is less defined [11, 23]. The present study evaluated the relation of BMI and IR with reproductive outcomes in women with PCOS undergoing the same COH protocol and aged <35 years. Briefly, the study showed that total oocyte retrieved, MII oocytes, and pregnancy rates declined in obese women with PCOS and women with PCOS and IR, without reaching statistical significance.

Thus far, studies have been unable to conclude the independent role of adiposity and IR in outcomes in patients with PCOS. Some studies suggested that gonadotropin resistance and a difference in lean and obese women with PCOS with regard to resorption or metabolism of subcutaneous injected FSH in women with PCOS [9, 15–18]. Dechaud et al. studied IVF outcomes of 789 cycles with respect to BMI. They have stated that obesity does not negatively affect IVF outcomes; however, higher total r-FSH doses are needed in overweight and obese patients [9]. McCornick et al., [19] reported that lean women with PCOS have more follicles, retrieved oocytes, and frozen embryos than lean women without PCOS. Moreover, obese women without PCOS had better grade embryos than obese women with PCOS. However, no clinical outcome differences were observed. According to Matalliotakis et al., number of follicles, total doses of gonadotrophin, and retrieved oocytes were lower in patients with BMI >24 kg/m^2. However, BMI did not affect clinical pregnancy, miscarriage, and delivery rates [20]. Beydoun et al. have investigated the effect of BMI on IVF/ICSI outcomes and they have compared women with and those without PCOS (69 each). Regardless of the PCOS status, BMI was inversely associated with total and mature oocytes retrieved. In addition, BMI did not influence IVF treatment success [21]. In our study, the number of total and mature oocytes were higher in healthy-weight women with PCOS than in overweight/obese women with PCOS, and the MII oocyte count was lower in the obese group. Tu et al. have studied IVF outcomes in 172 patients with PCOS undergoing ultra-long agonist protocol. They have reported that the higher the BMI, the longer the induction day and the higher the gonadotrophin consumption. However, clinical pregnancy, implantation, live birth, and miscarriage rates were similar between low and high BMI groups [18]. In our study, despite the clinical pregnancy rates tending to increase in healthy-weight women with PCOS and miscarriage rates tending to increase in obese women with PCOS, this increase did not reach statistical significance. These results suggested us that further studies with larger series including morbidly obese and lean women with PCOS may properly explain the exact association of BMI and IR on ICSI outcomes in women with PCOS.

The literature about IR and IVF success in women with PCOS is limited. Recently, the study by Chang et al. showed that PCOS with IR had significantly decreased implantation and pregnancy rates [22]. In our study, women with PCOS and IR had decreased total oocyte retrieved, MII oocyte count, and pregnancy rates, without reaching statistical significance. Moreover, in our study we determined IVF outcomes of overweight/obese women with PCOS with or without IR. Obese women with PCOS and IR tended to have decreased MII oocytes and total oocyte retrieved without decreased pregnancy rates, but this decrease did not reach statistical significance.

We investigated associated factors of ovarian response and pregnancy rate in women with PCOS via multiple regression analysis. These results showed that none of the factors independently predict ovarian response and pregnancy rates, when considering HOMA-IR, age, AMH level, AFC, and BMI. These results may partially be explained by the complexity of PCOS, and adiposity, IR, and ovarian reserve all effect reproductive outcomes. In this study, because of the small sample size that did not include morbidly obese and lean women with PCOS, a statistical significance could not be reached between the groups. Healthy-weight women with PCOS and those with PCOS without IR seem to have more favorable reproductive outcomes, but to conclude or reach a statistical power and significance, we need larger series including morbidly

obese and lean women with PCOS.

The main limitation of this study was its retrospective design. We have no data about the smoking status and male obesity, which are factors that may contribute to IVF outcomes. Our study is unique in that we included women <35 years undergoing the same COH protocol and studied both BMI and IR. However, prospectively designed studies, particularly in morbidly obese women, measurements of central adiposity, and effect of weight reduction on reproductive outcomes need further evaluation.

CONCLUSION

Healthy-weight women with PCOS and women with PCOS without IR seem to have favorable outcomes, but the comparison of pregnancy rates in women with PCOS with/without obesity and/or IR were similar. Future studies with larger series including lean and morbid obese women with standardized BMI and IR classification are needed for conclusion.

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