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# In vitro fertilization outcomes in obese women under and above 35 years of age

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**Summary**

*Purpose:* To explore the impact of obesity on in vitro fertilization (IVF) outcomes and comparing the results with regards to age groups. *Materials and Methods:* This retrospective cohort recruited 780 women that underwent IVF. Women with polycystic ovarian syndrome (PCOS) were excluded from the study. Women under and above 35 years were categorized into three groups as normal weight, overweight, and obese. The main outcome measures were ovarian response, oocyte maturity, and clinical pregnancy rates. *Results:* Despite oocyte count and fertilization rate that decreased in both younger and older obese women, this difference was not statistically significant. After age matched-normal weight controls, the clinical pregnancy rates were significantly decreased in older obese women. On the other hand, poor ovarian response observed significantly in young obese women without effect on pregnancy rates. *Conclusion:* These results suggested that obesity in young and old women has different outcomes and different steps of IVF process may be affected.

*Key words:* BMI; Obesity; IVF; ICSI; Ovarian response.

## Introduction

Obesity is associated with detrimental health consequences and it is a major public health problem with increasing incidence worldwide. Approximately half of the reproductive age women are overweight or obese [1]. Beside its health consequences, as hypertension, type II diabetes, coronary heart diseases, stroke, and gastrointestinal diseases, obesity has also a deleterious effect on reproductive functions [2-4].

The effect of obesity on reproductive system is a multifactorial and complex mechanism and results in disturbances of the hypothalamic pituitary axis, ovarian, and endometrial functions [5]. The effect of body weight changes on natural fecundity have been well demonstrated with decreased ovulation, increased time until pregnancy, and increased rates of miscarriages [6]. The impact of obesity on in vitro fertilization (IVF) outcomes is a debatable subject [7]. There are several studies with controversial results. Some of the previous studies showed lower ovarian response, lower pregnancy rates, decreased oocyte and embryo quality, while others showed no significant effect [5-10]. The impact of obesity on IVF outcomes is inconsistent with ongoing scientific discussion [7].

There are several causes of discrepancies in the previous studies, such as heterogeneity of the body mass index (BMI) classification, controlled ovarian hyperstimulation (COH) protocol, studied population that includes polycystic ovarian syndrome (PCOS) and old age women [7, 8]. Thus, standardized classification of body mass index (BMI) in the studies and exclusion of PCOS will give a chance of reproducibility and reliability of results [8]. There are few studies adjusting confounders [9, 10]. Age is also one of the most important factors in IVF success [11-13]. Furthermore the embryo quality is effected from patient age and sperm quality. For this reason the authors designed a study with adjusting the confounding factors age, PCOS, and male factor. The aim of the study was to explore the impact of obesity, overweight, and normal weight on ovarian response, oocyte maturity, embryo quality, and clinical pregnancy rates of women underwent IVF, excluding PCOS, male factor infertility cases, and comparing outcomes with regards to ages under and above 35 years.

## Materials and Methods

This study was conducted in women who underwent the IVF procedure in the Assisted Reproductive Unit of Kocaeli University, from 2011 to 2013. A total of 780 patients enrolled in the study. Data was collected retrospectively from hospital files. PCOS, male factor infertility, previous failed attempt of IVF, frozen-thawed embryo, BMI less than 18.5 kg/m$^2$), and ovarian stimulation other than GnRH antagonist protocol were excluded. This study was approved by the Ethic Committee of Kocaeli University.

*Baseline evaluation*

All patients had a routine infertility evaluation as ultrasonography, day 3 hormonal evaluations (serum FSH, LH, $E_2$, AMH, DHEAS,TSH, free $T_4$ levels), hysterosalphingography, and semen analysis. BMI is an index as weight in kilograms divided by the square of the height in meters (kg/m$^2$). Patients were categorized

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Table 1. — *The comparison of the characteristic findings of Groups 1, 2, and 3.*

| | Group 1 | Group 2 | Group 3 | *p value* |
|---|---|---|---|---|
| Age | 32.3 ± 3.2 | 33.4 ± 17.0 | 33.2 ± 4 | 0.246 |
| Infertility duration (years) | 5.6 ± 3.7 | 7.5 ± 4.8 | 8.7 ± 0.5 | 0.000 |
| Gravidity | 0.3 ± 0.9 | 0.4 ± 0.9 | 0.6 ± 1.1 | 0.06 |
| Parity | 0.08 ± 0.5 | 0.05 ± 0.2 | 0.14 ± 0.4 | 0.229 |
| Abortion | 0.2 ± 0.7 | 0.2 ± 0.7 | 0.3 ± 0.8 | 0.390 |
| Previous molar pregnancy | 0.02 ± 0.4 | 0.00 ± 0.06 | 0.00 | 0.768 |
| Previous biochemical pregnancy | 0.04 ± 0.4 | 0.03 ± 0.2 | 0.06 ± 0.5 | 0.766 |
| FSH level (mIU/ml) | 8.2 ± 4.4 | 7.8 ± 3.8 | 7.7 ± 3.4 | 0.339 |
| LH level (mIU/ml) | 5.4 ± 3.4 | 4.7 ± 2.7 | 4.4 ± 2.3 | 0.04 |
| $E_2$ level (pg/ml) | 56.6 ± 49 | 57.2 ± 104 | 55.5 ± 35 | 0.980 |
| AMH (ng/ml) | 1.5 ± 1.7 | 1.6 ± 2.3 | 1.5 ± 1.5 | 0.830 |
| DHEAS (ug/dl) | 176 ± 108 | 194 ± 106 | 168 ± 84 | 0.350 |
| Total gonadotropin dose | 2721 ± 1225 | 2739 ± 1102 | 2968 ± 1044 | 0.287 |
| COH days | 8.8 ± 2.5 | 8.9 ± 2.1 | 9.1 ± 2.1 | 0.467 |
| Total oocyte retrieved | 8.4 ± 7.4 | 7.6 ± 6.0 | 6.7 ± 5.6 | 0.487 |
| M II oocyte count | 6.4 ± 5.9 | 5.8 ± 4.3 | 4.7 ± 3.7 | 0.03 |
| Embryo count | 3.2 ± 3.1 | 2.8 ± 2.4 | 2.3 ± 1.7 | 0.07 |
| Embryo quality (% of 8 cell embryos & low fragmentation) | 90% | 85% | 85% | 0.342 |
| Fertilization rate | 69.5 ± 31.7 | 65.6 ± 30.1 | 66.6 ± 34.4 | 0.456 |
| Cycle cancellation rate (%) | 10 | 13 | 14 | 0.772 |
| Clinical Pregnancy rates (%) | 33 | 25.1 | 16.9 | 0.02 |

into three classes according to the BMI classification of the WHO. BMI < 25 kg/m$^2$ was accepted as normal weight women (Group 1, n=452), BMI 25-30 kg/m$^2$ were accepted as overweight (Group 2, n=230), and BMI ≥ 30 kg/m$^2$ were accepted as obese (Group 3, n=98).

*IVF protocol*

COH stimulation was performed via antagonist protocol and the dosage of gonadotropins were adjusted and individualized according to ovarian response of patients. The monitorization of COH stimulation was done via serum estradiol levels and follicular size was followed by transvaginal ultrasonography. Recombinant hCG was administered subcutaneously when follicles obtained 17-18 mm in size. Oocytes retrieval was carried out under transvaginal ultrasound under sedation-analgesia. Intracytoplasmic sperm injection (ICSI) was performed for all patients. Patients were categorized as normal, poor, and hyper-responders with regards to oocyte count retrieved (OR). OR less than 3 was accepted as a poor ovarian response. OR equal to 3-15 were accepted as normal ovarian response. The oocytes were categorized according to nuclear maturation grading as metaphase II (M II) (mature oocytes) and non-metaphase II. Clinical pregnancy is defined as ultrasonographically detected gestational sac, thus biochemical pregnancies were excluded.

The main measure outcomes were clinical pregnancy rates, fertilization rates, oocyte maturity, and total oocyte counts.

*Analysis*

Statistical evaluation was conducted with SPSS 18.0. A $p$ value < 0. 05 was accepted as statistically significant. All data were evaluated in 95% confidence interval. Descriptive statistics were expressed in absolute numbers and percentages for nominal data, and continuous variables were expressed as mean values and standard deviations. The comparison of groups was done by ANOVA test and $\chi^2$-test (or Fisher's exact test if appropriate). The homogeneity of variances analyzed by Levene and Welch test. The factors affecting pregnancy rates were analyzed by logistic regression analysis.

## Results

A total of 780 patients categorized into three groups with regards to BMI. Group 1 was normal weight women (n= 452). Group 2 was overweight women (n= 230) and Group 3 was obese women (n=98). The characteristics of women, basal hormonal evaluations and IVF outcomes of the general population are summarized in Table 1. The duration of infertility was significantly increased in Groups 2 and 3 compared to Group 1 ($p < 0.05$). The comparison between Groups 2 and 3 was similar as regard to age, gravidity, parity, and abortion. All the hormonal values were similar, except LH level of Group 1 that was significantly higher than Groups 2 and 3 ($p < 0.05$). The length of stimulation and gonadotropin dose increased while total oocytes retrieved, MII oocytes, embryo count, fertilization rates, and clinical pregnancy rates decreased in obese women compared to normal weight controls. Among these differences the reductions in MII oocytes ($p = 0.03$) and clinical pregnancy rates ($p = 0.03$) reached statistical significance. Logistic regression analysis was done to assess clinical pregnancy rates. Obesity, antral follicle count (AFC) less than 5, and age above 35 years were the independent variables entered into an equation to predict pregnancy rates. According to this equation, age was the only independent variable affecting pregnancy outcomes ($p < 0.05$) [Age above 35 years (RR: 3.09, $p = 0.01$), obesity (RR:0.639, $p = 0.564$), basal AFC < 5 (RR: 0563, $p = 0.336$)].

*Younger group (< 35 years old)*

The IVF outcomes of women under 35 years of age is presented in Table 2. The obese women compared to age matched normal weight controls. OR, oocyte maturity, fer-

Table 2. — *The comparison of Groups 1, 2, and 3 in women under 35 years age.*

| | Group 1 | Group 2 | Group 3 | *p value* |
|---|---|---|---|---|
| Age | 29.5 ± 3.2 | 30.3 ± 3.6 | 31.1 ± 2.8 | 0.182 |
| Total oocytes retrieved | 9.7 ± 7.7 | 8.3 ± 6.1 | 7.5 ± 6.1 | 0.203 |
| Infertility duration (years) | 5.1 ± 2.7 | 8.2 ± 4.8 | 7.2 ± 3.3 | 0.006 |
| M II oocyte count | 6.4 ± 4.3 | 6.5 ± 3.5 | 4.7 ± 3.9 | 0.087 |
| Embryo count | 3.0 ± 3.3 | 3.0 ± 2.5 | 2.4 ± 1.8 | 0.099 |
| Embryo quality (eight-cell embryos & low fragmentation) | 92% | 90% | 91% | 0.189 |
| Fertilization rate | 75.5 ± 28.0 | 67 ± 26.5 | 68.9 ± 20.6 | 0.101 |
| Gonadotropin dose | 2632 ± 1035 | 2665 ± 882 | 2916 ± 730 | 0.088 |
| Poor ovarian response rate (%) | 16.8 | 24.8 | 33.3 | 0.04 |
| Cycle cancellation rate | 10 | 14.4 | 9.2 | 0.211 |
| Pregnancy rate | 35 | 26.9 | 28.5 | 0.311 |

Table 3. — *The comparison of IVF outcomes of Groups 1, 2, and 3 in women above 35 years age.*

| | Group 1 | Group 2 | Group 3 | *p value* |
|---|---|---|---|---|
| Age | 38.5 ± 2.4 | 39.9 ± 5 | 39.1 ± 2.7 | 0.215 |
| Infertility duration (years) | 6.0 ± 4.7 | 6.7 ± 5.5 | 9.0 ± 5.5 | 0.01 |
| Total oocyte retrieved | 4.6 ± 4.9 | 5.5± 5.0 | 5.6 ± 4.8 | 0.641 |
| M II oocyte count | 3.4 ± 2.4 | 4.4 ± 3.2 | 2.7 ± 2.5 | 0.959 |
| Embryo count | 2.1 ± 2.1 | 2.2 ± 1.7 | 2.1 ± 1.6 | 0.984 |
| Embryo quality (eight-cell embryos & low fragmentation) | 92.4% | 84.3% | 81.8% | 0.271 |
| Fertilization rate | 71.6 ± 29.6 | 71.7 ± 25.7 | 69 ± 39.9 | 0.945 |
| Total gonadotropin dose | 3110 ± 1229 | 2695 ± 878 | 2789 ± 1485 | 0.964 |
| Stimulation duration(days) | 9.0 ± 2.7 | 8.5 ± 2.1 | 8.1 ± 3.0 | 0.867 |
| Poor ovarian response rate (%) | 55 | 45 | 41 | 0.341 |
| Cycle cancellation rate (%) | 28 | 18 | 32 | 0.509 |
| Pregnancy rate (%) | 24.5 | 21 | 10 | 0.02 |

tilization, and pregnancy rates decreased while gonadotropin dose and stimulation days increased. However, this difference did not reach statistical significance ($p > 0.05$). The duration of infertility in obese women was significantly increased ($p < 0.05$). Young obese women had significantly increased poor ovarian response rate (33%) compared to Group 1 (16.8 %) and Group 2 (24.8 %) ($p < 0.05$).

*Older group (> 35 years old)*

The IVF outcomes of women above 35 years of age is presented in Table 3. In older obese women, the pregnancy rates decreased significantly ($p < 0.05$). The duration of infertility in obese women was significantly increased ($p < 0.05$). Fertilization rate and M II oocyte count decreased despite an increase in total oocytes retrieved. The cycle cancellation rates increased. However this differences did not reach statistical significance. The clinical pregnancy rates were significantly decreased ($p = 0.02$) in older obese women (10 %) compared to Group 1 (24.5%) and Group 2 (21%).

## Discussion

Obesity is related to variety of reproductive disturbances and its relation to reproduction is complex and not fully understood. Since obesity has become a worldwide epidemic, this leads to more obese or overweight women attending fertility clinics. The impact of obesity on IVF outcomes is inconsistent with ongoing scientific discussion [1-4]. Considering the discrepancies in previous studies and adjusting the confounding factors, the present authors designed a study to explore the impact of obesity on IVF, comparing outcomes with regards to age groups.

In this study, the length of stimulation and gonadotropin dose increased while OR, MII oocytes, fertilization, and clinical pregnancy rates decreased in obese women compared to normal weight controls. Among these differences, the reductions in M II oocytes and clinical pregnancy rates reached statistical significance. Regression analysis showed that clinical pregnancy rates were independently affected by age. Variety of former publications have shown that fertility potential decreases after the mid-thirties. Furthermore, previous studies emphasized that oocyte cytoplasmic abnormalities were observed after 35 years [9-11]. However, most of the previous studies related obesity and IVF outcomes are unable to adjust age [7, 8]. For this reason the present authors categorized women as above and under 35 years age and searched IVF outcomes in specific age groups.

Ovarian response is an important factor in IVF success. Several studies have been done on this subject [12-17]. Former studies showed increased duration of gonadotropin

stimulation, higher cancellation rates, and lower ovarian response [12-17]. However some other studies showed no significant effect on ovarian response and in addition some studies found decreased gonadotropin requirements [7, 18-20]. In this study, young women with BMI $\geq$ 30 kg/m$^2$ had an increased need of gonadotropin dose, duration, and decreased amount oocytes retrieved. However this difference was not statistically significant. The rate of poor ovarian response significantly increased in young obese women. Old obese women gonadotropin dose decreased and oocytes retrieved increased, but this difference was not statistically significant.

Another important factor in IVF success is obtaining good quality oocytes that are defined as M II oocytes. The impaired oocyte quality may contribute to decreased conception rates. Several studies have shown detrimental effect of obesity on oocyte quality, maturity, and counts [14, 15, 20-22]. In this study both in young and old obese group M II oocytes decreased compared to age-matched normal weight controls; however this reduction was not statistically significant. Another surrogate marker of oocyte quality is fertilization rates. Some of the studies showed reduction in fertilization rates of obese women [23, 24], but some others did not observe weight related decrease in fertization rates. [14, 15, 21, 25]. In this search, the present authors found a slight reduction in fertization rates of young er and old obese women; however this comparison was insignificant. Embryo quality decreased in obese women, but this was not statistically significant.

Some studies reported significant differences in pregnancy, implantation, and miscarriage rates between obese and non-obese women [7,12]. In this study, the clinical pregnancy rates of older obese women were significantly decreased compared to overweight and normal weight older women (10%, 21%, 24%; $p$ = 0.02); however, a slight decrease in pregnancy rates of younger obese women did not reach statistical significance. In younger obese women oocyte count, maturity, and pregnancy rates decreased and gonadotropin dose increased compared to age matched normal weight controls; however, this difference did not reach statistically significance. Younger obese women had significantly increased poor ovarian response rate. Older obese women comparing older normal weight women had significantly decreased pregnancy rates without significant effect on oocyte count, maturity, and fertilization rates.

This study has some limitations. Similar to the present study, a majority of the previous studies were restrospectively design. This may be a limitation factor in the studies, because the present authors have no data regarding the smoking status of women and weight of males. Despite this limitation, design of women is satisfactory with the use of standard WHO classification, exclusion of PCOS, and male factor infertility cases, and consideration of different age groups make the results valuable. Further studies with prospective design with standard BMI classification and adjusting confounding factors as PCOS, age, smoking, and male body weight are needed. This study addressed the necessity of adjusting confounding factors in obesity and fertility studies.

## Conclusion

The impact of obesity on IVF outcomes in younger and older obese women have different results. Comparing age-matched normal weight women, obesity increased the risk of poor ovarian response in younger women and decreased pregnancy rates in older women. These results suggest that different steps of IVF process may be affected in women under and above 35 years of age. Prospectively designed further studies are needed in younger and older obese women with poor ovarian response.

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