

# In vitro Fertilization Outcome in Patients with Polycystic Ovary Syndrome: Role of Age and Maternal Body Weight

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## ABSTRACT

**Background & Objective:** This retrospective study aims to evaluate the impact of pre-gestational maternal age and body weight on the outcome of IVF in women with polycystic ovary syndrome (PCOS).

**Materials & Methods:** Medical records of 200 known cases of PCOS treated in a third level referral center by the same therapeutic protocol were evaluated retrospectively. Demographic data, maternal body mass index (BMI), hormonal profile (LH, FSH, estradiol, and anti-mullerian), IVF cycle parameters and outcomes were documented. Patients were categorized into three groups based on their BMI (normal=18.5-24.9, overweight=25-30, obese $\geq$ 30). IVF cycle parameters and outcomes were compared in the three groups. Effect of age was also evaluated by comparing the results in patients aged  $<$ 35 and  $\geq$ 35.

**Results:** Mean age of patients was 32.5 ( $\pm$ 5.2). A number of 72 patients had normal BMI, 85 patients were overweighted and 43 cases were obese. Baseline hormonal profile was similar in the three groups. Total dose of administered FSH was similar in the three groups. Number of retrieved oocytes was significantly higher in patients with BMI $>$ 30 but the number of mature oocytes and number of embryos were statistically lower in this group. Size of follicles showed no statistically significant difference in the three groups. Clinical pregnancy rate was significantly lower in patients with BMI $>$ 30 kg/m<sup>2</sup> and age $>$ 35 years old.

**Conclusion:** BMI $>$ 30 and age $>$ 35 years old have a statistically significant negative impact on IVF success rate.

**Keywords:** Body weight index, In-vitro fertilization, Outcome



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## Introduction

Ovulatory dysfunction is seen in about 6% of women with infertility (1). In about 70% of the cases, polycystic ovary syndrome (PCOS) is the main cause of ovulation failure (2). PCOS is the most common hormonal disorder in women of reproductive age (3) with a prevalence of 6-10%, which leads to hypergonadism, anovulation, and increased level of luteinizing hormone (LH), increased risk of early abortion, diabetes, hyperlipidemia, hypertension, cardiovascular disease, and obesity (4-5). Up to 65% of women with PCOS are overweighted or obese (6) and a body mass index (BMI)  $\geq$ 30 kg/m<sup>2</sup> is seen in more than 50% of the cases (7).

In-vitro fertilization (IVF) is a common therapeutic modality used in infertile women. IVF has different success rates in different subgroups of patients. It is

necessary to alter the common standard protocols to overcome the potential obstacles in some populations of patients and achieve the best results (8). Obesity per se or as a part of PCOS status of patient may decrease the fertilization rate and clinical pregnancy chance after IVF (probably by decreasing the oocyte count and increasing the gonadotropin resistance); however, the results of different studies are conflicting (9-11).

This study was conducted to evaluate the impact of pre-gestational maternal age and body weight on the outcome of IVF in women with PCOS.

## Materials and Methods

### Study Design and Setting

The study was carried out in an educational hospital from November 2016 to April 2018 after institutional ethics committee approval (Code: IR.SBMU.MSP-.REC.1398.070). The study was carried out in accordance with the Declaration of Helsinki (1989). We included cases conveniently after obtaining informed consents.

### Participants

All <40 years old women with PCOS who were attended in our institutional fertility clinic were eligible to participate in the study. We excluded women with BMI<18, history of previous systemic disease (diabetes mellitus, collagen-vascular diseases, hypo-/hyperthyroidism, psychotic diseases, and substance abuse), women whose partner had known aspermia and candidates of receiving egg donation. In our clinic, there is a separate division for PCOS patients. We included our cases from this division which is supervised by perinatologists.

### Study Protocol

Diagnosis of PCOS was made according to the Rotterdam criteria: presence of anovulation/oligo-ovulation, signs of high androgen level (especially hirsutism), presence of polycystic ovary and/or increased ovarian size. PCOS was diagnosed when two of these three criteria were documented in a patient. Other conditions causing high testosterone levels (like exogenous androgen administration, hyperprolactinemia, thyroid disorders, etc.) were excluded (12-13).

After including in study, demographic characteristics, weight, height, duration of infertility, duration of ovulation induction, total administered dose of FSH, IVF cycle parameters (number of retrieved and mature oocytes, mean size of follicles, and number of embryos), ovarian hyper-stimulation syndrome (OHSS) rate and clinical pregnancy rate were also derived and documented.

IVF success was defined as positive fetal heart rate in ultrasound scan 3-4 weeks after IVF. BMI was calculated as weight (kg)/height (m<sup>2</sup>). The world health organization (WHO) standard classification of BMI was used for patient categorization: BMI of 18.5–24.9 kg/m<sup>2</sup> was considered “normal”, BMI of 25–29.9 kg/m<sup>2</sup> was considered as “overweight” and a BMI ≥ 30 kg/m<sup>2</sup> was considered as “obese” (14).

### Data Analysis

We used following the formula to calculate the sample size of our study considering the power of 90% and confidence interval of 95% with this hypothesis

that the BMI impacts the outcome of IVF cycles in women with PCOS. Sample size was calculated as 176 but we included 200 cases to increase the strength of our results.

$$N = \frac{2 \times (Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}) \times \rho(1 - \rho)}{(P_1 - P_2)^2}$$

We used Student's t-test and Chi-Square test for analyzing our data and reported the findings as percentage and mean (±SD). Our analyses were done by SPSS 18 (SPSS, Inc., Chicago, IL, USA).

## Results

200 cases were included and analyzed. Mean BMI of studied cases was 26.88 (±6.55) with a minimum of 18 and maximum of 40.6. A number of 72 patients had normal BMI (18.5-24.9), 85 cases were overweighted (BMI=25-30) and 43 cases were obese (BMI>30). Mean duration of infertility was 5.2 (±2.1) years in studied patients with a minimum of 2 and maximum of 15 years.

### IVF Parameters

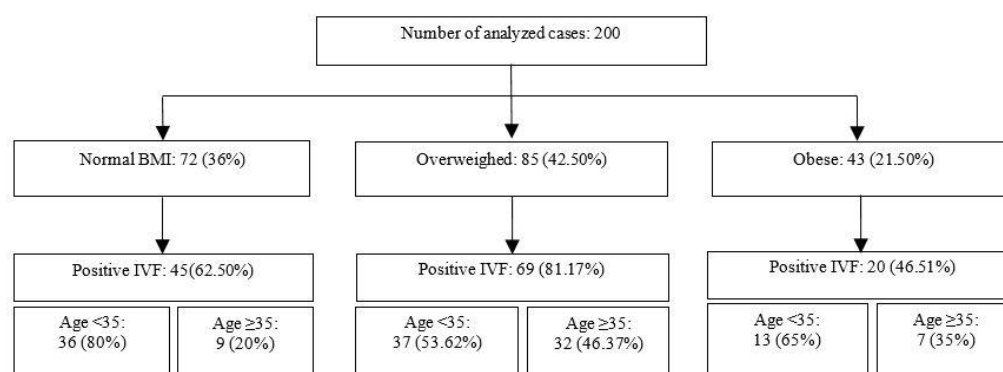
Duration of ovulation induction was significantly shorter in patients with normal BMI ( $P=0.02$ ). Number of retrieved oocytes was significantly higher in patients with BMI>30, but the number of mature oocytes and number of embryos were statistically lower in this group (Table 2). Total dose of administered FSH, mean size of follicles and day of transfer were similar in the three studied groups (Table 2).

### IVF Success Rate

IVF was successful in 134 (67%) cases. From 66 IVF failure cases, in 46 (69.69%) cases, beta-HCG was negative and in 20 (30.30%) cases, beta-HCG was positive but no fetal heart rate was detected in ultrasound scan. BMI had a statistically significant relationship with IVF success. Clinical pregnancy rate in obese patients was less than half of that of patients with normal or overweight BMI ( $P=0.01$ ). There was also a statistically significant relationship between age and IVF success ( $P=0.034$ ). Success rate was about 43% in patients younger than 35 years old and about 16% in patients older than 35 years old (Table 2).

### Effects of Age

Out of 200 studied PCOS cases, 133 women were younger than 35. From these 133 cases, 86 (64.66%) had positive IVF outcomes and 67 women were ≥35 years old. In 32 (48.5%) patients, IVF outcome was positive. Positive IVF outcome was significantly higher in <35 patients (Table 3) (Figure 1).



**Figure 1.** Summary of results

**Table1.** Baseline data

Variable	Minimum	Maximum	Mean (SD)
Maternal age, years	20	40	32.5 (5.2)
BMI(kg/m <sup>2</sup> )	18	40.6	26.88(4.3)
LH(IU/L)	1	15	5.63(0.34)
FSH(IU/L)	0	12	5.90(0.18)
E2(pg/mL)	10	250	70.55(4.2)
AMH (ng/mL)	3	13	8.45(0.14)
Age of partner, years	24	57	37.39(6.3)
Number of sperms	30	150	59.14(±30.7)
Motility of sperms	30	100	99.07(±6.8)
Antegrade sperm movement	0	87	61.43(±22.5)

Abbreviations-BMI: body mass index, FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: stradiol hormone, AMH: Anti-mullerian hormone

**Table 2.** IVF parameters and result in patients with different BMI

Parameter	BMI, kg/m <sup>2</sup>			P-value	
	18.5-24.9 (Normal)(n=72)	25-30 (Overweight) (n=85)	>30 (Obese) (n=43)		
Endometrial thickness, mean(SD)	7.13	7.97	8.09	0.02*	
Duration of ovulation induction, days, mean(SD)	9.80(1.72)	10.16(2.06)	10.50(1.12)	0.02*	
Total dose of administered FSH, IU/L, mean(SD)	2165.21(1257.85)	2408.9(1357.54)	2632.9(1336.53)	0.72*	
Number of retrieved oocytes, mean(SD)	21.73(11.85)	20.60(9.18)	23.72(11.72)	0.01*	
Number of mature oocytes, mean(SD)	18.40(17.63)	16.57(9.72)	16.40(5.22)	0.01*	
Mean size of follicles, mm, mean(SD)	16.69(2.25)	16.67(2.03)	16.23(1.72)	0.11*	
Number of embryos, mean(SD)	10.06(4.03)	9.91(4.12)	8.97(4.56)	0.00*	
OHSS occurrence, NO (%)	11(15.9%)	24(31%)	9(19.1%)	0.34†	
Day of transfer, NO (%)	D2	1(1.44)	2(2.44)	1(2.17)	0.86†
	D3	5(7.24)	9(10.74)	8(14.92)	0.92†
	D4	52(75.48)	56(66.77)	29(61.72)	0.06†
	D5	11(15.96)	17(20.28)	10(21.33)	0.53†
Clinical pregnancy, NO(%)	45(62.50)	69(81.17)	20(46.51)	0.01†	

\*Student's t-test, †Chi-square test

**Table 3.** IVF parameters and result in patients under and above 35 years old

	Age <35 years old (n=133)	Age >35 years old (n=67)	P-value
Duration of ovulation induction, days, mean(SD)	10.13(2.0)	10.21(1.3)	0.11*
Total dose of administered FSH (IU/L), mean(SD)	2182.8(1164.8)	2772.7(1534.9)	0.06*
Number of retrieved oocytes, mean(SD)	18.46(12.2)	17.19(7.2)	0.06*
Number of mature oocytes, mean(SD)	15.77(14.7)	13.92(4.3)	0.05*
Mean size of follicles, mm, mean(SD)	16.58(2.0)	16.56(2.0)	0.48*
Number of embryos, mean(SD)	9.41(3.4)	10.04(4.9)	0.10
OHSS occurrence, NO (%)	36(29.1%)	10 (15.2%)	0.06†
Day of transfer, NO (%)	D2	4(3)	0.15†
	D3	13(9.7)	0.85†
	D4	97(72.4)	0.07†
	D5	20(14.9)	0.87†
Clinical pregnancy, NO (%)	86(64.2)	32(48.5)	0.03†

\*Student's t-test, †Chi-square test

## Discussion

Our study evaluated the role of BMI and age in the IVF success rate in known cases of PCOS and showed that increased maternal BMI to >30 decreases the chance of clinical pregnancy, especially when the maternal age is  $\geq 35$ .

IVF success was significantly lower in women with BMI >30 than normal and overweighted women and the difference rate was not statistically significant them. This finding is not consistent with the results of some other studies, which have shown that overweighted women may have a decreased chance of pregnancy due to their increased body weight. A meta-analysis on 16 studies showed that increased maternal body weight to a BMI  $\geq 25$  can increase the miscarriage rate after both spontaneous and assisted conception (10). Another systematic review on 33 studies and 47967 IVF cycles outcomes showed that BMI  $\geq 25$  had a significant negative impact on the clinical pregnancy and live birth rate after IVF (11).

In a systematic review on 49 studies, Supramaniam *et al.* showed that overweighted and obese women (BMI  $\geq 25$ ) have lower live birth rate after assisted fertilization in comparison with women with normal body weight. This systematic review has also shown that miscarriage rate is significantly higher in women with a BMI  $\geq 30$  (12).

Some other studies have shown that maternal body weight has no significant effect on the outcome of assisted fertilization (13, 14). For example, Friedler *et al.* evaluated the effect of BMI on the live birth rate following IVF in 1654 cycles and showed that clinical pregnancy rate was similar in studied patients with BMI <25, 25-30, 30-35 and >35. Hormonal profile and response, mean number of retrieved and fertilized oocytes and number of transferred embryos were also similar in patients with different body weights in this

study (15). In another study, effects of extreme BMIs on assisted fertilization outcome was evaluated in 8145 cases and it was shown that patients with BMIs >36 or <19 were the only group of studied cases with decreased chances of clinical pregnancy and live birth (16).

There are several studies on the effect of PCOS and/or obesity on the IVF cycle parameters. For example, a systematic review on 1596 articles from 1950 to 2010 showed that the number of retrieved oocytes during IVF cycles is typically higher in women with PCOS but different extra-ovarian factors (endocrine and metabolic dysfunctions like decreased FSH and increased LH/estradiol level, hyperinsulinemia, etc.) and intra-ovarian abnormalities (abnormal level and function of follicle fluid factors and intra-follicular fluid micro-environment) impair the maturation, fertilization and implantation process in oocytes retrieved from PCOS women leading to decreased clinical pregnancy and live birth and increased miscarriage rate (17).

Evaluation of IVF cycle parameters in our PCOS patients showed that the number of retrieved oocytes was higher in patients with BMI >30 but the number of mature oocytes and number of embryos were statistically lower in this group. Although most available studies show the increased number of retrieved oocytes in PCOS patients in comparison with non-PCOS (18-19), there are other studies reporting the reduced number of oocytes retrieved from PCOS women during IVF cycles (20) (probably due to the effects of obesity in these women) (21-22).

Age-related results of our study showed that the IVF cycle parameters were similar in patients aged <35 and  $\geq 35$  years old but positive IVF outcome was significantly higher in patients younger than 35 years old. This finding is compatible with the results of Kalem M. *et al.* who showed that only the number of transferred

embryos were higher in patients  $\geq 35$  years old compared to the younger ones (23) but the clinical pregnancy rate was higher in patients  $< 35$  and the other studies which demonstrate the independent role of age in decreasing the chance of pregnancy after assisted fertilization (24-25).

### Limitations

Our study is a retrospective study with a small sample size. Other multi-center prospective studies are needed to determine the exact role of maternal body weight on the IVF success. In our study, IVF outcome was defined as “clinical pregnancy” but studies focusing on live birth rate per each IVF cycle may be more beneficial for health sector policy makers to evaluate the cost-effectiveness of infertility treatments more precisely and improve the therapeutic procedures to decrease the overall perinatal complications and increase the live birth rate.

### Conclusion

BMI  $> 30$  and age  $> 35$  years has a statistically significant negative impact on IVF success rate in women with PCOS.

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This study has no funding source.

### Conflict of Interest

The authors declare no conflicts of interest.

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