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Effect of Female Body Mass Index on the Outcome of IVF / ICSI Treatment Cycles in Saudi Women

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Abstract: **Objective: To assess the effect of female body mass index (BMI) on IVF outcomes in Saudi women undergoing IVF with or without intracytoplasmic sperm injection (ICSI).**
Design: Retrospective cohort analysis.
Setting: University-affiliated IVF Unit.
Patient(s): Patients undergoing fresh IVF cycle with or without ICSI treatment, 2011-2013.
Intervention(s): subjects divided into 4 subgroups according to their BMI: normoweight with BMI 18.5- 24.9 kg/m2 (n = 93) overweight with BMI 25.0 - 29.9 kg/m2 (n = 99), moderately obese (class I) with BMI 30.0 - 34.9 kg/m2 (n = 93) and severely obese (class II/III) with BMI ≥ 35.0 kg/m2 (n = 73).
Main outcome Measure(s): The primary outcome was biochemical pregnancy which was defined as the detection of a positive β- hCG concentration 2 weeks after embryo transfer. Ovarian stimulation parameters and IVF/ICSI cycle outcomes were compared. Other factors associated with BMI were demographic, clinical, and IVF lab data. Association between BMI and biochemical pregnancy was done by multivariate analyses to control for confounding.
Result(s): In our study, BMI was not found to be significantly associated with biochemical pregnancy. Compared to the normal BMI subgroup, the adjusted OR (95% CI) for the overweight, moderately obese and severely obese subgroups were 0.93 (0.43 – 2.00), 0.83 (0.38 – 1.84), and 1.67 (0.76 – 3.69), respectively.
Conclusion(s): Female BMI does not appear to have an adverse effect on biochemical pregnancy rates in women undergoing IVF/ICSI treatment. However, counseling women on the increased obstetric and neonatal complications associated with increased maternal BMI prior to undergoing this treatment is mandatory

Keywords: **Obesity, body mass index, in vitro fertilization, biochemical pregnancy, infertility.**

I. INTRODUCTION

Given the worldwide epidemic of obesity, an increasing proportion of women seeking medical help for infertility including IVF/ICSI will be overweight or obese. There are numerous deleterious consequences resulting from obesity. These virtually involve every tissue and organ of the body. Moreover, in women obesity is associated with ovulatory dysfunction, menstrual irregularities, subfecundity and infertility. [1] Even in obese women who have regular ovulation, the probability of spontaneous conception is diminished by 5% for every unit of body mass index (BMI) that exceeds 29 kg/m^2. 2It has also been demonstrated that the time to conception was increased more than twofold among overweight/obese women (BMI >25 kg/m^2) and more than fourfold among underweight women (BMI <19 kg/m2). [3]. Once pregnant, obese women are at increased risk of miscarriage, birth defects, and obstetric and neonatal complications. It is worth remembering that all obesity-related risks in spontaneous pregnancy are equally applicable to pregnancies conceived through ART.[1]

Although the influence of BMI on the outcome measures of IVF/ICSI has been addressed by several studies, the results of those studies have been conflicting and debate is still ongoing. [4-8]

As a result, understanding the effects of above-normal BMI on the outcomes of IVF treatment cycle is of interest to infertile couples, physicians and policy decision-makers. To date, the literature concerning the effect of obesity on assisted reproductive technology (ART) remains inconsistent and heterogonous. There remain controversies concerning the effects of female BMI on IVF treatment cycle parameters and its outcome. Therefore, we have conducted this study to assess the effects of female BMI on IVF / ICSI treatment cycles parameters in Saudi women in our university-affiliated IVF unit.

II. MATERIALS AND METHODS

This was a retrospective cohort study of a prospectively collected data from all fresh IVF/ICSI treatment cycles that were performed in our IVF unit, King Khalid university hospital during 2011- 2013 after exclusion of cycles in which the outcome of the cycle was not available.

Inclusion criteria were couples who are undergoing fresh IVF/ICSI using short protocol because of anovulation, PCOS (according to Rotterdam criteria), tubal factor, endometriosis ASRM stage 1, male factor or unexplained infertility.

Exclusion criteria women who had apparent endometrial or myometrial pathologies (polyps, submucous fibroid, uterine septum or uterine synechia) were excluded. Those with suspected hydrosalpinges on TVUS were also excluded. Cryopreserved embryo transfer cycles or cycles in which all embryos were cryopreserved without transfer were excluded from the study population. Natural cycle , long protocol and GnRh antagonist IVF treatment cycles were also excluded. Patients with laparoscopically diagnosed endometriosis with ASRM ≥ stage 2 were excluded from the analysis.

As part of our clinical practice, body weight and height are routinely recorded in patient medical chart by a clinic nurse before cycle initiation. They were retrieved from the database and the BMI was calculated using the following standard formula: BMI= weight in kilograms / height in meters squared (kg/m^2). According to their BMI, women were stratified into four subgroups according to the World Health Organization (WHO) classification cut-points : group 1 (normoweight , BMI 18.5- 24.9 kg/m^2, n= 93), group 2 (overweight , BMI 25.0 - 29.9 kg/m^2, n= 99) , group 3 (moderately obese, class I, BMI 30.0 - 34.9 kg/m^2, n= 93) and group 4 (severely obese, class II/III , BMI ≥ 35.0 kg/m2 , n= 73). Normoweight women were used as the referent population for all comparisons.

Demographic and clinical data on participants were also recorded. Potential confounding factors such as the woman's age, parity (defined as the number of deliveries before IVF treatment cycle that resulted in a birth at ≥ 20 weeks' gestational age) , etiology of infertility, semen characteristics, and type of fertilization (conventional insemination or ICSI) were also recorded.

We performed the first trans-vaginal ultrasound scan (TVUS) (using GE® Voluson E8 (5 MHz trans-vaginal transducer (GE Healthcare Technologies)) on days 2-3 of the treatment cycle. Follicles were counted and endometrium thickness was measured. Serial scans were done to assess ovarian response to controlled ovarian hyperstimulation and guide gonadotropin treatment.

Ovarian Stimulation Protocol:

Controlled ovarian hyperstimulation (COH) was carried out using modified short protocol commencing on day 3 of menstruation using either recombinant FSH (Gonal- F ® ; EMD Serono, Geneva, Switzerland; or Puregon ® ; MSD Merck Sharp & Dohme AG, Switzerland) administered subcutaneously or a highly purified human menopausal gonadotropin (Merional ® ; IBSA Institut Biochimique SA, Lugano, Switzerland) administered subcutaneously . Pituitary suppression was achieved using gonadotropin releasing hormone agonist (GnRH-a) (Decapeptyl ® ; Ferring Pharmaceuticals , Switzerland) 0.1 mg daily subcutaneously started concurrently with gonadotropin administration . The starting gonadotropin dose was based on woman's age, basal FSH values, AFC at baseline TVUS, and ovarian response in previous treatment cycle, if data available. Further adjustments of dose were made based on individual ovarian responses as shown by serial TVUS.

When at least 3 follicles had attained a minimum mean diameter of ≥ 17 mm on TVUS, follicular maturation was triggered with the intramuscular injection of 10,000 IU human chorionic gonadotropin (hCG) (Choriomon® ; IBSA, Institut Biochimique SA, Lugano, Switzerland) . Daily administration of gonadotropins and GnRh agonist was discontinued on the day of hCG administration. Transvaginal Ovum Pick up (OPU) under conscious sedation and ultrasound guidance was performed 36 hours after hCG injection. Fertilization was carried out by either conventional insemination or intracytoplasmic sperm injection (ICSI). The latter was performed in the presence of severe male factor or in the presence of previous fertilization failure.

The cancellation rate included women who started COH stimulation with gonadotropins but did not undergo OPU. Cycles were cancelled for suboptimal follicular development.

The fertilization rate was defined as the number of normally fertilized oocytes divided by the number of oocytes inseminated. Normal fertilization was defined as the presence of two pronuclei (PN) and two polar bodies. Failed fertilization was defined as a lack of fertilization in a treatment cycle with at least one mature oocyte. Embryos were routinely examined by our embryologists on the evening of day 1 and the morning of day 2 after OPU. Standard embryo grading protocol is used utilizing the three commonly used morphological characteristics: shape of blastomere, cytoplasm texture and degree of fragmentation.

Based on conventional morphologic features including regularity of blastomeres and percentage and pattern of anucleate fragments, the best - quality embryos were transferred on day 3 or 5 following OPU in all women in whom embryos were obtained. Embryo Transfer (ET) was carried out using a soft replacement catheter Sure-Pro Ultra Wallace Embryo Replacement Catheter (Smiths Medical International, Ltd, Hythe, Kent, United Kingdom). The number of embryos transferred was determined according to the following criteria: the age of the woman, quality of COH in current cycle , number of failed previous IVF cycles, fertilization rate, morphologic quality of the embryos as well as wishes of couples with proper counseling. Luteal phase support was done using micronized intravaginal progesterone (Cyclogest ® ; Actavis, Barnstaple, UK) 400 mg twice daily starting 1 day after OPU and continued until serum pregnancy test was performed 2 weeks after ET. A positive pregnancy test was defined as a serum hCG level of > 25 IU/L at ≥ 14 days post ET. For those with positive results, a transvaginal ultrasound exam was done about 20 days after to verify the viability of the pregnancy. The protocol for COH, hCG administration and luteal support remained consistent throughout the study period. The primary end-point assessed was biochemical pregnancy rate. Secondary end-points included : daily and total required dose of gonadotropins consumed, duration of COH in days, number of follicles on day of hCG injection, cycle cancellation rate, mean number of oocytes retrieved on OPU day , number of normally fertilized oocytes (2PN) , fertilization rate , day of ET, number of embryos transferred and number of embryos cryopreserved.

III. STATISTICAL ANALYSIS

Data collected were entered into a Microsoft Excel spreadsheet, which was then transferred into the Statistical Package for Social Sciences (SPSS) version 21, which was used for data cleaning, management, and analyses. The main exposure of this study was the BMI, which was divided into 4 groups: 18.5- 24.9, 25.0 -29.9, 30.0 - 34.99, and ≥35.0.

Descriptive statistics were carried out by calculating the number and percent for categorical variables, whereas continuous ones were summarized by the mean and standard deviation (SD). The association between BMI and different demographic, clinical, and IVF-specific variables was assessed using the chi-square test for categorical variables, whereas the student's t-test was used to assess the association with continuous ones.

To identify the association between BMI and biochemical pregnancy, which was considered the primary outcome, we carried out stepwise multivariate logistic regression analyses, where factors which shoed statistical significance at the bivariate levels, and those of clinical importance were included in the regression model. Statistical significance was defined as a p-value of <0.05.

IV. RESULTS

A total of 358 IVF/ICSI cycles were included in the analysis. 93 cycles were performed in normal weight women (25.9 %), 99 cycles (27.6 %) in overweight women, 93 cycles (25.9 %) in moderately obese (class I) women and 73 cycles (20.3 %) in severely obese (class II/III) women. The demographic characteristics of all women included in the study are summarized in table 1 [Appendix I]

Patient demographic:

There was statistically significant difference in the mean female age between normoweight group and the other 3 groups ($p < 0.0001$). The mean duration of infertility was significantly longer for obese and severely obese than for normal weight or overweight women ($P < 0.02$) . Regarding infertility diagnoses, there was a significantly higher proportion of women with oligo-ovulation or anovulation in the normoweight and obese women, being particularly more noticeable in the latter group. Moreover, obese women had significantly increased tubal factor infertility compared to all other BMI subgroups. However, normoweight and obese women had significantly reduced rates of male factor infertility compared to overweight women (table 1, $P = 0.001$). Mean basal serum FSH level was not significantly different among the 4 groups.

The results of COH and IVF/ICSI outcome in each BMI group are shown in table 2 [Appendix II].

Cycle characteristics and embryo quality and transfer:

The patients included in each BMI subgroup were similar with respect to type of FSH administered during COH, indicating minimum bias in stratifying patients among the various BMI groups. Although there were statistically significant differences in daily FSH, total FSH dose and COH duration, there was no such difference in the number of follicles at the time of hCG administration.

With respect to IVF laboratory parameters, a similar number of oocytes were retrieved regardless of the woman's BMI. ICSI cycles were employed more often in severely obese and obese women than in normal weight or overweight women.

The overall cycle cancellation rate was 7.2 % (26 cycles) .There was no significant difference among the four BMI subgroups with regard to cancellation rate due to insufficient follicular development (table 2 , P = 0.10).

High BMI was not associated with any significant decline in the fertilization rates. However, using the number of cryopreserved embryos as a surrogate of embryo quality, there was a statistically significant negative correlation with BMI. There were no differences in the embryo transfer day among the 4 BMI subgroups.

Cycle outcome:

Severely obese women had higher biochemical pregnancy rate per embryo transfer compared other 3 BMI subgroups.

V. DISCUSSION

The correlation between different BMIs on the outcome of IVF/ICSI has been reported by several investigators. In this study we report that in women undergoing IVF/ICSI treatment, female BMI after adjustment for relevant confounders did not appear to exert an adverse effect on biochemical pregnancy as our primary outcome.

The evidence in the literature regarding the effect of BMI on IVF outcomes is far from certain and reaching solid consensus remains elusive. There are a number of factors contributing to the lack of such a consensus which includes small samples sizes, lack of uniform definition or reporting of outcomes, differences in COH protocols, disparate BMI classification systems, inconsistent cut-off limits used to define obesity and varying focus of the investigators.

The data highlighting the effects of obesity on IVF/ICSI outcomes are still conflicting. Employing a ranking based on 3 BMI groups for 775 couples undergoing ICSI treatment (18.5 -24.9, 25.0-29.9, > 30), albeit not statistically significant, there was a trend of superior pregnancy rate with higher BMI subgroups (44.6%, 45.4%, 48.1%) respectively. [9] Analyzing a dataset of about 700,000 ART-cycles that reported both female and male obesity, obese couples in the ICSI group had statistically significant increased pregnancy rate [10]. A systematic review and meta-analysis of 7848 IVF cycles in 21 studies have shown that female BMI > 30 yielded some advantage within the obese group when compared with one of BMI ≤ 30. [4] Comparing different BMI groups a recent systematic review and meta-analysis of 33 studies has shown significantly lower clinical pregnancy and live birth rates among overweight and obese women than their normoweight controls [11]. However, it is hard to draw robust conclusion given the considerable amount of methodological and clinical heterogeneity among the included studies.

As a result, there is still an ongoing debate about imposing BMI cutoffs or mandating weight restrictions by IVF clinics as a criterion of eligibility for publicly-funded IVF programs. This practice will potentially lead to that women who are morbidly obese or have obesity-related comorbidities will be disproportionally represented in published data. However, in light of our study and awaiting the results of larger prospective studies, we believe that high BMI per se should not be the sole justification to withhold IVF treatment in overweight or obese infertile women.

Another technical hurdle associated with high BMI in women undergoing IVF treatment is that obesity renders oocyte pick up and ET technically difficult. [12], [13]

Dose and duration of FSH:

While it is conceptually feasible to hypothesize that in order to exceed a certain serum FSH concentration threshold to achieve adequate follicular response in women undergoing IVF treatment, obese women require significantly higher doses of gonadotropins than their normoweight counterparts, suggestive of a special state of " gonadotropin resistance" [5]. This may be attributable to the greater amount of body surface, suboptimal estradiol metabolism and decreased sex hormone-binding globulin (SHBG). Metabolically, fat tissue serves both as a steroidal reservoir and site of steroid metabolism. Contemporary literature on this issue shows conflicting results.

In this study, there were statistically significant differences between the 4 BMI groups in daily FSH dose, duration of stimulation and total dose of FSH used during COH. However, although the increase in duration of stimulation in our study is statistically significant but is clinically insignificant.

Our findings corroborate those reported from other studies demonstrating a correlation between body weight and increased requirements for gonadotropin for COH to attain adequate follicular maturation. [4], [5], [14], [15], [16], [17], [18], [19] On the other hand, however, other investigators have found no adverse effect of obesity on ovarian response parameters [20], [21], [22], [23],[24] . Furthermore, some studies have demonstrated that obese women undergoing IVF paradoxically require significantly lower doses of gonadotropins to attain sufficient follicular response compared with their normoweight counterparts [25], [26]. Few studies could not find a clear-cut correlation between BMI and response to COH or to IVF outcome. [27]

Given these contradictory findings, apparently there is no consensus from the available published data regarding the effect of obesity on gonadotropin dose requirements in women undergoing IVF treatment. Hence, large scale controlled studies that can address relevant issues such as drug absorption and metabolic clearance would be needed to clarify this issue.

Cancelled cycles:

Although our study did not find an increase in cancellation rates with high BMI, other studies have demonstrated a higher frequency of cycle cancellation owing to inadequate ovarian response to COH. , [5], [26], [28]

It has also been shown in a study of almost 1300 women that the cancellation rate in the morbidly obese group and norm weight subject was 25% and 10.9 % respectively. Those morbidly obese women without PCOS had a noticeably higher cancellation rate of 33%. [28]

Oocyte and embryo parameters:

Oocyte quality also may be impaired as a result of obesity, with subsequent lower fertilization rates. However, although some investigators have shown a poorer oocyte and embryo quality in obese women, [5],[7],[23],[29],[30],[31] others have failed to show such an association. [24],[32]

Apart from number of embryos cryopreserved, our study demonstrates that, oocytes and embryos quality parameters are not affected by female BMI. Conflicting literature exists regarding the effect of high BMI on oocyte and embryo quality. In one report, it has been found that in women undergoing IVF/ICSI obesity adversely affected embryo quality in young (<35 years) women, whilst oocyte quality remained unaffected. [7] However, in agreement with other investigators ([16])

Our study could not demonstrate a statistically significant difference between the 4 BMI sub groups in quality of oocyte (in the form of fertilization rate as a surrogate marker) . Arguably, embryo quality may also be affected by sperm quality. We do not believe that this could represent a confounding factor since oocyte exerts a predominate influence on embryo morphology compared to sperm whose role is limited to the blastomere cleavage rate. [33] Using the donor oocyte model to investigate the effects of various patient characteristics and preconception exposures on endometrial receptivity and contribution to adverse outcomes of IVF since oocytes are often obtained from young healthy women. Using such a model, a recent meta-analysis has shown that obesity in donor oocyte recipient does not affect IVF outcomes including embryo implantation, clinical pregnancy, and miscarriage and live birth rates. They have concluded that oocyte quality rather than endometrial receptivity may be the overriding factor influencing IVF outcomes in this group of women. [34]

Regarding the statistically significant difference in the number of cryopreserved embryos among the 4 BMI groups shown in this study, it has been demonstrated that cryopreservation of embryo can serve as a strong marker of embryo quality. [35]

It has been shown that normal weight women have had significantly more embryos cryopreserved compared with their overweight and obese counterparts. [9], our findings are congruent with this observation. A recent study using supernumerary embryos from overweight and obese women undergoing IVF treatment has shown that a high BMI of women is associated with distinct phenotypic and metabolic abnormalities of the embryos.

Number of oocytes retrieved:

Some reports have shown reduced number of oocytes retrieved in overweight and obese women. [4], [19], [26],[29] ,[36],[37] However, other studies including ours were not able to demonstrate a statistically significant difference in the number of retrieved eggs among different bmi groups [17],[24], [26], [28], [38]

Fertilization rate:

Although some studies have shown that female obesity is associated with lower fertilization rates [26], [39], [40] most of the studies including ours found no such association [5],[7],[16],[17],[28],[41] In our study, ICSI was utilized in a relatively large number of treatment cycles as the mode of fertilization (64.6 - 86.3%) despite that male factor contributed to only approximately 60% of infertility diagnoses. This is attributable to the fact that clinicians when deciding on the most appropriate mode of fertilization take into consideration not only semen parameters but also other factors including female age, any prior lower than expected or failed fertilization with conventional insemination. With this caveat in mind, our result may not be directly comparable to other studies.

Incidence of ET and number of transferred embryos:

Some reports have demonstrated lower incidence of ET and lower mean number of transferred embryos (5, 7, 28). However, some other studies have shown no difference [9]

VI. CONCLUSION

Strengths: unlike some other studies [38], [42] where body height was self-reported and its potential inaccuracy error, all height data in our study were measured at the start of each treatment cycle. All treatment cycles were performed in the same center with the same clinical COH protocol. We also controlled for important confounding factors including a woman's age, baseline FSH serum levels, etiology and duration of infertility, semen parameters and the use of ICSI and the number of embryos transferred. Semen parameters and use of ICSI are particularly important variables to control for given their potential effect on the outcomes of IVF treatment cycles. However, male partner's BMI could not be controlled for in this study, and therefore we cannot categorically rule out the possibility of residual confounding of these results. We analyzed pcos and pcos women to exclude an influence of pcos-related comorbidities e.g., HTN, DM other than body weight on IVF cycle outcomes.

Because our university-affiliated IVF unit serves as a tertiary referral center for infertile women deemed "poor" IVF candidates because of various reasons including high BMI, our cohort encompassed a broad spectrum of women representing typical infertility patients seeking ART treatment. It contains large percentage of moderately (class I) obese (26%) and severely (class II/III) obese (20%) women. We think this could facilitate large-scale study of reproductive outcomes related to BMI.

Limitations:

As the great preponderance of studies conducted to date addressing the issue of obesity in women undergoing ART treatment, we have used BMI as a surrogate marker of obesity. Since BMI cannot differentiate between truncal and central obesity, it has been suggested that waist-hip ratio (WHR) is a better predictor of reproductive outcomes. (43, 44) Since our patients are referred from all over the country, a limitation of our study is that clinical pregnancy rates and live birth rate could not be captured owing to inability to reliably complete follow up after pregnancy test results are reported. Also, because we had no women of subnormal BMI, we cannot comment on the effect of low BMI on IVF treatment cycle outcomes in this BMI group.

We also acknowledge that our study may have been statistically underpowered to detect a small but clinically important difference in biochemical pregnancy. A study of a bigger sample size will therefore be needed to address this issue without controversy.

We concur with other investigators that weight loss counseling prior to embarking on IVF treatment is highly recommended. Weight loss is the best, cheapest and cause-related therapy of infertile, obese women. (45) BMI reduction has led to significant improvement in the odds of conception following IVF. (46)

A unique situation arises when advanced maternal age and high BMI coexist. It is well established that there is a significant and robust negative correlation between female age and reproductive potential. It has been shown that the negative influence of higher BMI on fertility potential is attenuated as age increased. (38) In the subset of women 35 years of age or above, postponing IVF treatment for the woman to lose weight may be injudicious and counterproductive. Confronted with this situation, age should be given primacy in the risk-benefit calculus. Our study findings lend further support to the prudence of this approach.

Despite our findings in this study, we also recommend that women should aim to keep their body weight in the normal weight range by adopting a healthy lifestyle prior to attempting to conceive. Notwithstanding not having an adverse influence on biochemical pregnancy rates per se, it is well established that high BMI predisposes women to a myriad of general health and obstetric problems, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, fetal anomalies, dystocia , higher rates of cesarean deliveries with their own attendants risks , increased hospitalization and associated costs. [28, 47] Most 2nd and 3rd -trimester complications are a consequence of maternal manifestations of the metabolic syndrome of obesity. A recent systematic review and meta-analysis has shown that even modest increases in maternal BMI were associated with high risk of fetal death, stillbirth, and neonatal, perinatal, and infant death. [48] Maternal body weight and weight gain during pregnancy, moreover, are associated with elevated risk of cardiovascular and metabolic disorders in the offspring in later life. [49]

Infertility physicians should discuss pregnancy-related complications with women with high BMI to devise risk-reducing strategies prior to embarking on fertility treatments including IVF/ICSI. In order to further improve IVF and optimize pregnancy outcome in overweight and obese women, it is necessary to conduct more studies to evaluate and quantify accurately and reproducibly the impact of weight reduction on IVF and pregnancy outcomes.

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APPENDIX - A

Table I Participant demographic and baseline characteristics in association with BMI categories

	BMI (kg/m2)				P value
	Normoweight	Overweight	Moderately obese	Severely obese	
	18.5-24.9 n= 93	25.0 -29.9 n= 99	30.0 -34.99 n= 93	≥35.0 n = 73	
	(25.9%)	(27.6%)	(25.9%)	(20.3%)	
Age (year)	29.0 (5.7)	32.1 (5.8)	32.4 (6.7)	32.5 (6.6)	< 0.0001
Duration of infertility (years)	54.0 (43.7)	45.7 (33.2)	63.8 (57.6)	63.6 (46.4)	0.02
Infertility Diagnosis: Oligo-ovulation/anovulation	10 (10.8%)	9 (9.1%)	15 (16.1%)	2 (2.7%)	0.04
PCOS	22 (23.7%)	11 (11.1%)	20 (21.5%)	13 (17.8%)	0.12
Male factor	43 (46.2%)	72 (72.7%)	51 (54.8%)	49 (67.1%)	0.001

Endometriosis Tubal disease	4 (4.3%) 12 (12.9%)	8 (8.1%) 11 (11.1%)	3 (3.2%) 20 (21.5%)	0 (0.0%) 0 (0.0%)	0.07 < 0.0001
Idiopathic/ Unexplained	17 (18.3%)	7 (7.1%)	21 (22.6%)	17 (23.3%)	0.01
Type of cycle:					
IVF	32 (34.4%)	35 (35.4%)	26 (28.0%)	10 (13.7%)	0.009
IVF with ICSI	61 (65.6%)	64 (64.6%)	67 (72.0%)	63 (86.3%)	

APPENDIX - B

Table II

IVF cycle parameters in association with BMI categories					
	BMI (kg/m2)				P value
	Normoweight	Overweight	Moderately obese	Severely obese	
	18.5-24.9 n= 93	25.0 -29.9 n= 99	30.0 - 34.99 n= 93	≥35.0 n = 73	
	(25.9%)	(27.6%)	(25.9%)	(20.3%)	
FSH baseline (IU/L)	6.7 (2.5)	7.3 (4.7)	6.7 (3.5)	5.9 (1.6)	0.06
Type of FSH					
- Merional	67 (72.0%)	85 (85.9%)	72 (77.4%)	62 (84.9%)	
- Puregon	25 (26.9%)	14 (14.1%)	18 (19.4%)	11 (15.1%)	0.06
- Gonal F	1 (1.1%)	0 (0.0%)	3 (3.2%)	0 (0.0%)	
Total FSH dose (IU)	1816.8 (1183.8)	2256.1 (1143.2)	2194.6 (941.1)	3276.5 (15441.9)	<0.0001
Daily FSH dose (IU/day)	224.8 (124.3)	252.3 (114.3)	244.9 (89.4)	339.0 (122.6)	<0.0001
Duration of COH (days)	7.9 (1.9)	8.9 (1.9)	8.6 (2.6)	9.1 (2.5)	0.003
Cancelled cycles (per IVF cycle start)	5 (5.4%)	6 (6.1%)	12 (12.9%)	3 (4.1%)	0.10
Number of follicles on hCG day	22.5 (19.3)	19.4 (14.4)	22.4 (15.9)	17.9 (15.1)	0.18
Total number of oocytes retrieved	9.5 (8.3)	8.4 (6.7)	8.9 (7.0)	7.3 (6.2)	0.24
Number of normally fertilized oocytes (2PN embryos)	4.8 (4.9)	3.6 (3.3)	4.0 (4.3)	3.3 (2.9)	0.07
Fertilization rate % (per IVF cycle start)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.45
Number of transferred embryos	1.5 (0.9)	1.5 (1.0)	1.5 (1.1)	1.4 (1.0)	0.87
Number of embryos available for cryopreservation	0.8 (2.0)	0.5(1.4)	0.3 (1.0)	0.2 (0.6)	0.02
Day of ET	3.5 (0.9)	3.2 (0.9)	3.4 (0.8)	3.4 (0.8)	0.11

APPENDIX - C

Table III: Biochemical Pregnancy in association with BMI categories

		BMI (kg/m2) (n=358)		
	Normoweight 18.5-24.9 n= 93	Overweight 25.0 -29.9 n= 99	Moderately obese 30.0 -34.99 n= 93	Severely obese ≥35.0 n= 73
Biochemical Pregnancy n (%)	17 (18.3)	18 (18.2)	17 (18.3)	17 (23.3)
Crude OR (95%CI) Crude P-value	REFERENCE REFERENCE	0.99 (0.48 – 2.07) 0.99	1.00 (0.48 – 2.10) 1.00	1.36 (0.64 – 2.89) 0.43
Adjusted OR (95%CI) Crude P-value	REFERENCE REFERENCE	0.93 (0.43 – 2.00) 0.86	0.83 (0.38 – 1.84) 0.65	1.67 (0.76 – 3.69) 0.21