 https://dx.doi.org/10.4314/rjmhs.v2i1.3

Body mass index and Ovarian response in an In-Vitro Fertilization Cycle

Rufus Obose[1*], James Osaikhuwuomwan[2], Michael Aziken[2]

[1]*Department of Obstetrics and Gynaecology, University of Gitwe, Rwanda.*
[2]*Department of Obstetrics and Gynaecology, College of Medical Sciences, University of Benin, Nigeria.*

***Corresponding author:** Rufus Obose, Department of Obstetrics and Gynaecology, University of Gitwe, Gitwe, Ruhango District, Southern Province, Republic of Rwanda, Email: rufbos@yahoo.co.uk

Abstract

Background: In-vitro fertilization (IVF) has established its place in the management of infertility cases that has defied conventional treatment. A successful In-vitro fertilization outcome is based on a good ovarian response to gonadotrophin stimulation. Body mass index has been identified as one factor that can affect ovarian response however; there is no consensus about its impact outcome.
Objectives: To determine the effect of body mass index (BMI) on ovarian response in an In-vitro fertilization cycle.
Method: A Prospective cohort study to determine the response to Controlled Ovarian Hyperstimulation (COH) in women with normal and abnormal BMI in an IVF cycle. One hundred and four (104) consenting women undergoing non-donor IVF cycles in a university teaching hospital were recruited for the study. Selected participants had their body mass indices (BMI) assessed and classified into 3 groups: Normal weight (18.5-24.9kg/m^2), overweight (25-29.9kg/m^2) and obese (≥30kg/m^2). There were no underweight women-BMI <18.5kg/m^2. All the participants had Controlled Ovarian Hyperstimulation with the long agonist protocol. Selected participants had follicular count assessed using a transvaginal sonography on day 3, 5, 10 and at retrieval. The effect of ovarian response with the IVF treatment assessed based on total number of follicles and oocyte yield on the day of retrieval.
Results: Female participants with normal weight women were thirty-six (34.6%), overweight were forty (38.5%) and obese, twenty-eight (26.9%). There was no statistical significant difference when the ages of women at presentation, total gonadotrophins requirements, duration of stimulation and number of oocytes retrieved were compared in the three groups.
Conclusion: Increase in body mass index does not appear to have an adverse effect on ovarian response in an In-vitro fertilization cycle.

Keywords: body mass index, infertility, ovarian stimulation, gonadotrophins, IVF cycle.

Introduction

Infertility is a major public health challenge worldwide. In developing countries, a paradox of infertility has been described whereby there is the presence of an over-population crisis in the background of very high level of infertility constituting about 60% of all gynaecological consultations.[1] This is however not very surprising, particularly in Africa, where very high premium is placed on childbirth and the inability to procreate have far reached effect at the individual, community and societal levels.[2, 3] The direct causes of infertility in the female are many with the major contributors being tubal and endometrial problems as well as problems with ovulation. However, the effect of these direct causative factors is strongly modified by biophysical factors particularly the age of the woman and her body habitus. For an ovulation many contributors are recognized with notable factors being the age of the woman, the presence of the polycystic ovary syndrome (PCOS), endometriosis and obesity.[4–6]

Overweight and Obesity, defined by the World Health Organization as body mass indices of 25.0-29.9 kg/m^2 and ≥30 kg/m^2 respectively.[7] Elevated BMI can affect the outcome of both conventional infertility management and assisted conception. Obesity is also associated with PCOS and is an important determinant of response to conventional treatment. The polycystic ovary syndrome is a noted determinant of IVF outcome and is presently the subject of many researches. Both PCOS and obesity are associated with low fertility, menstrual disturbance and poor response both to ovulation induction during routine infertility treatment as well as during super-ovulation required with assisted reproduction technology (ART). In ART, despite no consensus being reached, recent systematic reviews and retrospective studies with large sample sizes have highlighted a significant reduction

in implantation, pregnancy and life birth rates in obese women undergoing IVF.[8] In some study, overweight and obesity were associated with increased amount of gonadotrophin use, decreased number of oocyte retrieved, and increased cycle cancellation in IVF.[9]

The lack of consensus on the impact of BMI on ovarian response in an IVF cycle against a backdrop of increasing prevalence of women with elevated body mass indices presenting at the infertility clinic for IVF, necessitated the need to ascertain the impact body mass index has on ovarian response following routine long agonist protocol stimulation. Findings from the study can help improve fertility treatment and counselling.

Methodology

Setting The study was conducted at the Human Reproduction and Research Programme (HRRP) Unit of the Obstetrics and Gynaecology department of the University of Benin. The HRRP is a dedicated infertility management unit with Assisted Reproduction Technology (ART) services located within the teaching hospital complex. The ART services currently available in the centre include: intra-uterine insemination (IUI), in-vitro fertilization/embryo transfer (IVF/ET), intra-cytoplasmic sperm injection (ICSI) and cryopreservation of embryos.

Study design It was a prospective cohort study over a 5-month period (June 2013 to October 2013) inclusive of all consenting female partners of infertile couples with good ovarian reserve (Basal FSH ≤ 10IU/L) attending the infertility clinic at the University of Benin Teaching Hospital, Benin city.

Exclusion Criteria:

1. Women whose ovaries could not be assessed by transvaginal ultrasonography.
2. Those who refused to give consent.
3. Women with basal FSH >10IU/L.

Methods A detailed history was taken as well as general and physical examination done for female partners of infertile couples attending the infertility clinic. Selected participants with basal follicle stimulating hormone (day 3 of the cycle) of ≤10IU/L had their weight (kilogram), height (metre) and body mass indices (kilogram/metre^2) measured. Based on their BMI they were classified into underweight (<18.5kg/m^2), normal weight (18.5 – 24.9kg/m^2), overweight (25 – 29.9kg/m^2) and obese (≥ 30kg/m^2). They all had the long as detailed below and transvaginal ultrasound assessment of the follicles on day 3 prior to commencement of stimulation, as well as on days 5, 8, 10 and the day of egg retrieval. The number of oocytes retrieved at retrieval was assessed.

Procedure Blood sample was collected for basal Follicle Stimulating Hormone (bFSH) prior to the treatment cycle in the early follicular phase (day 3) of the cycle. Selected patients were commenced on combined oral contraceptive pill in order to synchronize their menses to the time scheduled for the IVF. Controlled Ovarian Hyperstimulation (COH) for all the patients was carried out using the long agonist protocol. First, the pituitary gland was down-regulated by daily subcutaneous injections of 0.5 mg of Buserelin starting on day 21 (mid-luteal phase) of the synchronized menstrual cycle preceding the treatment cycle. Gonadotrophin suppression was assessed by transvaginal scan showing endometrial thickness <5mm and few or no antral follicles, or onset of menstruation. The dose of Buserelin was then reduced to 0.25mg per day on day 3 of the new menstrual cycle at the commencement of stimulation. Transvaginal scanning was also performed to determine the follicular count. The stimulation was effected by daily injections of 225-450IU of highly purified Human Menopausal Gonadotrophin (Menopur^R). The dose was adjusted depending on the age of the patient as well as the ovarian response afterwards. Serial transvaginal scanning was done from day 5 to monitor ovarian response and the Menopur dose adjusted according to ovarian response. Cycles were cancelled when the follicles remained <10mm after 10 days of stimulation. Intramuscular injections of Human Chorionic Gonadotrophin (HCG) 10,000 IU were given when the leading follicles reached 18mm or more in diameter to effect the final maturation of the follicles. Oocytes retrieval was subsequently performed 34-36 hours after HCG administration under ultrasound guidance. The numbers of follicles aspirated and oocytes retrieved were carefully noted.

Outcome measures The primary outcome measure was the number of oocytes retrieved following COH in women with normal and abnormal BMI. The secondary outcome measures were the total dose of gonadotropins used, duration of stimulation, presence of ovarian hyperstimulation syndrome (OHSS) and cancellation rates.

Sample size Determination Orhue et al.[1] showed in Benin that 60% of infertility cases may need assisted reproductive technology. Using the result of the study, sample size calculation was done using the formula.[10]

$$Ns = (Z/E)^2P(1-P)$$

Where Ns = the required sample size

Z = standard score corresponding to given confidence level-1.96

E = the proportion of sample error in a given situation

P = the estimated proportion of incidence of cases in the population

Also, a confidence level of 95% is desired hence a tolerable error of not greater than 0.1 is taken.

Hence, our sample size is:$(Z/E)^2P(1-P) = (1.96/0.10)^20.6(1-0.6) = Ns = 92.198$

With an attrition rate of 10%, the minimum sample size was 101. However, to broaden the base of the study the total number of women who met the criteria within the study period was used, hence a sample size of 104.

Data Management Data entry and analysis were done using SPSS Statistical Software Version 20. Results were presented as means, standard deviations, frequencies and percentages. Statistical analysis of generated data was calculated using the Chi-square test. Statistical significance was set as $P \leq 0.05$.

Ethical Consideration Approval for the study was obtained from the Ethical and Research Committee of the University of Benin Teaching Hospital. The study was carefully explained to the patients and informed consent obtained before being recruited into the study. Participation in this research was entirely voluntary. Participants were counselled that they could opt out of the study at any time they so desired and it will not be held against them in any way, now or in future in their clinical management in the hospital or any of its affiliated institutions.

Results

There were a total of 104 women recruited for the study. Those with normal weights were 36 (34.6%), overweight, 40 (38.5%) and obese, 28 (26.9%). There were no underweight patients (BMI <18.5kg/m^2). Table 1 shows that most of the women recruited for the study were in the age group of 30-34 years (38.5%) and had primary infertility (83.7%). Majority of participants (73.1%) had tertiary education.

Table 1. Socio-demographic Characteristic of Participants

Characteristics	Frequency	%
Age		
20-24	9	8.7
25-29	12	11.5
30-34	40	38.5
35-39	29	27.9
≥40	14	13.5
Parity		
0	87	83.7
1	14	13.5
≥2	3	2.9
Educational Status		
Completed Primary	3	2.9
Completed Secondary	25	24.0
Tertiary	76	73.1
BMI		
Normal	36	34.6
Overweight	40	38.5
Obese	28	26.9

Table 2 shows the descriptive characteristics of the participants during the study. It shows the participants in the various groups to be comparable in terms of age, total dose of gonadotrophins (Menopur) used and days of stimulation. The differences were not statistically significant (P>0.05).

Table 2: Descriptive characteristics of the study group

Parameters	Stratified BMI (kg/m^2)			P. value
	Normal (23.66±1.02)	Overweight (27.65±1.29)	Obese (33.71±2.94)	
Age (yrs)	31.94±6.99	32.98±3.98	35.14±5.69	0.080
Total dose of Gonadotrophin used (IU)	3966.67±927.23	4222.50±1014.40	4307.14±874.51	0.314
Duration of stimulation (days)	12.46±1.09	12.48±1.06	12.89±1.03	0.200

Values are expressed as Mean ± Standard Deviation

Table 3 shows the mean follicle count on trans-vaginal scanning during stimulation, at follicle aspiration and eventual number of oocytes retrieved was compared between groups. The differences in ovarian response on day 5 and 10 in terms of the follicle count were statistically significant among the BMI groups. However, at retrieval, the follicular count and number of oocytes retrieved were not statistically different amongst the groups with a P-value of 0.155 and 0.193 respectively.

Table 3. BMI and COH response

Patient Type	Normal BMI	Overweight	Obese	p-value
Follicular Count				
Day 3	2.33±0.58	1.33±0.58	1.50±0.71	0.199
Day 5	9.83±5.81	7.85±4.95	6.22±4.04	0.021
Day 10	13.92±7.75	10.63±6.51	8.81±5.62	0.011
At Retrieval				
Follicular Count	10.25±3.93	9.58±5.29	7.88±5.05	0.155
Number of oocytes	9.11±6.58	7.13±5.69	6.50±4.66	0.193

Values are expressed as Mean ± Standard Deviation

Discussion

Ovarian response to stimulation can be affected by factors such as the woman's age, BMI, the cause of the infertility amongst others. However, the effect of BMI has not been clearly defined, with different authors reporting conflicting findings. This study showed that all three groups of BMI were comparable in terms of gonadotrophins requirements as well as duration of stimulation. There were no cases of ovarian hyperstimulation syndrome or cycle cancellation and the number of oocytes retrieved was not significantly affected by the BMI of participants.

In line with our study findings, Marci *et al.* [11] in a study of ovarian stimulation in women with high and normal body mass index compared the long agonist protocol to the short antagonist protocol; reported no significant differences in the length of stimulation, number of oocytes retrieved or number of embryos transferred using either of the protocols. This shows that the choice of stimulation protocol does not significantly influence ovarian response. This buttresses the validity of our study findings despite using only the long agonist protocol.

Furthermore, we observed that the total dose of gonadotrophins as well as the days of stimulation was comparable with BMI groups. Other studies also showed similar reports.[12–15] However, Maheshwari *et al.*[8] in a systematic review of the effect of overweight and obesity on assisted reproduction technology noted that statistically significant higher doses of gonadotrophins were needed for ovulation induction in women with elevated BMI (BMI≥25kg/m^2). They suggested a suspected phenomenon of gonadotrophin resistance as BMI increases and consequently, longer periods of ovarian stimulation and higher cancellation rates. The findings in the study may be compromised by the fact that it was a systematic review of studies which showed a variation in their choice of subjects. Still contrary to our study findings, other researchers noted that with increasing BMI the number of oocytes retrieved reduces.[8, 16] Pinborg *et al.*[16] observed a reduction in the number of oocytes retrieved as the BMI increases which was statistically significant (P<0.001).

In this study we demonstrated that the mean number of oocytes retrieved from women with normal BMI was more than that retrieved from those with elevated BMI but the difference was not statistically significant. This is similar to the reports of other research work which show that the number of retrieved oocytes, fertilization rate, embryo quality, dose of gonadotrophins, number of transferred and frozen embryos, hyperstimulation, pregnancy rates, miscarriage rates and live birth rates showed no statistically significant differences among BMI groups.[12, 14] They concluded that BMI did not appear to be a good parameter for the definition of IVF success.

Conclusion

Based on the findings from this study we can conclude that increase in body mass index does not appear to have an adverse effect on ovarian response amongst female partners of infertile couples in an IVF cycle. There is however, no controversy that overweight and obesity have become major health concerns worldwide and the benefits of weight control cannot be over emphasized. Female partners of infertile couples with elevated BMI seeking IVF infertility treatment can be reassured that their BMI may not adversely affect their ovarian response as well as their quest for conception but overall obesity is discouraged for healthy living.

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