Original Article

Effect of Body Mass Index on the Outcome of *In-Vitro* Fertilization/ Intracytoplasmic Sperm Injection in Women

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Abstract

Background: Obesity, a known epidemic, is a leading cause of various reproductive disorders. Association of body mass index (BMI) with pregnancy outcomes, either ovarian or endometrial, is controversial and least elucidated. **Aim:** This study aimed to analyze the effect of BMI on *in-vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcome in women using self-oocytes, embryos prepared from donor oocytes (DE), or vitrified/frozen embryos (VE) obtained from both the SE and DE groups. **Materials and Methods:** A 9-month retrospective study was conducted on women undergoing IVF/ICSI. The women were grouped according to the World Health Organization classification of BMI (<18.50, 18.50–24.99, 25.00–29.99, and ≥30.00 kg/m^2). They were further subcategorized as SE, DE, and VE groups. Ongoing pregnancy rate (OPR) was recorded as primary, whereas pregnancy rate (PR), clinical PR (CPR), implantation rate (IR), and clinical abortion rate (CAR) were secondary endpoints. Age, number of mature eggs, usable embryos, and embryos transferred were also measured. The data were statistically analyzed using chi-square and analysis of variance. *P*-value <0.05 was considered statistically significant. **Results:** OPR was statistically insignificant across all the groups. Secondary outcomes were statistically insignificant in all the groups except in VE, where IR ($P = 0.008$) and CAR ($P = 0.0002$) were statically significant. Other parameters were statistically insignificant among all the groups. However, in the SE and VE groups, the mean age was statistically significant (SE, $P = 0.0001$; VE, $P = 0.0191$). **Conclusion:** This study showed marginal/no effect of BMI on oocyte quality/endometrial receptivity and, subsequently, on the pregnancy outcome. However, well-designed, larger prospective studies are needed to clarify the role of BMI in pregnancy outcome in women undergoing IVF/ICSI.

Keywords: *Assisted reproductive technology, BMI, clinical abortion rate, implantation rate, obesity, ongoing pregnancy rate, pregnancy rate*

Introduction

Obesity is one of the leading global risk factors affecting both men as well as women.[1] The prevalence of obesity has increased dramatically over the past two decades. In the United States, about 66.7% of women and 75% men of are overweight or obese; out of which, nearly 50% of the women are of reproductive age, and about 17% of their children are aged 2–19 years.[2] In India, according to the National Family Health Survey (NFHS), the percentage of ever-married overweight/obese women (aged 15–49 years) has increased from 11% in NFHS-2 to 15% in NFHS-3.[3]

Obesity is usually assessed using body mass index (BMI), which is calculated by dividing the weight (kg) of a person with the square of her/his height (m^2).[4] The World Health Organization (WHO) considers a person as obese if her/his BMI ≥30 kg/m^2 [Table 1].[5] Besides the

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Table 1: Categorization of obesity by body mass index as per the World Health Organization

Category	BMI (kg/m^2)
Underweight	<18.50
Normal range	18.50–24.99
Overweight	25.00–29.99
Obese	≥30.00

BMI = body mass index.

association of obesity with cardiovascular diseases, diabetes, ortho-arthiritis, etc., a raised BMI is also related with a high risk of reproductive complications in women such as menstrual dysfunction, anovulation, and infertility.[6,7] The women with a higher BMI also show a lower conception rate and higher abortion rate (AR), and they usually experience other reproductive complications.[8] Alteration in the secretion of pulsatile gonadotropin-releasing hormone (GnRH), sex hormone-binding globulin levels, ovarian and adrenal androgens, and luteinizing hormone might be the probable reasons for this dysfunction. Other mechanisms suggest an increased serum and follicular fluid leptin concentration, which in turn inhibits ovarian steroidogenesis. A decrease in serum adiponectin levels might cause hyperandrogenaemia.[6,11,12] However, mechanisms underlying the adverse outcomes of raised BMI, whether ovarian or endometrial, still remain to be fully elucidated.

In-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) involve the process of embryo transfer (ET) using embryos prepared from either self-oocytes (SE), donated oocytes (DE), or vitrified/frozen embryos (VE). Females using DE are generally incapable of producing their own oocytes due to their advanced age or other conditions leading to poor ovarian reserve.[13] The vitrification of embryos plays an important role in assisted reproduction technology (ART) by offering the patients a prospect to take more chances to conceive without undergoing another fresh cycle.[14,15]

It has been reported that women with BMI more than 35 kg/m^2 are at high risk during ART.[4] Therefore, many prior studies have investigated the impact of raised BMI on the pregnancy outcomes of IVF/ICSI but with disparate results.[16,17] Some studies conducted on the patients undergoing IVF/ICSI using DE reported the negative impact of BMI, whereas others reported no difference in the reproductive outcomes in obese and normal DE recipients.[18-20] Similarly, there has been a debate on the effect of BMI on IVF patients using VE.[21,22] The present study was conducted to investigate the effect of BMI on IVF/ICSI outcomes in women using SE, DE, and VE to evaluate whether the effect of BMI, if any, was due to oocyte quality or endometrial receptivity.

Materials and Methods

Patients

A retrospective study was conducted on women, who underwent ICSI from March 1, 2015 to November 30, 2015. This study was approved by an Independent Ethics Committee.

Data collection

The medical records of women were reviewed to calculate their BMI as per formula, weight/height^2 (kg/m^2), on starting of the treatment. According to WHO classification of BMI, the patients were divided into four groups, that is, <18.50 kg/m^2, 18.50–24.99 kg/m^2, 25.00–29.99 kg/m^2, and ≥30.00 kg/m^2. They were further categorized into three groups on the basis of the type of embryo used for transfer, that is, SE, DE, and VE.

The ongoing pregnancy rate (OPR; the ratio of pregnancy continued beyond 12 weeks of pregnancy to the total number of women who have undergone ET) was the primary outcome measure. The pregnancy rate [PR; the ratio of patients with positive β-human chorionic gonadotropin (β-hCG) to the total number of patients who underwent ET], clinical pregnancy rate (CPR; the ratio of women with sonographically confirmed gestation sac after 3 weeks of ET to the total number of patients undergoing ET), implantation rate (IR; the ratio of the number of gestational sacs observed during sonography screening after 3 weeks of ET to the total number of embryos transferred), and clinical abortion rate (CAR; ratio between the number of abortions occurring before 12 weeks of pregnancy to the total number of sonographically confirmed pregnancies) were assessed as secondary outcomes during the study.

The women in the SE groups were also assessed to calculate their mean age, average mature (M II) oocytes, average number of utilized embryos (the number of embryos for transfer plus the number of embryos for freezing), and the average number of embryos transferred. Only the mean age and the average number of embryos transferred were determined in the case of the DE group, because all the patients received almost similar number of oocytes from donors. In the VE group, only the parameters related to ET and mean age were recorded.

Treatment protocol

SE group

The patients were stimulated from second day (D2) of menstrual cycle with a flexible antagonist protocol. When the majority of the follicles reached 17 mm, rec hCG (250 μg) was used to trigger ovulation. The oocytes retrieval procedure (OPU) was followed 35 h later under general anesthesia. Luteal phase was supported by vaginal

micronized progesterone (400 mg) twice a day, 1 day after OPU. ET was performed on D3 or D5, and a maximum of two embryos were transferred. The surplus good quality embryos were vitrified for future use.

DE group

Hormone replacement therapy (HRT) for the preparation of endometrial lining was started from the second day of menstrual cycle by increasing the dose of estradiol valerate tablets from 4 mg to 8 mg per day. When endometrial lining sized ≥8 mm, serum progesterone level was measured. If the progesterone level was found to be ≤0.5 ng/ml, then on the day of donor oocytes retrieval, vaginal micronized progesterone (400 mg) twice a day was added. Subsequently, ET was performed on D3 or D5 with a transfer of maximum two embryos. The surplus good quality embryos were vitrified for future use. All the donors were stimulated with flexible antagonist protocol as in the SE group, but final oocyte maturation was triggered with GnRH agonist.

VE group

HRT for endometrial lining preparation was started from D2 of menstrual cycle by increasing the dose of estradiol valerate tablets from 4 mg/day to 8 mg/day. When the size of endometrial lining was found to be ≥8 mm, serum progesterone level was measured. If it was found to be ≤0.5 ng/ml, then vaginal micronized progesterone (400 mg) twice a day was added. A maximum of two embryos were transferred 3 or 5 days after starting the progesterone injection depending on the stage at which the embryos were vitrified.

All the patients underwent serum β-hCG testing 14 days after the ET. If it was positive, the patients underwent transvaginal sonography 1 week later for the confirmation of pregnancy and the estimation of the number of gestational sacs. All the patients were followed up to 12 weeks of pregnancy at Nova IVI Fertility center or at a referral doctor clinic, and the outcomes were noted.

Statistical analysis

The study data were statistically analyzed using the Statistical Package for the Social Sciences version 19 software (SPSS Inc., Chicago, IL, United States; IBM Corp., Armonk, NY, United States). Age, number of mature oocytes, usable embryos, and embryos transferred were presented as mean ± SD. In all the three groups, the association between BMI and OPR, IR, CAR, CPR, and PR was analyzed using chi-square test, whereas the effect of BMI on age and number of embryos transferred was investigated using the analysis of variance (ANOVA) procedure. In the SE and DE groups, the ANOVA procedure was also used to analyze the effect of BMI on a number of mature oocytes retrieved and total usable embryos. A *P* value of <0.05 was considered statistically significant.

Results

Patients

A total of 812, 665, and 1130 women underwent ET using SE, DE, and VE, respectively. The women in each group were divided into four categories as per their BMI <18.50 kg/m^2 (n = 108), 18.50–24.99 kg/m^2 (n = 1048), 25.00–29.99 kg/m^2 (n = 885), and ≥30.00 kg/m^2 (n = 566), respectively.

Data analysis

The demographic profile of women in SE, DE, and VE is presented in Table 2. The pregnancy outcome

Table 2: Demographic profiling of women as per body mass index

Groups	Variables	BMI (kg/m^2)				*P*
		<18.5	18.5–24.99	25–29.99	≥30	
SE	Total patients	39.00	333.00	285.00	155.00	–
	Mean age[!,#]	29.57 ± 3.05	30.28 ± 3.66	31.07 ± 3.65	31.57 ± 3.46	0.0001[*,a]
	M II oocytes[#]	7.72 ± 4.39	7.86 ± 4.29	8.32 ± 4.08	8.68 ± 4.34	0.1851[a]
	Usable embryos[#]	3.42 ± 2.13	3.29 ± 1.85	3.41 ± 1.85	3.48 ± 1.95	0.7404[a]
	ET[#]	1.81 ± 0.39	1.81 ± 0.39	1.79 ± 0.40	1.83 ± 0.38	0.8374[a]
DE	Total patients	26.00	262.00	222.00	155.00	–
	Mean age[!,#]	35.97 ± 5.68	36.53 ± 5.49	36.79 ± 5.41	37.56 ± 5.22	0.2200[a]
	M II oocytes[#]	12.47 ± 2.63	11.84 ± 3.08	11.25 ± 2.87	11.59 ± 3.59	0.0823[a]
	Usable embryos[#]	3.94 ± 1.58	4.20 ± 1.69	4.02 ± 1.68	3.94 ± 1.64	0.4139[a]
	ET[#]	1.91 ± 0.29	1.86 ± 0.34	1.86 ± 0.35	1.86 ± 0.35	0.9000[a]
VE	Total patients	43.00	453.00	378.00	256.00	–
	Mean age[!,#]	32.08 ± 4.87	31.79 ± 5.19	32.63 ± 5.36	33.01 ± 5.54	0.0191[*,a]
	ET[#]	1.90 ± 0.30	1.83 ± 0.37	1.84 ± 0.37	1.84 ± 0.36	0.5567[a]

SE = the group of patients using self-oocytes, DE = the group of patients using donated oocytes, VE = the group of patients using vitrified embryos. [#]Data presented as mean ± SD unless otherwise specified. [!]Years. [*]Statistically significant (P < 0.05). [a]The ANOVA procedure.

Table 3: Pregnancy outcome measures in women as per body mass index

Groups	Variables	BMI (kg/m^2)				*P*
		<18.5	18.5–24.99	25–29.99	≥30	
SE	Total patients	39.00	333.00	285.00	155.00	–
	OPR (%)	35.90	37.84	39.65	47.10	0.137[a]
	IR (%)	29.58	34.33	35.35	40.64	0.078[a]
	CAR (%)	12.50	20.25	16.30	14.12	0.4082[a]
	CPR (%)	41.03	47.45	47.37	54.84	0.159[a]
	PR (%)	41.03	52.55	51.93	56.77	0.374[a]
DE	Total patients	26.00	262.00	222.00	155.00	–
	OPR (%)	50.00	42.75	48.65	39.35	0.185[a]
	IR (%)	40.00	38.73	46.73	39.93	0.691[a]
	CAR (%)	7.14	17.65	21.74	29.07	0.103[a]
	CPR (%)	53.85	51.91	62.16	55.48	0.378[a]
	PR (%)	61.54	58.02	66.22	58.06	0.492[a]
VE	Total patients	43.00	453.00	378.00	256.00	–
	OPR (%)	27.91	38.85	32.01	32.81	0.0761[a]
	IR (%)	38.55	34.22	30.32	34.04	0.008[*,a]
	CAR (%)	52.00	16.59	27.54	31.15	0.0002[*,a]
	CPR (%)	58.14	46.58	44.18	47.66	0.076[a]
	PR (%)	65.12	52.32	52.12	55.08	0.158[a]

SE = the group of patients using self-oocytes, DE = the group of patients using donated oocytes, VE = the group of patients using vitrified embryos, OPR = ongoing pregnancy rate, IR = implantation rate, CAR = clinical abortion rate, CPR = clinical pregnancy rate, PR = pregnancy rate. [*]Statistically significant ($P < 0.05$). [a]Chi-square test.

measures of women as per BMI in all the groups are presented in Table 3.

SE group

The mean age ranged between 29.57 and 31.57 years, across the BMI categories with ≥30.00 kg/m^2 and <18.50 kg/m^2, being highest in ≥30.00 kg/m^2 group ($P = 0.0001$). The number of M II oocytes ranged from 7.72 to 8.68, being highest in ≥30.00 kg/m^2 BMI category. The usable embryos and average number of ETs ranged 3.48–3.29 and 1.83–1.79, respectively. The number of mature eggs, usable embryos, and embryos transferred were insignificant among all the BMI groups [Table 2].

OPR was found to be highest in the BMI group ≥30.00 kg/m^2 and lowest in the group with lowest BMI level (<18.50 kg/m^2). PR, CPR, and IR were highest in the group with BMI ≥30.00 kg/m^2; however, none of these were statistically significant. Probably, the highest OPR (47.10%) was observed in BMI category with ≥30.00 kg/m^2 owing to a comparatively higher number of M II oocytes and usable embryos in this group [Table 3]. However, neither M II oocytes ($P = 0.1851$) nor OPR ($P = 0.137$) was significantly different among the groups. CAR was highest (16.30%) in the category with BMI ranging between 25.00 and 29.99 kg/m^2, whereas the lowest CAR (12.50%) was observed in the group with BMI <18.50 kg/m^2. However, it was found statistically insignificant among all the groups.

DE group

The mean age ranged between 35.97 and 37.56 years, and all the recipients received almost the same number of eggs from donors, ranging 11.35–12.47. Usable embryos ranged 3.94–4.20, whereas the range of average number of embryos transferred was 1.86–1.91. All these three parameters were found statistically insignificant [Table 2].

OPR was highest (50%) in the group with BMI <18.50 kg/m^2. The lowest OPR (39.35%) was found in the group with BMI ≥30 kg/m^2. However, this difference among the groups was insignificant. PR, CPR, IR, and CAR were highest (66.22, 62.16, 46.73, and 46.73%, respectively) in the group with BMI ranging between 25.00 and 29.99 kg/m^2. However, their difference among the groups was insignificant. CAR was found to be lowest (7.14%) in the lowest BMI category (<18.50 kg/m^2). It increased with increasing BMI but was statistically not significant among the BMI groups [Table 3].

VE group

The mean age ranged 32.08–33.01 years, being highest in the group with BMI level ≥30.00 kg/m^2 ($P = 0.0191$). The average number of embryos transferred ranged 1.84–1.90 and were found to be statistically insignificant across all the groups [Table 2].

The OPR (38.85%) was highest in the BMI category ranging 18.50–24.99 kg/m^2, but the difference among

the various groups was insignificant. PR, CPR, CAR, and IR were highest (65.12, 58.14, 52.00, and 38.55%, respectively) in the group with BMI <18.5 kg/m^2 [Table 3]. Moreover, IR and CAR were found statistically significant among the BMI groups ($P = 0.008$ and 0.0002, respectively).

Discussion

Obesity is a highly prevalent medical condition characterized by high BMI, that is, ≥30 kg/m^2.[23] It is associated with many diseases such as diabetes, hypertension, hypothyroidism, and cardiovascular diseases.[4] Obesity also has a profound impact on the reproductive health of women. It increases the risk of incidence of infertility and related disorders in women by three times as compared to women with normal BMI.[24] Many studies also report a relationship between high BMI and female sexual disorders including infertility.[25-27]

The relationship between raised BMI and poor reproductive outcomes is an ambiguous issue. Endometrium and ovaries, alone or together, might result in poor reproductive outcome in overweight/obese women. Many studies suggest the effect of alteration in ovarian response leading to significant changes in the follicular fluid levels of insulin, lactate, C-reactive protein, and androgens.[28] Though many extra-ovarian factors also contribute to the adverse outcomes of pregnancy in obese infertile women, the accurate mechanism is still unclear.

The risks associated with obese women who conceive naturally are similar to those who conceive with IVF.[29,30] However, the effect of obesity on ART is controversial due to contradiction in the studies reported by various researchers. A bunch of studies report poor pregnancy outcomes in obese women undergoing ART.[4,8,31] As per studies, obesity increases pregnancy risks in women undergoing ART. They need a higher level of gonadotropins as compared to women having normal BMI. The procedure to recover oocytes is more tedious and challenging in an obese woman. The number of oocytes retrieved during the IVF of an obese woman is comparatively lesser than in a woman with normal BMI. However, the quality of oocytes is unaffected by variation in BMI. The increased risk of early pregnancy loss is also observed in obese women.[12] Many studies suggest that the pregnancy outcome followed by ART is not influenced by BMI. However, they might require a high dose of gonadotropin and a longer period of stimulation.[17,31]

According to a systematic review and meta-analysis, a decreased incidence of pregnancy is associated with raised BMI in women undergoing IVF using SE. The authors also suggested the use of DE, as the chance of attaining pregnancy was found similar in the women with higher as well as normal BMI levels.[13] However, the transfer of VE is not recommended in cases with higher BMI range in other studies.[21,32]

The present study analyzed the effect of BMI on IVF-/ICSI-related pregnancy outcomes. The effect of raised BMI/obesity was observed on three groups, that is, women using SE, DE, and VE for transfer or implantation. OPR was assessed as the primary endpoint in the study. Many studies have considered OPR as one of the major outcomes to be measured for the assessment of the success rate of ART. However, the time period for the confirmation of pregnancy was different.[33-37] The effect of BMI on OPR has always been conflicted, because a deleterious impact of BMI on OPR has been reported in the study conducted by Loveland *et al.*,[38] whereas a study conducted by Madkour *et al.*[33] suggested no such association. The present study reports an insignificant effect of BMI on OPR in all the three groups.

The secondary outcomes, that is, CPR, PR, IR, and CAR are important measures of successful pregnancy outcome in ART.[36] There are contrasting reports on the effect of BMI on CPR.[38-41] Similarly, an inconsistency in the effect of BMI on PR has been observed in the previous studies.[42,43] However, the current study reports an insignificant impact of BMI on CPR and PR. IR and CAR are important factors to determine the reproductive outcome in IVF/ICSI. A decrease in IR is attributed to a poor embryo quality and genetic abnormality in embryos.[44,45] Some studies suggest a significant adverse effect of obesity on IR, which is independent of embryo quality, whereas others show no such association.[29,38-41] As per the study conducted by Styne-Gross *et al.*,[20] IR is not affected by obesity in donor oocyte recipients. In the present study, IR in the SE, DE, and VE groups was highest in the categories with BMI level ≥30.00, 25.00–29.99, and <18.50 kg/m^2, respectively. Moreover, the difference among the BMI categories was found to be statistically significant in the VE group ($P = 0.008$). However, no specific pattern could be observed. Similarly, CAR was highest in the categories with BMI levels 18.50–24.99 (SE), ≥30.00 (DE), and <18.50 (VE) kg/m^2, respectively. Though no specific pattern was observed, the difference among the BMI categories was found statistically significant in only the VE group ($P = 0.0002$). The observed trend revealed an increased CAR in the patients with abnormal BMI range, that is, <18.50 and ≥30.00 kg/m^2, whereas a low CAR was observed in the patients with normal BMI levels (18.50–29.99 kg/m^2). According to Veleva *et al.*,[9] underweight women have an increased miscarriage risk, and approximately, 1.7-fold higher AR is found among hormonally substituted Frozen embryo transfer (FET) in contrast with the fresh cycles. A systematic review and meta-analysis on

the association of pre-pregnancy underweight and miscarriage by Balsells *et al.*[10] concluded that the maternal underweight is related to a marginally increased risk of clinical miscarriage. These might be the reasons for a higher AR in the VE group. All other parameters in all the groups were insignificant.

Oocytes number is essential to be measured for the successful outcome of ARTs. A woman with raised BMI might retrieve a lesser number of oocytes as observed in previous studies.[41,46,47] A retrospective cohort study conducted by Zhang *et al.*[48] reported a retrieval of less oocytes from obese women as compared to normal women. However, in the present study, the SE group retrieved the highest average M II oocytes (8.68 ± 4.34) in the BMI ≥30.00 kg/m^2, whereas the lowest average number of oocytes (7.72 ± 4.39) was obtained in the lowest BMI range (<18.50 kg/m^2). However, the difference among the groups was insignificant. The results indicated that the BMI does not affect the number of oocytes retrieved. A study by Sneed *et al.*[49] suggested that the chance of positive IVF pregnancy declines steadily with age, whereas obesity plays a limited or no role in older women. In the present study, difference in mean age was found to be significant in the SE as well as VE groups. In the SE group, a trend was observed, where BMI was found to be increasing with advancing age. However, the present study did not present such a pattern. In the SE group, the lowest mean age (29.57 ± 3.05 years), observed in the patients with lowest BMI group (<18.50 kg/m^2), did not show best OPR, whereas a group with highest BMI and a highest mean age (31.57 ± 3.46 years) presented highest OPR. In case of the VE group, the mean age was almost similar in all the groups ranging from 31.79 to 33.01 years.

The limitations of the present study include its retrospective nature. The unequal distribution pattern across BMI categories with the largest difference in the VE group with 43 patients in BMI category with <18.50 kg/m^2 and 453 in BMI ranging from 18.50 to 24.99 kg/m^2 could also affect the results. Uniformity in sample size might help in omitting such differences and disorganization of results. However, the study by Kilic *et al.*[50] also supported that BMI does not have a strong influence on successful outcome of pregnancy.

Conclusion

Overall, the OPR was found unaffected by BMI in any of the three groups, which brought us to a conclusion that BMI does not have any effect on oocyte quality or endometrial receptivity. Hence, BMI does not affect the chance of achieving pregnancy in infertile women following IVF/ICSI. However, IR and CAR were found to be statistically significant in the VE group presenting no specific pattern. Therefore, more robust studies, with large and comparable sample size, are needed to substantiate this fact.

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Conflicts of interest

There are no conflicts of interest.

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