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ORIGINAL ARTICLE

Obesity adversely impacts the number and maturity of oocytes in conventional IVF not in minimal stimulation IVF

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Abstract

Objective: The objective of this study is to assess the relationship between BMI and oocyte number and maturity in participants who underwent minimal stimulation (mini-) or conventional IVF.
Methods: Participants who underwent their first autologous cycle of either conventional ($n = 219$) or mini-IVF ($n = 220$) were divided according to their BMI to analyze IVF outcome parameters. The main outcome measure was the number of oocytes in metaphase II (MII). Secondary outcomes included the number of total oocytes retrieved, fertilized (2PN) oocytes, cleavage and blastocyst stage embryos, clinical pregnancy (CP), and live birth (LB) rates.
Results: In conventional IVF, but not in mini-IVF, the number of total oocytes retrieved (14.5 ± 0.8 versus 8.8 ± 1.3) and MII oocytes (11.2 ± 0.7 versus 7.1 ± 1.1) were significantly lower in obese compared with normal BMI women. Multivariable linear regression adjusting for age, day 3 FSH, days of stimulation, and total gonadotropin dose demonstrated that BMI was an independent predictor of the number of MII oocytes in conventional IVF ($p = 0.0004$). Additionally, only in conventional IVF, BMI was negatively correlated with the total number of 2PN oocytes, as well as the number of cleavage stage embryos.
Conclusions: Female adiposity might impair oocyte number and maturity in conventional IVF but not in mini-IVF. These data suggest that mild ovarian stimulation might yield healthier oocytes in obese women.

Keywords

Adiposity, infertility, IVF, minimal stimulation, obesity

History

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Introduction

Obesity has become a major global health challenge with the proportion of overweight and obese adults worldwide increasing between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women [1]. Obesity is a key player in the pathogenesis of cardiovascular disease, diabetes, hypertension, dyslipidemia, obstructive sleep apnea, and even cancer [2–4]. Contributions of female obesity to anovulation, menstrual cycle abnormalities, infertility, sexual dysfunction, and fetal loss have been well documented by others and us [5–13]. Although infertility associated with obesity has been related to anovulation [14], time to spontaneous pregnancy is much longer in obese women even with regular menstrual cycles [15,16]. Moreover, obese women undergoing controlled ovarian hyperstimulation (COH) with oocyte retrieval and in vitro fertilization (IVF), where spontaneous ovulation is not a factor, still have worse outcomes than normal weight women in terms of number of oocytes retrieved, fertilization, implantation, miscarriage, clinical pregnancy, and live birth rates [17–21]. Obesity also poses an adverse impact on endometrial receptivity [19]. Recent data have pointed out to a relationship between recipient body mass index (BMI) and poor reproductive outcome that may be mediated by a reduction in uterine receptivity [6,19,22,23].

Minimal stimulation IVF refers to the use of a sequential administration of clomiphene citrate (CC) followed by low-dose gonadotropins [24,25]. The use of CC allows an endogenous rise in follicle-stimulating hormone (FSH) to be additive to the ovarian stimulation, thus requiring low doses of gonadotropins [26,27]. Minimal stimulation IVF has the potential to reduce ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy rates without significantly lowering pregnancy rates [24]. Interestingly, embryo implantation rate after minimal stimulation IVF was similar to that observed in conventional IVF protocols [28]. Compared with conventional IVF protocols, additional advantages of minimal stimulation include a much lower cost of medications, fewer days of monitoring with ultrasound and blood assays, and fewer injections [29,30]. Some minimal stimulation IVF protocols, including ours, involve the addition of a freeze-all-embryo policy in order to lessen any negative effect of ovarian stimulation on endometrial receptivity [31].

Although there are several data addressing the impact of obesity on conventional IVF outcome, we are not aware of any study evaluating the relationship between obesity and oocyte number and quality in minimal stimulation IVF. The aim of the present study was to assess the reproductive outcome, in particular, the number of total and mature oocytes in metaphase

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II (MII), according to BMI category (normal, overweight, or obese) in participants who underwent minimal stimulation IVF or conventional IVF. Comparison of minimal versus conventional IVF protocol outcomes was beyond the scope of this study.

Materials and methods

Participants

Women aged between 18 and 38 with normal menstrual cycles and requiring a first IVF treatment were included between February 2009 and August 2013. After complete history taking and physical examination, women with pre-existing medical conditions including hypothyroidism and hyperprolactinemia were excluded. Inclusion criteria included women with infertility diagnoses of male, unexplained, and tubal factors. Ultrasound testing was performed at baseline and women with any submucosal or large intramural fibroids requiring surgery were excluded from the study. The study was conducted at New Hope Fertility Center (NHFC), New York. The study was approved by the Institutional Review Board of New York Downtown Hospital (IRB approval reference number: JZ-09-08). All participants were consented before entering the study. Female weight and height were measured and body mass index was calculated using the height and weight in kg/m^2. BMI was categorized based on the World Health Organization (WHO) classification [32] of normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese ($\geq$30 kg/m^2).

Conventional IVF

Conventional ovarian stimulation consisted of a long GnRHa protocol using mid-luteal down-regulation (Leuprolide Acetate, Teva, Sellersville, PA) followed by stimulation with daily gonadotropins injections (Bravelle and/or Menopur, Ferring, Parsippany, NJ; Follistim, Merck, White House Station, NJ; or Gonal F, EMD Serono, Rockland, MA) at a dose of 150–300 IU's daily starting in the early follicular phase (cycle day 3). The final maturation of oocytes was induced with hCG (Novarel, Ferring, Parsippany, NJ; Pregnyl, Merck, White House Station, NJ; or Ovidrel, EMD Serono, Rockland, MA) when at least two follicles reached 18 mm or greater. Oocyte retrieval was performed 34 h later under transvaginal ultrasound guidance. Retrieved oocytes were fertilized by conventional IVF or ICSI as indicated. Fertilization was evaluated 12–20 h after insemination. The presence of two PN confirmed normal fertilization and embryos were subsequently cultured until the blastocyst stage. One or two blastocysts were transferred in the fresh cycle. Remaining supernumerary blastocysts were vitrified and thawed blastocysts were transferred in subsequent naturally or artificially prepared cycles with oral Estrace (Actavis Pharma, Inc, Parsippany, NJ).

Minimal stimulation IVF (mini-IVF)

After oral contraceptive pill pre-treatment for 10–14 d, adequate suppression was confirmed with an estradiol (E_2) level of <75 pg/mL. Minimal ovarian stimulation was started with an extended regimen (from cycle day 3 until the day before triggering) of CC (50 mg/d orally) in conjunction with gonadotropin injections (Bravelle and/or Menopur, Ferring, Parsippany, NJ; Follistim, Merck, White House Station, NJ; or Gonal F, EMD Serono, Rockland, MA) starting on cycle days 4–7 with 75–150 IU's daily. No hypothalamic–pituitary suppression was performed and the final maturation of oocytes was induced by a GnRHa nasally (Synarel nasal spray, Pfizer, New York, NY) when the lead follicle reached a diameter of 18 mm or greater. Retrieved oocytes were fertilized by conventional IVF or ICSI as indicated and subsequently cultured until the blastocyst stage. All blastocysts were vitrified using the CryoTop method (Kitazato Biopharma, Shizuoka, Japan) [33]. A single thawed blastocyst was transferred in a subsequent natural or artificially prepared cycle with oral Estrace (Actavis Pharma, Inc, Parsippany, NJ) [30].

Statistical analysis

In order to assess the effect of ovarian stimulation (i.e., conventional versus minimal), the number of metaphase II (MII) oocytes was the main outcome of interest because fertilization, implantation, and achieving pregnancy depend on other factors, such as ICSI, sperm, and endometrium. Secondary outcomes included total number of oocytes retrieved, number of fertilized oocytes, number of embryos at the cleavage and blastocyst stages, clinical pregnancy (defined as intrauterine gestational sac on transvaginal sonogram), and live birth rates. A clinical pregnancy was defined as at least one intrauterine sac at 6 weeks gestation and live birth was defined as a child born after 22 weeks of gestation or weighing at least 500 g.

For continuous outcomes, data were expressed as mean $\pm$ standard error of the mean (SEM). Categorical data were expressed as frequency and percentage. In each of the mini-IVF and conventional IVF, comparison in demographic and cycle characteristics between the three groups of BMI (normal, overweight, and obese) were assessed using ANOVA with *post hoc* analysis because the data were normally distributed. Chi-square test was used for categorical variables as appropriate. Pearson correlation was performed between BMI and other clinical parameters in the conventional IVF and mini-IVF groups separately. Multivariable linear regression adjusting for age, day 3 FSH, days of ovarian stimulation, and total gonadotropin dose per cycle was performed to assess BMI as an independent predictor on the number of MII oocytes as a dependent variable. p Value <0.05 was considered statistically significant.

Results

In the conventional IVF group, 219 participants were enrolled that resulted in cumulative live birth rate of 68.5% (150/219). Comparison between normal BMI ($n = 121$), overweight ($n = 73$), and obese ($n = 25$) women revealed that the three groups were similar in age (Table 1) and that cumulative pregnancy rate (67.7% versus 72.6% versus 57.7%, respectively, $p = 0.4$) and live birth rate (67.5% versus 69.7% versus 56%, respectively, $p = 0.4$) were not statistically different. However, as seen in Table 1, the number of oocytes retrieved (14.5 ± 0.8 versus 8.8 ± 1.3, $p = 0.005$), the number of mature oocytes reaching MII (11.2 ± 0.7 versus 7.1 ± 1.1, $p = 0.02$) significantly differed between the normal BMI and the obese groups. There was no difference in the number of fertilized (2PN) oocytes or the number of embryos at the cleavage and blastocyst stages between the three groups of BMI (Table 1). Although day 3 FSH was statistically significantly (although not clinically significant) higher in normal weight women compared with overweight women (7.8 ± 0.1 versus 7.1 ± 0.2, $p = 0.04$), peak E_2 levels on day of hCG was significantly lower in overweight (2674.0 ± 215.1) and obese (2037.0 ± 271.9) women compared with normal weight (3883.0 ± 244.9) women ($p < 0.0001$; Table 1).

In the mini-IVF group, 220 participants were enrolled that resulted in cumulative live birth rate of 50.5% (111/220). Comparison among normal BMI ($n = 124$), overweight ($n = 69$), and obese ($n = 27$) women revealed that the three groups were similar in age (Table 2) and that cumulative pregnancy rate (53.2% versus 42.6% versus 59.3%, $p = 0.2$) and live birth rate (51.7% versus 36.0% versus 54.2%, $p = 0.1$) were not statistically significant. As seen in Table 2, the number of oocytes retrieved, the number of MII oocytes, the number of 2PN oocytes, and the

Table 1. Demographics, clinical characteristics, and IVF outcome in women who underwent conventional ovarian stimulation.

	Normal weight ($n = 121$)	Overweight ($n = 73$)	Obese ($n = 25$)	p Value
Age (years)	31.9 ± 0.3	31.8 ± 0.5	31.6 ± 0.7	0.9
BMI (kg/m^2)	22.1 ± 0.1[a]	27.5 ± 0.2[b]	31.3 ± 0.2[c]	<0.0001
Day 3 FSH (mIU/mL)	7.8 ± 0.1[a]	7.1 ± 0.2[b]	7.8 ± 0.3	0.04
Day 3 estradiol (pg/mL)	51.4 ± 1.9	54.6 ± 2.7	56.1 ± 5.9	0.5
Antral follicle count	14.2 ± 1.1	15.1 ± 0.7	13.4 ± 0.8	0.7
Days of ovarian stimulation, no.	10.6 ± 0.7	10.1 ± 0.2	10.5 ± 0.5	0.9
Total dose of gonadotropins per cycle (IUs)	2046.0 ± 37.0	2096.0 ± 46.4	2087.0 ± 107.8	0.7
Peak estradiol on day of hCG (pg/mL)	3883.0 ± 244.9[a]	2674.0 ± 215.1[b]	2037.0 ± 271.9[b]	<0.0001
Oocytes retrieved, no.	14.5 ± 0.8[a]	11.7 ± 0.8	8.8 ± 1.3[b]	0.005
Metaphase II oocytes, no.	11.2 ± 0.7[a]	9.2 ± 0.7	7.1 ± 1.1[b]	0.02
Fertilized oocytes (2PN), no.	9.1 ± 0.6	7.9 ± 0.6	6.0 ± 1.0	0.06
Cleavage stage embryos, no.	9.5 ± 0.6	8.5 ± 0.7	6.7 ± 1.1	0.1
Blastocyst stage embryos, no.	6.2 ± 0.4	5.8 ± 0.5	5.1 ± 0.8	0.5
Blastocyst (s) transferred, no.	1.8 ± 0.04	1.7 ± 0.06	1.6 ± 0.1	0.3
Clinical pregnancy rate	82 (67.7%)	53 (72.6%)	15 (57.7%)	0.4*
Live birth rate	81 (67.5%)†	46 (69.7%)‡	14 (56.0%)¶	0.4*

Data are presented as mean ± SEM or n (%). ANOVA was performed with *post hoc* analysis.
[a, b,] and [c] indicate statistically different groups.
*Chi-square test.
†One pregnancy pending.
‡Seven pregnancies pending.
¶One pregnancy pending.

Table 2. Demographics, clinical characteristics and IVF outcome in women who underwent minimal ovarian stimulation.

	Normal weight ($n = 124$)	Overweight ($n = 69$)	Obese ($n = 27$)	p Value
Age (years)	32.3 ± 0.3	32.6 ± 0.5	31.6 ± 0.7	0.5
BMI (kg/m^2)	21.8 ± 0.2[a]	27.2 ± 0.2[b]	31.5 ± 0.2[c]	<0.0001
Day 3 FSH (mIU/mL)	7.8 ± 0.1	7.6 ± 0.2	7.5 ± 0.3	0.5
Day 3 Estradiol (pg/mL)	54.7 ± 2.4	57.2 ± 5.7	48.0 ± 3.6	0.5
Antral follicle count	14.8 ± 1.1	14.0 ± 0.6	14.3 ± 1.0	0.9
Days of stimulation, no.	10.9 ± 0.7	10.8 ± 0.3	10.6 ± 0.5	1.0
Total dose of gonadotropins per cycle (IUs)	434.2 ± 10.7[a]	547.7 ± 41.9[b]	477.8 ± 25.0	0.003
Peak Estradiol on day of hCG (pg/mL)	1837.0 ± 113.1	1631.0 ± 112.1	1317.0 ± 201.3	0.08
Oocytes retrieved, no.	4.8 ± 0.3	4.2 ± 0.3	3.9 ± 0.8	0.3
Metaphase II oocytes, no.	4.1 ± 0.3	3.5 ± 0.3	3.6 ± 0.6	0.4
Fertilized oocytes (2PN), no.	3.4 ± 0.2	2.9 ± 0.3	3.1 ± 0.5	0.4
Cleavage stage embryos, no.	3.6 ± 0.2	3.2 ± 0.3	3.3 ± 0.5	0.6
Blastocyst stage embryos, no.	2.7 ± 0.2	2.9 ± 0.3	2.6 ± 0.4	0.9
Embryo (s) transferred, no.	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0
Clinical pregnancy rate	66 (53.2%)	29 (42.6%)	16 (59.3%)	0.2*
Live birth rate	62 (51.7%)†	22 (36.0%)‡	13 (54.2%)¶	0.1*

Data are presented as mean ± SEM or n (%). ANOVA was performed with *post hoc* analysis.
[a, b,] and [c] indicate statistically different groups.
*Chi-square test.
†Four pregnancies pending.
‡Seven pregnancies pending.
¶3 pregnancies pending.

number of embryos at the cleavage and blastocyst stages did not significantly differ between the three groups of BMI.

In each of the conventional and the mini-IVF groups, correlation analysis was performed between BMI and other clinical parameters. As seen in Table 3, BMI was negatively correlated with the number of oocytes retrieved ($r = -0.24$, $p = 0.0005$), the number of MII oocytes ($r = -0.20$, $p = 0.004$), and the number of 2PN oocytes ($r = -0.17$, $p = 0.02$) in the conventional IVF group, but not in the mini-IVF group. In conventional IVF, multivariable linear regression adjusting for age, day 3 FSH, days of stimulation, total gonadotropin dose, demonstrated that BMI is an independent predictor of the number of MII oocytes ($p = 0.0004$).

Discussion

This study evaluated IVF outcome according to BMI category within a group of participants who underwent minimal stimulation IVF and another group of participants who underwent conventional IVF. In the minimal stimulation IVF group, our results revealed that the number of total, MII and fertilized oocytes, and the number of embryos at either cleavage or blastocyst stages did not differ among normal, overweight, and obese women. Among all participants who underwent minimal stimulation IVF, BMI did not correlate with any of the clinical outcomes. However, in women who underwent conventional IVF, obese (not overweight) women had significantly lower total number of oocytes retrieved and lower number of MII oocytes

Table 3. Correlation between BMI and IVF clinical parameters in both conventional and mini-IVF.

	Day 3 FSH	Day 3 E2	AFC	Days of stimulation	Oocytes retrieved	M II oocytes	2PN oocytes	Day 3 embryos	Blastocyst embryos
Conventional IVF ($n = 219$)	$r = -0.11$ $p = 0.09$	$r = 0.045$ $p = 0.5$	$r = 0.028$ $p = 0.7$	$r = -0.02$ $p = 0.7$	$r = -0.24$ $p = 0.0005$	$r = -0.20$ $p = 0.004$*	$r = -0.17$ $p = 0.02$	$r = -0.14$ $p = 0.04$	$r = -0.083$ $p = 0.3$
Mini-IVF ($n = 220$)	$r = -0.095$ $p = 0.2$	$r = -0.068$ $p = 0.3$	$r = -0.059$ $p = 0.4$	$r = 0.022$ $p = 0.7$	$r = -0.13$ $p = 0.05$	$r = -0.13$ $p = 0.06$	$r = -0.12$ $p = 0.07$	$r = -0.11$ $p = 0.1$	$r = -0.050$ $p = 0.5$

Pearson correlation was performed. FSH, follicle-stimulating hormone; E2, estradiol; AFC, antral follicle count; MII, metaphase II; PN, pronuclei.
*Remained statistically significant in a multivariable linear regression adjusting for age, day 3 FSH, days of ovarian stimulation, and total gonadotropin dose per cycle.

compared with normal weight women although clinical pregnancy and live birth rates did not differ. Additionally, among all women who underwent conventional IVF, BMI was negatively correlated with total oocytes, MII oocytes, and fertilized oocytes as well as the number of day 3 embryos formed.

To our knowledge, this study is the first to address the relationship between obesity and the clinical outcome of minimal stimulation IVF. In the current study, all cycle data were derived from a single large institution, thus increasing the consistency between physician practices, treatment protocols, and patient populations. We analyzed only the first fresh ART cycle of every patient who met the inclusion criteria to minimize additional confounding by a history of repeatedly failed cycles. Most importantly, the strength of the present study is derived from an analysis that included live birth rates, the most clinically important outcome of ART.

Our results indicated that obese women who underwent minimal stimulation IVF did not have poorer clinical outcome in any aspect. This suggests that mild ovarian stimulation by using lower doses of gonadotropins could be protective for the oocyte in obesity state. On the other hand, we found that obese women who underwent conventional IVF had fewer total oocytes, fewer oocytes in MII, and that BMI was positively correlated with 2PN oocytes and cleavage stage embryos. In the conventional IVF group, although clinical pregnancy and live birth rates did not differ statistically between normal-weight (67.5%) and obese (56%) women because of the small sample size, the 11.5% difference between both groups could become clinically meaningful with large sample sizes. The relationship between obesity and the outcome of conventional IVF treatments has been the subject of several investigations that continues to yield conflicting results. Some studies pertaining to conventional IVF have assessed oocyte quality (or maturity) using a graded scoring system. Wittemer et al. [34] reported that the ratio of good quality oocytes obtained by conventional IVF was significantly reduced in women with a BMI $\geq 25\,kg/m^2$ compared with those with normal BMI. A larger study on conventional IVF found that the number of mature oocytes, by nuclear assessment, was significantly reduced in morbidly obese women [35]. Another study reported that compared with normal weight women, overweight women displayed significantly less fertilized oocytes and fewer embryos in the cleavage stage [20].

Our results showing no statistically significant difference in clinical pregnancy or live birth rate among normal weight, overweight, and obese women in conventional IVF and minimal simulation IVF are in agreement with several published studies on conventional IVF [35–38]. It is important to note that, unlike our study where the highest BMI was $33\,kg/m^2$, most other studies have included participants with much higher BMI classifications ($>40\,kg/m^2$). Additionally, despite live birth being the optimal ART outcome to be studied, the majority of studies used clinical pregnancy as their primary outcome owing to relative ease of data collection. Interestingly, studies with large sample sizes have reported an adverse impact of obesity on clinical pregnancy and live birth rates. For instance, a retrospective study of 1721 first conventional IVF cycles found lower clinical pregnancy rates in obese participants and a lower live birth rates in morbidly obese participants [39]. Another retrospective study of 6500 conventional IVF cycles demonstrated decreased implantation, clinical pregnancy, and live birth rates in obese patients [40]. A larger retrospective study of 8457 first conventional IVF cycles found a significantly lower live birth rate per cycle in women with BMI $>27\,kg/m^2$ [41]. Similarly, a study of 5019 IVF cycles found increased live birth rates after three conventional IVF cycles in patients with BMI $\geq 30\,kg/m^2$ [42]. However, in that study, when analyzing only the first IVF cycles ($n = 2660$), they failed to report a statistical significance. Similar results of significantly lower live birth were found in patients with BMI $\geq 25\,kg/m^2$ [43] as well as in those with BMI $>36\,kg/m^2$ [44] compared with normal weight controls. Additionally, several studies have demonstrated decreased odds of clinical pregnancy rates in patients with elevated BMI [41,45,46].

We acknowledge the limitations of this study that include the relatively small sample size especially in the obese group in both the conventional and minimal stimulation IVF. Despite the small sample sizes, obese groups in each of the conventional ($n = 25$) and minimal stimulation ($n = 27$) IVF were similar. Additionally, we did not have morbidly obese participants, as the highest BMI was $33\,kg/m^2$. Despite these limitations, this study is the first to address the relationship of obesity by BMI categories in minimal stimulation IVF setting with the aim to start ground for larger prospective studies.

In summary, this study extends the body of literature on the impact of obesity on ART outcome in conventional IVF. It also reports for the first time that obese women might not have a worse ovarian response if they undergo minimal ovarian stimulation IVF. As high doses of gonadotropins have been shown to be detrimental to human oocyte [47,48], minimal stimulation IVF might represent a potential alternative to conventional IVF in obese women with poor oocyte/embryo quality. The mechanism behind this relationship are still poorly understood, and further knowledge is needed in order to increase the safety of ovarian stimulation and to reduce potential effects on oocyte/embryo development which will ultimately be translated into increased pregnancy rates and healthy offspring.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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