

Body mass index is not associated with donor oocyte recipient success: an ideal study using a paired analysis of sibling-oocytes

Robert Setton, M.D.,^a Alice Chung, B.A.,^b Lilli Zimmerman, M.D.,^a Alexis Melnick, M.D.,^a Zev Rosenwaks, M.D.,^a and Steven D. Spandorfer, M.D.^a

^a The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, New York; and ^b Weill Cornell Medicine, New York, New York

Objective: To determine whether a higher body mass index (BMI) adversely affects endometrial receptivity.

Design: Retrospective cohort study.

Setting: Academic medical center.

Patient(s): All donor egg recipients (DERs) who received fresh sibling-oocytes (oocytes from a donor that were retrieved from a single controlled ovarian hyperstimulation [COH] cycle and split between two recipients) at our center over a 7-year period were included.

Intervention(s): COH of a donor with fresh embryo transfer to recipients of differing BMI. The two recipients of the sibling-oocytes were paired and categorized based on BMI: group A (normal weight, BMI 18.5–24.9 kg/m²) and group B (overweight/obese, BMI >25.0 kg/m²).

Main Outcome Measure(s): The primary outcome was implantation rate. Secondary outcomes were positive pregnancy rate and live birth rate.

Result(s): A total of 408 patients had received oocytes from a split donor oocyte cycle. There were 71 pairs of patients (142 recipients) that had discrepant BMI categories and were analyzed. Implantation rates were similar for the two groups (54.5%±5.3% vs. 56.3%±4.8% for group A and B, respectively, $P=0.72$). The positive pregnancy rate (77.5% vs. 80.3%, $P=0.28$) and live birth rate (54.9% vs. 60.6%, $P=0.33$) for groups A and B were also found to be similar.

Conclusion(s): In this idealized model that controls to the greatest degree possible for factors that would impact implantation, we found that a higher BMI did not reduce implantation, positive pregnancy, or delivery rates. These findings suggest that a higher BMI does not adversely affect uterine receptivity. (*Fertil Steril Rep*® 2020;1:25–9. ©2020 by American Society for Reproductive Medicine.)

Key Words: Obesity, donor oocyte recipient, sibling-oocytes, endometrial receptivity

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The rise in the prevalence of obesity worldwide has been dramatic over the last several decades. Between 1980 and 2013, the rates of overweight and obese adult women have risen from 29.8% to 38.0%, with higher rates of obesity in the United States than in

other developed nations (1). Furthermore, it is projected that by 2030, almost 60% of the world's population will be overweight or obese (2). In 2002, among reproductive-age women in the United States, 23% were estimated to be obese and 24.5% overweight (3), and the rate

of obesity has been consistently increasing by about 0.5 percentage points yearly since then (4). There are several medical consequences of obesity, including effects on fertility.

The adverse sequelae of obesity on fertility in reproductive-aged women include anovulation and a greater risk of miscarriage, which may be increased by about 30% (5). With obesity, insulin resistance and a hyperinsulinemic state contribute to increased stimulation of the ovaries, leading to hyperandrogenemia. Higher levels of circulating androgens are further aromatized to estrogen by excess adipose tissue, which leads to dysregulation of the hypothalamic–pituitary–ovarian (HPO)

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Reprint requests: Steven D. Spandorfer M.D., The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, 1305 York Avenue, New York, New York 10021 (E-mail: sdspando@med.cornell.edu).

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axis and consequent subfertility (6). Findings of increased rates of spontaneous abortions and lower pregnancy rates in obese women have led to suggestions that obesity is associated with worsened oocyte quality (7). Abnormal endometrial development may also contribute to these risks, as patients with obesity have been shown to have different endometrial gene expression compared to those with normal body mass index (BMI) (8).

In assisted reproductive technology (ART), the reported effects of obesity on reproductive outcomes have been inconsistent. Some studies found worse implantation, pregnancy, and live birth rates in higher BMI groups, whereas others reported that BMI had no impact on reproductive outcomes (9). Because of the complex nature of how the oocyte–endometrium relationship affects implantation and pregnancy, further studies are warranted for a more targeted investigation of the relationship between BMI and endometrial receptivity.

This study aimed to analyze the relationship between BMI and endometrial receptivity by analyzing outcomes from sibling–oocyte recipients from the same donor egg cycle. Through this idealized model, oocyte quality was controlled to a greater degree than in any prior study in order to investigate the impact on endometrial receptivity.

MATERIALS AND METHODS

Cycle Inclusion Criteria

For this retrospective cohort study, all patients who underwent a donor egg recipient (DER) cycle at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine between January 2010 and December 2016 were screened for potential inclusion. Included in the study were patients who had a fresh embryo transfer and had received oocytes from a donor that were retrieved from a single controlled ovarian hyperstimulation (COH) cycle and split between two recipients (sibling–oocytes). The two recipients of the sibling–oocytes were paired and categorized based on BMI: group A (normal weight, BMI 18.5–24.9 kg/m²) and group B (overweight/obese, BMI >25.0 kg/m²). Recipients who were underweight (BMI <18.5 kg/m²), were in similar BMI categories as the other paired recipient, had a transfer using frozen–thawed oocytes or embryos, had PGT-A performed, had uterine factor infertility (Asherman syndrome or history of myomas), or severe male factor infertility (azoospermia or other abnormal parameter necessitating the surgical retrieval of sperm) were excluded from the study. There is no set BMI cutoff at our center, although patients who are morbidly obese must have a consultation with a maternal–fetal medicine specialist for medical clearance for pregnancy. Chart review was performed to collect cycle outcomes. The institutional review board at Weill Cornell Medicine approved this study.

Clinical and Laboratory Protocols

Ovarian stimulation, triggering, oocyte retrieval, embryo culture, and embryo transfer were performed as per our previously described protocols (10, 11). Anonymous oocyte donors were started on oral contraceptive pills (norethindrone

1 mg/ethinyl estradiol 35 µg, Ortho-Novum 1/35, Janssen Pharmaceuticals, Beerse, Belgium) for pretreatment follicular synchronization. Ovarian stimulation was carried out to maximize follicular response while minimizing the risk of ovarian hyperstimulation syndrome. The starting gonadotropin dose was based on age, weight, antral follicle count, anti-Müllerian hormone level, and, if applicable, prior response to COH. Donor stimulation was performed with gonadotropins (Gonal-F, EMD-Serono, Geneva, Switzerland; or Follistim, Merck, Kenilworth, NJ; and Menopur, Ferring Pharmaceuticals Inc, Parsippany, NJ) along with the addition of GnRH-antagonist (Ganirelix Acetate, Merck, Kenilworth, NJ, or Cetrotide, EMD-Serono, Geneva, Switzerland) once serum estradiol levels exceeded 300 pg/mL or the presence of a lead follicle with a mean diameter >13 mm was detected by transvaginal ultrasonography.

Ovulation trigger was given once at least two lead follicles attained a mean diameter >17 mm. A dual trigger was used with hCG and GnRH-agonist (Leuprolide Acetate, San-do Inc., Princeton, NJ), or GnRH-agonist trigger was used alone. Oocyte retrieval under transvaginal ultrasound guidance was performed under conscious sedation approximately 35–36 hours after trigger. Retrieved oocytes were exposed to 40 IU recombinant hyaluronidase (Cumulase, Halozyme Therapeutics Inc., San Diego, CA) to remove the cumulus–corona complex, and intracytoplasmic sperm injection (ICSI) was performed as per our center’s policy of performing ICSI for all patients undergoing IVF with donor oocytes in split cycles to allow determination of maturity (12). Oocytes were examined 12–17 hours after ICSI to assess for normal fertilization. All embryos were cultured using an in-house culture medium.

All donor oocyte recipients were down-regulated with leuprolide acetate in the preceding luteal phase, and then the endometrium was synchronized to their respective donor’s stimulation cycle with estradiol patches 0.1 mg (Vivelle-Dot, Novartis International AG, Basel, Switzerland) changed every other day, with number of patches up-titrated as needed and the initiation of intramuscular progesterone (50 mg/mL) the evening after donor ovulation trigger with a half-dose (25 mg or 0.5 mL) followed by a full dose (0.1 mL) thereafter. Recipients underwent fresh embryo transfer on day 3 or day 5 with one or two embryos. Transfer was performed with the use of a Wallace catheter (Smiths Medical Inc., Norwell, MA). Titration of estrogen patches and progesterone doses were made based on measured serum levels, with adjustments of doses as deemed necessary, and continued until 10–12 weeks of gestation. Serum hCG, estradiol, and progesterone levels were obtained on cycle day 28 (date of pregnancy test) and, if the bHCG was positive, then again on cycle day 30, and then followed as per routine protocol. Patients were monitored at our center until the detection of a fetal heartbeat, at which point they were referred to an obstetrician. Final pregnancy outcomes after patients were transferred out of our center were obtained via mail, e-mail, and phone call follow-up.

Outcome Variables

The primary outcome studied was implantation rate. Secondary outcomes included were positive pregnancy rate and live

birth rate. Implantation rate was defined as the number of gestational sacs seen on ultrasonography divided by the number of embryos transferred. Positive pregnancy rate was defined as the proportion of patients who underwent embryo transfer that resulted in a positive serum β -hCG on cycle day 28. Live birth rate was defined as the proportion of cycles resulting in at least one live-born infant delivered at >24 weeks gestation out of all included pregnancy cycles. Baseline patient demographic and IVF characteristics were collected for recipients and donors for all included cycles. Primary and secondary outcomes were compared between groups A and B.

Statistical Analysis

Categorical variables were expressed as number of cases (n) and percentage of occurrence (%). Continuous variables were checked for normality and expressed as mean \pm standard deviation. Statistical analysis included paired *t*-test, χ^2 test, and Fisher's exact test. $P < .05$ was deemed statistically significant. Analyses were implemented in SPSS Version 26 (IBM Corporation, Armonk, NY).

RESULTS

A total of 1,013 patients who underwent DER cycles between January 2010 and December 2016 were screened for inclusion in the study. Of those patients, 408 had received sibling-oocytes from 204 donors who had the yield of a single COH cycle split between two recipients. Paired recipients (recipients who received oocytes from the same donor) were excluded if they were in similar BMI categories or if one of the two recipients was underweight (BMI < 18.5 kg/m²). A total of 142 recipients, or 71 paired recipients, who were in discrepant BMI categories (n = 71 for group A and n = 71 for group B) met inclusion criteria and were analyzed. Baseline demographics are presented in Table 1. The two groups were similar for age, gravidity, parity, number of embryos transferred, and peak endometrial stripe. The mean BMI was 21.9 kg/m² for group A and 29.5 kg/m² for group B. Most patients in group B were in the overweight BMI range. A BMI of 42.6 kg/m² was the highest that was identified during the study period. The mean donor age was 27.2 \pm 0.16 years, and none of the donors were obese. Estradiol levels on the day of starting progesterone were higher for group A than for group B (Table 1). Of all transfers performed, 61.4% in group A and 60.5% in group B were performed on day 3.

Table 2 presents the primary and secondary outcomes for the two groups. The implantation rates were similar for group A (54.5% \pm 5.3%) and group B (56.3% \pm 4.8%). In addition, the positive pregnancy rates (77.5% vs. 80.3%) and live birth rates (54.6% vs. 60.6%) were similar for groups A and B, respectively. The miscarriage rate was 29.1% for group A and 24.6% for group B. When subgroup analysis was performed on only patients who were obese (n = 24), outcomes were in a similar range, with an implantation rate of 56.5%, positive pregnancy rate of 73.9%, and live birth rate of 60.8%. The miscarriage rate in the subgroup of obese patients was low (13.1%), but that was based on only three patients. A post hoc power analysis that was performed for the primary endpoint showed that this retrospective negative study had

TABLE 1

Comparison of baseline characteristics of recipients			
Characteristic	Group A: normal weight (n = 71)	Group B: overweight/obese (n = 71)	P
Age (y)	42.4 \pm 0.4	42.9 \pm 0.5	.41
BMI (kg/m ²)	21.9 \pm 0.2	29.5 \pm 0.5	<.001 ^a
Overweight (BMI 25–29.9 kg/m ²)	N/A	47 (66.2%)	
Class I obesity (BMI 30–34.9 kg/m ²)	N/A	14 (19.7%)	
Class II obesity (BMI 35–39.9 kg/m ²)	N/A	7 (9.9%)	
Class III obesity (BMI >40 kg/m ²)	N/A	3 (4.2%)	
Gravidity	1.7 \pm 0.2	1.7 \pm 0.3	.91
Parity	0.3 \pm 0.06	0.3 \pm 0.06	.77
Number of oocytes allotted	11.8 \pm 0.6	11.4 \pm 0.6	.18
Number of embryos transferred	1.7 \pm 0.06	1.8 \pm 0.05	.20
Peak endometrial stripe (mm)	10.5 \pm 0.3	10.7 \pm 0.3	.53
Estradiol level (pg/mL) on day of progesterone start	706.4 \pm 43.5	551.9 \pm 42.0	.01 ^a

BMI = body mass index; N/A = not applicable.

^a $P < .05$ is statistically significant. *P* values are for comparisons between group A (normal weight) and group B (overweight/obese).

Setton. BMI in Donor Sibling-Oocyte Recipients. Fertil Steril Rep 2020.

a 56.4% power for the observed effect difference in implantation rate in this study population.

Subsequent subanalysis was performed comparing implantation rates between sibling-oocyte recipients who both underwent either day 3 or day 5 embryo transfer. In the 38 paired recipients who underwent day 3 transfer, implantation rates were similar for group A (49.1%) and group B (48.7%). Likewise, implantation rates were similar for groups A and B in paired recipients who both underwent day 5 transfer (55.6% \pm 11.4% vs. 72.2% \pm 8.3%, respectively, $P = .27$), although the number of patients in that subanalysis was low (n = 18). Furthermore, the overall rates of multiple gestation were calculated based on the peak number of fetal heart activities detected. Although group A had a higher proportion of multiple gestations compared to group B, the difference was

TABLE 2

Comparison of cycle outcomes of recipients			
Outcome	Group A: normal weight (n = 71)	Group B: overweight/obese (n = 71)	P ^a
Implantation rate	54.5%	56.3%	.72
Positive pregnancy rate	77.5%	80.3%	.28
Miscarriage rate	29.1%	24.6%	.79
Live birth rate	54.9%	60.6%	.33
Multiple gestation rate	23.9%	14.1%	.13

^a $P < .05$ is statistically significant. *P* values are for comparisons between group A (normal weight) and group B (overweight/obese).

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not statistically significant ($23.9\% \pm 5.1\%$ vs. $14.1\% \pm 4.1\%$, respectively, $P=.13$).

DISCUSSION

In this study, we sought to determine whether a higher BMI would negatively affect endometrial receptivity. By using a study model in which oocytes were obtained from a single donor during a single stimulation cycle and split between two different recipients, we have ensured, to the greatest degree possible, that oocyte quality was controlled for and that any differences seen in outcome would reflect an endometrial abnormality. We found no difference in implantation, positive pregnancy, or live birth rates between patients who were normal weight and those who were overweight or obese. These findings suggest that the adverse effect seen in IVF pregnancy outcomes in fresh cycles in the overweight and obese population is attributable to oocyte quality rather than a defect in endometrial receptivity.

Obesity is a disease of excess body fat that is associated with increased risk of cardiovascular disease, insulin resistance, diabetes, hypertension, metabolic syndrome, sleep apnea, cancer, and all-cause mortality (13). Obesity is known to cause menstrual cycle abnormalities, with more than half of women with obesity having abnormal cycles (14), ovulatory dysfunction, and infertility in reproductive-aged women. It is postulated that in the presence of excess fat with higher levels of adipose aromatase enzymes, there is increased androgen conversion to estrogen, with subsequent reduction in gonadotropin secretion, which leads to ovulatory and menstrual dysfunction (15). These abnormalities have been demonstrated not only in obese patients but also in individuals who are simply overweight by BMI category (16). Furthermore, adipokines such as leptin may directly affect ovarian function (17). Spontaneous pregnancy rates have been shown to be reduced in patients with increasing BMI in both retrospective (18) and prospective studies (19).

Although many presume that the state of obesity and the presence of excess body fat are the etiologies of decreased reproductive potential, it has recently been suggested that this presumption is misleading and that the true culprit is a sedentary lifestyle (20). In an observational cohort study, Palomba et al. (21) found that obese women who were physically active were more likely to achieve pregnancy and live birth in IVF cycles compared to obese women who did not engage in physical activity, regardless of weight loss. Although that study did not account for dietary intake, the LIFeStyle study (22) randomized obese infertile patients to lifestyle intervention with diet and exercise modification with intention for weight loss versus no intervention with immediate fertility treatment, and found no difference in live birth rates between the two groups.

With the pandemic rise in overweight and obesity, an increasing number of patients with this condition are pursuing parenthood and seeking care with reproductive endocrinologists. Obese patients face several obstacles when undergoing ART, including increased gonadotropin requirements (higher daily dose and longer duration of stimulation), decreased ovarian responsiveness (23), and increased miscarriage rates.

Obese infertile patients have also been found in two meta-analyses to have reduced clinical pregnancy and live birth rates compared to normal-weight infertile patients (24, 25). Furthermore, obesity has been demonstrated to alter oocyte morphology, reduce impact fertilization, and impair embryo quality and development (26).

In a meta-analysis of five retrospective studies, Jungheim et al. (6) found that when obese patients received donor oocytes, there were no differences in implantation, clinical pregnancy, miscarriage, and live birth rates compared to normal-weight controls. This would suggest that oocyte quality, rather than endometrial receptivity, is primarily responsible for the deleterious effects of obesity on reproductive outcomes. However, data from obese gestational carriers suggests that endometrial receptivity is adversely affected in these patients as well. In a study by DeUgarte et al. (27), gestational carriers with a BMI <35 kg/m² had nearly double the implantation rates (34% vs. 16%) and live birth rates (49% vs. 28%) compared to gestational carriers who were >35 kg/m². Furthermore, it has been suggested that the endometrial transcriptome is altered in the window of implantation in obese patients. With these discrepant findings, it remains controversial as to whether or not endometrial receptivity plays an important role in poor reproductive outcomes in overweight and obese patients.

Our findings lend further support to the notion that endometrial receptivity does not play a significant role in poor IVF outcomes in overweight and obese patients, and that these effects are likely dependent on oocyte quality. Our study's strength is its unique design, which controls to the greatest degree possible for oocyte quality by comparing outcomes of sibling-oocytes from the same stimulation that were transferred to recipients of varying weights. This study design controls for confounders in a way that is nearly equivalent to twin studies. By excluding significant male factor and uterine factor, we refined the study even further. Although the mean estradiol levels were different between the two groups, this is explained by an expected difference in absorption of transdermal estradiol patches, and it should not impact the results, as the mean level for the overweight group was still in an acceptable range. The number of patients included in the study is reasonable, given the limitations on inclusion for the study design.

Our study is limited by its retrospective nature; thus, we cannot guarantee that specific details of patients' histories that may have been grounds to exclude them from the study were accounted for, even with a thorough chart review. Another limitation is that most of the patients in the study group were overweight rather than obese, and so a meaningful comparison between normal-weight versus overweight versus obese categories could not be performed. In particular, for patients who are morbidly obese, it is feasible that an extreme excess of adipose tissue and the associated alterations in the adipokine milieu may effect endometrial receptivity. Further studies would be warranted to determine whether there are any differences in patients who are obese or morbidly obese compared to normal-weight controls.

In conclusion, increased BMI does not confer a negative impact on uterine receptivity. The adverse IVF outcomes

seen in overweight and obese women appear to be predominantly due to an altered oocyte quality in these patients. Further studies are warranted to determine whether endometrial receptivity is affected specifically in morbidly obese patients.

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