JWH-2021-0433-ver9-Moreta_1P
Type: research-article

JOURNAL OF WOMEN'S HEALTH
Volume 00, Number 00, 2022

DOI: 10.1089/jwh.2021.0433

Original Article

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AU1 ▶ Elevated Body Mass Index in Donor Oocyte Recipients Does Not Affect Implantation of Euploid Embryos

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AU4 ▶ **Abstract**

Background: Obesity is a worldwide epidemic that has been shown to have serious implications on health outcomes. Regarding reproductive health, increased body mass index (BMI) reduces fertility and increases the time to conceive. It is unclear how excess weight in females affects the development of oocytes and embryos or the impact of implantation.

Materials and Methods: This retrospective single-center study aimed to determine if overweight and obese oocyte recipients had similar pregnancy outcomes compared with healthy weight controls after the transfer of a AU5 ▶ single euploid frozen–thawed embryo (FET). Five hundred twenty-eight patients who underwent a transfer from 2016 to 2021 were included. The primary outcome studied was the clinical pregnancy (CP) rate. Secondary outcomes included live birth (LB) rate, biochemical pregnancy loss (BPL) rate, and clinical pregnancy loss (CPL) rate.

Results: The overall CP rate was 54.9% and did not differ significantly among normal weight ($n=318$), overweight ($n=129$), and obese ($n=81$) BMI categories (0.56 vs. 0.56 vs. 0.49, $p=0.56$). There were no significant differences in LB rate (0.47 vs. 0.43 vs. 0.38, $p=0.33$), BPL rate (0.14 vs. 0.09 vs. 0.11, $p=0.59$), and CPL rate (0.15 vs. 0.21 vs. 0.18, $p=0.38$) among BMI groups.

Conclusions: Our findings provide support that BMI alone does not adversely alter endometrial receptivity and AU6 ▶ is not the cause of poor IVF outcomes in patients with increased BMI. These deleterious IVF outcomes might be to the result of diminished oocyte and/or embryo quality or other factors that have not yet been elucidated.

Keywords: BMI, obesity, donor oocyte, endometrial receptivity, euploid embryo, IVF

Introduction

Obesity is a worldwide epidemic that has been shown to have serious implications on health outcomes. From 1999 to 2018, the age-adjusted prevalence of obesity (body mass index [BMI] $\geq 30\,kg/m^2$) in the United States increased from 30.5% to 42.4%, and from 4.7% to 9.2% for severe obesity (BMI $\geq 40\,kg/m^2$). Women had a higher prevalence of severe obesity (11.5%) than men (6.9%).[1] Although obesity is a widely known risk factor for diabetes and cardiovascular disease, it also has been recognized to impact reproductive outcomes.

Increased BMI reduces fertility and increases the time to conceive.[2] In an observational study of negative lifestyle habits and fecundity, a survey of 2112 pregnant women in the United Kingdom demonstrated that women who had a pre-pregnancy weight >80 kg or BMI $> 25\,kg/m^2$ experienced a twofold longer time to conceive than women with BMI

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between 19 and 24 kg/m^2. The effects remained unchanged after adjustment for the woman's age, the menstrual pattern, and other lifestyle variables.

Morbidly obese women were 3.8-fold more likely to be subfecund than those who had a normal BMI.[2] A review by Poston et al. that described trends in the global prevalence of obesity among women showed that assisted reproductive technology (ART) did not provide a simple solution to obesity-related infertility, as a high BMI reduced the chances of pregnancy success with ART.[3]

A retrospective cohort study supported these findings as AU7 ▶ obese women undergoing their first fresh IVF or IVF-intracytoplasmic sperm injection (ICSI) cycle experienced up to a 68% reduction in live birth (LB) rate when compared with women of normal weight, after adjusting for multiple factors, including maternal and paternal age, baseline serum follicle-stimulating hormone (FSH) levels, duration of stimulation, daily gonadotropin dose, peak serum estradiol, number of oocytes retrieved, use of ICSI, embryo quality score, day of embryo transfer, and number of embryos transferred.

However, obese patients require higher doses of medication and more ART cycles than their normal weight patients to achieve optimal dosing regimens. Thus, the lower LB rates seen in obese patients may be partly the result of conservative dosing associated with their first ART cycles.[4]

There is continued debate among reproductive specialists and researchers about which components of reproduction are affected most by obesity. How excess weight in females affects the development of oocytes and embryos or the impact of implantation is not clear.[5] Data regarding obesity and female reproduction are scarce and often sourced from animal models.[6]

The negative effect of obesity on human reproductive potential has been suggested to be the result of functional alteration of the hypothalamic-pituitary-ovarian (HPO) axis; however, obese women appear to remain subfertile even in the absence of ovulatory dysfunction.[7] Some studies have focused on adverse endometrial alterations resulting from obesity. The combination of adverse effects on oocytes, embryos, ovulation function, and endometrial function may impact the reproductive potential of women with elevated BMI.

In an attempt to isolate the etiology of obesity-associated subfecundity, studies have focused on the effects of BMI on pregnancy outcomes among donor oocyte recipients, thereby eliminating possible ovarian effects of obesity. Results of these studies are conflicting with some demonstrating a possible adverse effect of obesity on implantation and others showing no effect.[8]

This study aimed to determine if overweight and obese oocyte recipients had similar pregnancy outcomes compared with healthy weight controls after the transfer of a single euploid frozen–thawed embryo (FET), thereby controlling for embryo ploidy. The findings from this study could provide reproductive specialists with pertinent data to appropriately counsel oocyte recipients with elevated BMI on the chances of a successful outcome with FET of a euploid embryo.

Materials and Methods

Study design

This single-center study consisted of a retrospective cohort of all oocyte recipients who underwent transfer of a single frozen–thawed embryo (FET) from 2016 to 2021. Oocyte donors were included if they met the following eligibility criteria: ages 21 through 34 years, normal BMI (19–24 kg/m^2), no significant toxic exposure, no known genetic, medical, or sexually transmitted diseases, and reassuring measurements of antral follicle count, anti-mullerian hormone, and FSH levels in the early follicular phase. Controlled ovarian hyperstimulation protocols were performed as described hereunder.

At the initial visit, donor oocyte recipients' height and weight were measured. Patients were separated into BMI cohorts: (normal weight: 18.5–24.99 kg/m^2; overweight: 25–29.99 kg/m^2; obese: ≥30.0 kg/m^2). Underweight patients (BMI ≤ 18.49 kg/m^2) were excluded. Chart reviews were performed to collect data. The study (18-00441) was approved by Mount Sinai School of Medicine's Institutional Review Board (IRB) with waiver of consent due to the retrospective nature of the study design.

Controlled ovarian hyperstimulation protocol

When two or more follicles reached 18 mm, final oocyte maturation was induced with either recombinant or purified human chorionic gonadotropin (hCG) alone, leuprolide acetate alone, or a combination of hCG and leuprolide acetate. Transvaginal oocyte retrieval was performed 36 hours after surge. ICSI was performed on Metaphase II oocytes ~5 hours after retrieval.

Embryos were cultured to the blastocyst stage and subsequently underwent assisted hatching. Trophectoderm biopsy was performed on day 5, 6, or 7 when the embryo achieved hatching and reached a morphological grade of at least 4CC (Modified Gardner morphological score). It is thought that slow developing embryos result in lower pregnancy rates; therefore, data collected were limited to those cases with day 5 biopsies for uniformity.

All blastocysts were vitrified and cryopreserved immediately after trophectoderm biopsy. Chromosome analyses were performed exclusively using next-generation sequencing as the preimplantation genetic testing platform for aneuploidy. Only cycles in which one or more embryos were confirmed to be euploid were included in the study.[9,10]

Frozen embryo transfer protocol

Patients underwent a synthetic stimulation cycle to prepare the endometrium for implantation. To evaluate the uterine cavity, a three-dimensional saline sonohysterogram or hysterosalpingogram was performed before cycle start. On day 3 of the subsequent menstrual cycle, patients were started on 2 mg micronized oral estradiol twice daily for 4 days and continued on estradiol 2 mg three times daily thereafter. After ~9 to 11 days of estradiol stimulation, a transvaginal ultrasound was performed to evaluate the endometrial thickness and echogenic pattern.

Intramuscular progesterone or a combination of oral and vaginal progesterone was administered according to patient preference once the thickness of the endometrial lining reached 7 mm or greater. Patients with an endometrial thickness <7 mm at the time of transfer were excluded from the analysis because values below this cutoff have been associated with poor obstetric outcomes.[11] Embryo transfer was performed on the sixth day of progesterone administration.

Table 1. Patient Demographics and Cycle Characteristics by Body Mass Index Category

	Normal weight (n = *318*)	*Overweight* (n = *129*)	*Obese* (n = *81*)	p
Age	44.1 ± 4.5	43.8 ± 3.7	43.8 ± 3.8	0.70
Nulligravid	53 (16.67%)	21 (16.3%)	12 (14.8%)	0.78
Nulliparous	115 (36.16%)	58 (45.0%)	33 (40.7%)	0.35
Endometrial thickness at time of transfer	9.1 ± 2.1	9.4 ± 2.0	9.5 ± 2.3	0.21
Embryo biopsy on day 5	207 (65.0%)	92 (71.3%)	44 (54.3%)	0.04
Embryo expansion grade 4	141 (44.3%)	57 (44.2%)	36 (44.4%)	1.00
Embryo inner cell mass grade A	232 (73.0%)	103 (79.8%)	59 (72.8%)	0.29
Embryo trophectoderm grade A	123 (38.7%)	54 (41.8%)	23 (28.4%)	0.13

Outcome assessment

The primary outcome studied was the clinical pregnancy (CP) rate, defined as the sonographic presence of a gestational sac. Secondary outcomes included LB rate, biochemical pregnancy loss (BPL) rate, and clinical pregnancy loss (CPL) rate. LBs were gestations ≥24 weeks. BPL was defined as positive urinary hCG or serum β-hCG >5 IU/L with no sonographic evidence of a pregnancy. CPL was calculated as the total number of pregnancies confirmed by ultrasound or histologically that failed to progress up to 20 weeks gestation.

Statistical analyses

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). They were calculated across BMI categories (normal weight, overweight, and obese) for demographic and clinical characteristics of the recipients. BMI was analyzed as a categorical variable. Data were analyzed using analysis of variance, Chi squared/Fisher's exact tests, and multivariate logistic regression. $p < 0.05$ was considered to be statistically significant for differences among the groups.

Results

The study included a total of 528 oocyte recipients who underwent transfer of a single frozen–thawed euploid embryo. Patients in all BMI groups had similar age, gravidity, parity, and endometrial thickness at time of transfer (Table 1). A larger percentage of patients in the overweight category (92/129 [71.3%]) had an embryo biopsy performed on day 5 compared with those in the normal weight (207/318 [65%]) and obese groups and (44/81 [54.3%]; $p = 0.04$). No differences were detected in blastocyst morphology.

The overall CP rate was 54.9% and did not differ significantly among normal weight ($n = 318$), overweight ($n = 129$), and obese ($n = 81$) BMI categories (0.56 vs. 0.56 vs. 0.49, $p = 0.56$) (Table 2). There were no significant differences in LB rate (0.47 vs. 0.43 vs. 0.38, $p = 0.33$), BPL rate (0.14 vs. 0.09 vs. 0.11, $p = 0.59$), CPL rate (0.15 vs. 0.21 vs. 0.18, $p = 0.38$) among BMI groups, before and after adjusting for confounders.

Discussion

This study aimed to analyze the relationship between BMI and pregnancy outcomes among oocyte recipients who underwent single FET of euploid embryos. By using this model, and by including only oocyte donors of normal body weight, we eliminated the potential effects of BMI on oocyte quality and thereby focused on endometrial receptivity. In addition, the study negated the adverse effects of aneuploidy and poor embryo morphology on pregnancy outcomes.

The study demonstrated overweight and obese patients had similar CP, LB, EPL, and CPL rates compared with normal weight controls. This study adds to a growing body of literature that maternal obesity does not adversely affect the endometrium's ability to establish or maintain a pregnancy, particularly in patients undergoing ART cycles with adequate synthetic endometrial preparation.

Given the growing prevalence of obesity among reproductive age women, there is an increased focus on the mechanisms by which obesity affects female reproduction. Although the maternal metabolic environment has been shown to adversely affect IVF outcomes in obese women, the underlying mechanism of action is not fully understood. Numerous studies have analyzed the specific components of reproduction that are most affected by elevated BMI. Obesity may contribute to oligo/anovulation, abnormalities of the HPO axis that may adversely affect follicular development, impaired oocyte maturation leading to poor oocyte and embryo quality, and an altered endometrial genetic profile leading to decreased uterine receptivity and increased risk of miscarriage.[12,13]

Several studies have attempted to explore the relationship between increased BMI and implantation. Jungheim

Table 2. Pregnancy Outcomes Based on Body Mass Index Category

	All (n = *528*)	*Normal weight* (n = *318*)	*Overweight* (n = *129*)	*Obese* (n = *81*)	p
Clinical pregnancy rate	290 (54.9%)	178 (55.9%)	72 (55.8%)	40 (49.3%)	0.56
Live birth rate	237 (44.9%)	150 (47.1%)	56 (43.4%)	31 (38.2%)	0.33
Biochemical pregnancy loss rate	64 (12.1%)	43 (13.5%)	12 (9.3%)	9 (11.1%)	0.59
Clinical pregnancy loss rate	49 (16.9%)	27 (15.2%)	15 (20.8%)	7 (17.5%)	0.38

et al. performed a meta-analysis and reviewed five related studies that analyzed IVF outcomes in obese donor oocyte recipients after fresh embryo transfers. Two of these studies demonstrated a mild effect of obesity on embryo implantation, CP, miscarriage, and LB in women receiving donor oocytes, whereas the other studies showed no effect.[14,15] Collectively, obesity was not associated with a difference in implantation or CP rates compared with a BMI in the normal range. Furthermore, obesity was not associated with a difference in miscarriage or LB rates compared with normal BMI.[8]

Bellver et al. demonstrated similar implantation and pregnancy rates among the BMI groups for 2656 ovum donation cycles. Despite nonsignificant differences among the groups, a trend toward poorer implantation, pregnancy, ectopic pregnancy, and miscarriage rates was evident as BMI increased.[14] Noting that women with obesity frequently have AU9 ► comorbidities such as PCOS, diabetes, and hypertension that could affect reproductive success, DeUgarte et al. evaluated the impact of increasing BMI on CP rates in 551 IVF cycles in which embryos derived from oocyte donors were transferred into healthy gestational surrogates.

Higher BMI was associated with a trend in worse outcomes among LB and CP rates, although the differences were not statistically significant. There was, however, a significant decrease in implantation rate for every 1 kg/m^2 increase in AU10 ► BMI above BMI ≥35/kg/m^2 by a factor of 0.98 and no impact of BMI on clinical miscarriage. As the cycles involved gestational surrogates without comorbid conditions and healthy oocytes donors, these findings support the theory that obesity negatively affects fertility through a uterine mechanism, particularly at the level of implantation.[15]

A possible explanation for discrepant findings among studies is that obese and even morbidly obese women may not be well represented in the data due to potential weight restrictions in ART treatment eligibility.[8] In addition, obese women may have the comorbid conditions that may influence pregnancy outcomes independently of high BMI.[14] There are limited national guidelines for the clinical management of obese reproductive age women with reduced fertility. Thus, treatment decisions are made at the provider and/or clinical level.[15]

Our study findings provide additional support that BMI alone does not adversely alter endometrial receptivity and is not the cause of poor IVF outcomes in patients with increased BMI. A strength of this study is its unique model. We analyzed only frozen transfers of euploid embryos, theoretically negating adverse effects on pregnancy success associated with aneuploidy. Our study is limited by its retrospective nature. In addition, the number of overweight and obese patients was not equally represented in the analysis compared with normal weight patients and other patient information, such as comorbidities or male partner demographics, were not considered. A higher number of obese women would provide more comprehensive data for analyses.

Conclusions

Elevated BMI does not appear to have a deleterious effect on endometrial receptivity. Adverse IVF outcomes observed in overweight and obese women might be the result of diminished oocyte and/or embryo quality or other factors that have not yet been elucidated. Future studies are needed to improve our understanding of the precise impact of obesity on human reproductive success.

Authors' Contributions

L.E.M. contributed to the study design and concept. W.H. performed the statistical analysis. L.E.M., J.A.L., A.B.C., and D.S. contributed to the analysis of the results and the writing of the article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

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