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REPRODUCTIVE PHYSIOLOGY AND DISEASE

Increased body mass index negatively impacts blastocyst formation rate in normal responders undergoing in vitro fertilization

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Abstract
Purpose The aim of this study is to investigate the effect of female BMI and metabolic dysfunction on blastocyst formation rate.
Methods This was a retrospective cohort study that was performed in an academic center for reproductive medicine. Patients who were normal weight, overweight with metabolic dysfunction, or obese who had ≥6 oocytes retrieved in a fresh IVF cycle were included in the study. The blastocyst formation rate was calculated from the number of ≥5 cell embryos on day 3 observed in culture until day 5 or day 6. Only good quality blastocysts were included in the calculation as defined by a morphologic grade of 3BB or better.
Results The blastocyst formation rate was significantly better in the normal-weight controls versus overweight/obese patients (57.2 versus 43.6 %, $p<0.007$). There was no difference in blastocyst formation between the patients with a BMI 25–29.9 kg/m^2 with metabolic dysfunction and those with a BMI ≥30 kg/m^2.
Conclusion The maternal metabolic environment has a significant impact on embryo quality as measured by blastocyst formation. A decreased blastocyst formation rate is likely a significant contributor to poorer reproductive outcomes in overweight and obese women with infertility.

Keywords Obesity · Blastocyst · IVF outcome · Metabolic dysfunction · Embryo quality

Capsule Obesity is associated with an increased risk of infertility and a decreased response to assisted reproduction. Studies have shown lower clinical pregnancy rates, higher miscarriage rates, and decreased live birth rates in women with an elevated body mass index (BMI). This study demonstrates that the maternal metabolic environment has a significant impact on embryo quality as measured by blastocyst formation. Our findings suggest poorer blastocyst formation rates in overweight patients may contribute to the lower IVF success rate in this population. Obese women undergoing infertility treatment should be counseled regarding the negative impact that obesity has on IVF outcomes and encouraged to participate in weight loss programs to maximize their success rates.

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Introduction

Obesity has become a worldwide epidemic. In the USA, approximately two thirds (64 %) of women of reproductive age are considered to be overweight (body mass index (BMI)≥ 25 kg/m^2) or obese (BMI≥30 kg/m^2) with 36 % meeting criteria for obesity [1]. In addition to increasing the risk of medical comorbidities such as hypertension, cardiovascular disease, abnormal lipid concentrations, and type 2 diabetes [2], obesity has been shown to negatively impact reproduction. It has been reported that overweight and obese women are three times more likely to have anovulatory infertility than normal-weight women [3]. In those patients who do become pregnant, obesity is associated with complications of pregnancy including miscarriage, gestational diabetes, hypertensive

disorders, fetal macrosomia, stillbirth, and congenital anomalies [4–6].

Not only is obesity a risk factor for infertility, it appears that obesity negatively impacts response to fertility treatments. Several studies have reported that obese women require higher doses of gonadotropins and have a reduced number of mature oocytes retrieved in in vitro fertilization cycles [7–9]. Obesity is also associated with decreased fertilization rates and fewer transferred embryos [10, 11]. However, the evidence is conflicting regarding the effect that obesity has on live birth rates in assisted reproductive outcomes. Studies have shown lower clinical pregnancy rates, higher miscarriage rates, and decreased live birth rates in women with an elevated body mass index [9, 12–14]. Other studies, however, have shown no difference in live birth rates when comparing IVF outcomes between normal-weight and obese patients [7, 8, 15].

The largest study in the literature on oocyte and embryo parameters reported fewer than two pronuclei embryos, lower clinical pregnancy, and live birth rates in their obese patients [16] compared with normal-weight controls. In this study, there was no association between obesity and the quality of day 3 embryos. However, blastocyst formation rate was not examined.

The purpose of this study was to investigate the effect of female BMI and metabolic dysfunction on blastocyst formation rate in patients who had at least six oocytes retrieved.

Materials and methods

Study design

This was a retrospective cohort study of fresh IVF cycles initiated between January 1, 2012 and December 31, 2012 at the Stanford University IVF clinic and was approved by the Stanford Institutional Review Board. Height and weight were measured on each patient on the day of oocyte retrieval. Patients were then grouped according to the World Health Organization (WHO) obesity classification system [17]. Normal-weight patients were defined as those having a BMI of 19–24.9 kg/m^2, overweight have a BMI of 25–29.9 kg/m^2, and obese have a BMI of ≥30 kg/m^2. Patients with ≥6 oocytes retrieved were included in the study. Data on blastocyst formation was obtained from review of embryo reports.

Patients

A total of 120 patients were included in this study. Cases were patients who were overweight with evidence of metabolic dysfunction, or obese with/without metabolic dysfunction. We required overweight individuals to have at least one metabolic dysfunction to identify individuals at sufficient risk from their adiposity. Overweight individuals have the greatest metabolic heterogeneity with up to 25 % being insulin sensitive compared with 75 % of normal-weight individuals and 5 % of obese individuals [18]. Metabolic dysfunction was defined as having one or more of the following: fasting glucose ≥100 mg/dL, 2-h glucose ≥140 mg/dL following a 75-g oral glucose challenge, hemoglobin A1c ≥5.7 %, fasting insulin ≥15 μIU/mL, 2 h insulin level ≥100 μIU/mL, LDL >130 mg/dL, HDL <50 mg/dL, or triglycerides ≥150 mg/dL. The proportion of metabolic dysfunction in the overweight patients was as follows: 5/11 (45 %) had insulin resistance only, 1/11 (9 %) had dyslipidemia only, 1/11 (9 %) had type 2 diabetes mellitus (DM) only, 1/11 (9 %) had type 2 DM and dyslipidemia, and 3/11 (27 %) had insulin resistance and dyslipidemia.

We chose two normal-weight controls per case whose retrievals were performed during the same week. Metabolic screening for normal-weight and obese patients, however, was not required since there is no uniform practice for screening these patients at our clinic.

Only patients with a reasonable chance to reach blastocyst stage were included as defined by ≥6 oocytes retrieved. Patients with any etiology of infertility were included in this study, including a diagnosis of polycystic ovarian syndrome. The Rotterdam criteria were used to diagnose polycystic ovarian syndrome (PCOS) and required patients to exhibit two of the following three signs/symptoms: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and sonographic evidence of polycystic ovaries [19]. Oocyte donors, poor responders, and those undergoing fertility preservation with cryopreservation of day 2 embryos were excluded from the study population. Patients undergoing preimplantation genetic diagnosis for single gene disorders or gender selection were also excluded.

IVF protocol

The patient's individual physician determined the IVF protocol used for controlled ovarian hyperstimulation during each cycle. The gonadotropin dose was chosen based on the patient's age, antral follicle count, and patient's previous response to gonadotropins. When two or more lead follicles measured at least 18 mm, human chorionic gonadotropin (HCG) 10,000 IU was administered for final maturation of the oocytes with the oocyte retrieval approximately 35 h later. Patients undergoing a fresh embryo transfer received vaginal progesterone supplementation for luteal support.

Embryo grading

The embryos generated from each cycle were graded according to their morphologic characteristics. The day of transfer was determined based on the quality of day 3 embryos according to the embryologist's standard protocol. If a patient had

fewer than four 8-cell embryos on day 3, typically the embryo transfer was performed on that day, and any remaining embryo not transferred was left in culture. If there were more than four 8-cell embryos, all embryos were cultured to day 5.

Outcomes

The main outcome of the study was usable blastocyst formation rate. This was calculated from the number of ≥5 cell embryos on day 3 observed in culture until day 5 or day 6. Only usable blastocysts, defined as 3BB or better on day 5 or day 6, were included in the calculation as defined by those that would be either transferred or cryopreserved. Other cycle parameters, such as duration of stimulation, total dose of gonadotropins, and number of oocytes retrieved, were also compared.

The secondary outcomes of oocyte and embryo quality between the two groups measured were fertilization rate, number of ≥5 cell embryos, day 3 versus day 5 embryo transfer, clinical pregnancy, miscarriage, and live birth rates. A clinical pregnancy is defined as the detection of a gestational sac on ultrasound. A clinical miscarriage is one in which there is a documented loss of fetal cardiac activity in an intrauterine pregnancy, loss of a gestational sac, or lack of development of an embryo after at least seven days. A live birth is defined as a viable infant born after 24 weeks of gestation.

Statistical analysis

Outcome measures between groups were compared using Student's *t* test and chi-square tests where appropriate. $p<0.05$ was considered statistically significant.

Results

A total of 120 patients undergoing a fresh IVF cycle were included in this analysis. Eighty normal-weight patients served as the control population. Cases included 11 patients (9.2 %) who were overweight (BMI 25–29.9 kg/m^2) with metabolic dysfunction and 29 patients (24.2 %) who were classified as obese (BMI ≥30 kg/m^2) with/without metabolic dysfunction.

Table 1 summarizes the main outcomes of our study. The mean age of the patients initiating cycles during this time period was similar between the two groups. The percentage of patients with a PCOS diagnosis was significantly higher in the overweight/obese group than in the controls, 35 % (14/40) versus 8.8 % (7/80), respectively. The duration of the ovarian stimulation and the total dose of gonadotropins were similar between the overweight/obese women and normal-weight controls.

Compared with normal-weight women, those in the overweight/obese group had a similar number of oocytes retrieved, fertilization rate, and number of day 3 ≥5 cell embryos. Similarly, there was no difference in the percentage of patients undergoing preimplantation genetic screening (PGS) for aneuploidy between the two groups.

During these IVF cycles, 7/80 controls and 1/40 overweight/obese patients did not undergo a fresh transfer due to either having an early progesterone rise or having no euploid embryos to transfer after PGS. When looking at those who did have a fresh transfer, there was no difference in the number of patients having a day 3 versus day 5 embryo transfer. Additionally, 15/80 normal-weight patients and 16/40 overweight/obese patients had no day 3 ≥5 cell embryos remaining in culture after embryo transfer. Therefore, the 395 embryos assessed for blastocyst formation in the controls were from 65 patients, and the 149 embryos in the overweight/obese group were from 24 patients.

Despite having similar embryo development up until day 3, the blastocyst formation rate was significantly better in the normal-weight group (57.2 versus 43.6 %, $p<0.007$). There was no difference in blastocyst formation between the patients with a BMI 25–29.9 kg/m^2 with metabolic dysfunction and those with a BMI ≥30 kg/m^2 (45.4 versus 42.1 %, $p=0.69$) (data not shown). However, a post hoc power analysis was performed and revealed a 3.9 % power to detect a difference in blastocyst formation rates between these two groups. Additionally, a sample size calculation was performed and indicated that 3546 embryos (or 591 patients) would have to be included in each of the overweight and obese groups to yield a statistical power of 80 and 5 % alpha error.

When examining whether a PCOS diagnosis would influence blastocyst production, there was no statistically significant difference between blastocyst formation rates in normal-weight PCOS patients versus overweight/obese PCOS patients (53.7 versus 45.6 %, $p=0.37$) (data not shown). Furthermore, the blastocyst formation rate was compared between all PCOS patients, regardless of weight, and those with infertility of other etiologies. Interestingly, PCOS patients collectively had a higher blast formation rate of 63.6 % (89/140) versus 50 % (202/404) in those with another infertility diagnosis ($p=0.006$) despite being similar in age (36.7 versus 37.3 years, $p=0.51$) (data not shown). This suggests that the decrease in blastocyst formation in overweight/obese patients is not secondary to the effect of PCOS on oocyte/embryo quality.

Regarding IVF outcomes, after excluding patients undergoing PGS and those who had a freeze-all cycle (Table 2), overweight and obese women had a lower clinical pregnancy (39.5 versus 48.5 %) and live birth rate (23.7 versus 39.7 %), respectively, as compared with normal-weight controls. These differences, however, were not statistically significant. Additionally, there was a nonsignificant trend toward an increased miscarriage rate in overweight patients (18.2 versus 40 %).

Table 1 Demographics and characteristics

	BMI 19–24.9 kg/m^2	BMI ≥25 kg/m^2	*p* value
Number	80	40[a]	
Age (years)	36.9±3.5	37.7±3.9	0.27
BMI (kg/m^2)	21.6±1.7	32.1±4.8	0.0001
PCOS diagnosis (%)	7/80 (8.8 %)	14/40 (35 %)	0.0004
Duration of stimulation (days)	10.1±1.2	10.6±1.3	0.07
Total dose of gonadotropins	3858±1265	4000±1345	0.57
Retrieved mature oocytes	13.7±6.2	14.1±6.7	0.72
Fertilization rate (%)	629/1095 (57.4 %)	326/565 (57.7 %)	0.70
Total # day 3 embryos ≥5 cells	395	149	
# of day 3 embryos ≥5 cells/patient	6.4±4	5.7±4	0.33
Day 3 transfer (%)	45/73 (61.6 %)	26/39 (66.7 %)	0.60
Day 5 transfer (%)	28/73 (38.4 %)	13/39 (33.3 %)	0.60
Blast formation rate (%)	226/395 (57.2 %)	65/149 (43.6 %)	0.007
Preimplantation genetic screening (%)	9/80 (11.3 %)	2/40 (5 %)	0.08

[a] This includes 11 overweight (BMI 25–29.9 kg/m^2) patients with evidence of metabolic dysfunction and 29 obese (BMI ≥30 kg/m^2) patients with/without metabolic dysfunction

Discussion

Our data demonstrates that in vitro blastocyst formation is affected by a patient's BMI status. The quality of embryos is frequently utilized to predict implantation rates and subsequent clinical pregnancy rates. Similar to prior studies [15, 16, 20, 21], we did not observe a significant difference in embryo morphology at the cleavage stage. However, we did observe a statistically significant decline in blastocyst formation rate in patients who were overweight/obese versus normal-weight controls (43.6 versus 57.2 %, respectively). This decline was independent of PCOS diagnosis. We hypothesize that this decreased blastocyst formation rate is a significant contributor to poorer reproductive outcomes in overweight and obese women with infertility.

Animal studies have indicated that obesity significantly impacts oocyte quality [22–25]. Researchers have used a murine model of mice fed a high-fat diet (HFD) to mimic the effects of obesity and metabolic dysfunction in humans. In a recent study, oocytes of obese mice at the meiosis II stage displayed significant spindle defects and chromosome misalignment leading to early embryonic loss [25]. Others have found that obese mice exhibit significantly more apoptotic ovarian follicles, smaller oocyte size, and fewer mature oocytes when compared to control mice [24]. Furthermore, studies have reported mitochondrial dysfunction [25] as well as lipotoxicity, increased oxidative stress, and increased apoptosis in the cumulus-oocyte complexes of mice fed an HFD [26].

Table 2 IVF outcomes

	BMI 19–24.9 kg/m^2	BMI ≥25 kg/m^2	*p* value
Clinical pregnancy rate	33/68 (48.5 %)	15/38 (39.5 %)	0.27
Live birth rate	27/68 (39.7 %)	9/38 (23.7 %)	0.09
Miscarriage rate	6/33 (18.2 %)	6/15 (40 %)	0.11

Excluding those who had PGD/PGS and freeze-all cycles

It is well known that morphologic characteristics of a day 3 embryo are inadequate to predict blastocyst formation or implantation. Our study suggests that maternal weight-related oocyte dysfunction only becomes apparent after day 3 with a decline in the progression of these embryos to the blastocyst stage. It is clear, in animal studies, that obesity adversely affects oocyte maturation and metabolism leading to impaired embryonic development. However, human data on the exact mechanisms are still lacking. Time-lapse imaging may shed some additional light on the kinetic differences that exist between embryos of normal-weight and overweight/obese women leading to decreased blastocyst formation and implantation rates [27]. A recent study utilizing this technique reported that embryos from overweight/obese women were less likely to reach the blastocyst stage. Furthermore, those that did develop into blastocysts showed accelerated preimplantation development with fewer trophectoderm cells [28].

Although the results presented in our study do not show a statistically significant difference in clinical pregnancy rate, miscarriage rate, or live birth rate, there is a downward trend for these parameters in the overweight/obese population. This trend is consistent with other studies examining the effect of BMI on pregnancy, live birth, and miscarriage rates which have found similar associations [9, 11, 20, 29, 30]. Rittenberg et al. [30] reported a significantly lower live birth rate in patients with a BMI ≥25 kg/m^2 when compared to patients with a normal BMI (64 versus 81 %, p=0.005). Additionally, the

overweight patients were nearly twice more likely to have a miscarriage than normal-weight controls (35 versus 19 %, p= 0.001). We observed a similar two-fold increase in miscarriage rate in the overweight/obese group although it did not reach statistical significance. These clinical outcomes may be due to either embryo or endometrial factors, and further studies are needed to elucidate these factors leading to adverse IVF outcomes in the overweight population.

Due to the size and retrospective nature of this study, some limitations should be considered. With a prospective study design, we would have been better able to control for potential confounders such as anti-Mullerian hormone (AMH) levels, ethnicity, smoking status, weight of the male partner, and metabolic factors that may be associated with poorer IVF outcomes. If a larger number of overweight individuals were screened for metabolic dysfunction, this would provide a more accurate representation of whether BMI alone or the presence of metabolic dysfunction has a greater effect on blastocyst production. Also, a greater number of subjects may have better powered the study to examine the clinical outcomes of the IVF cycles. Approximately two thirds of patients included in the study had their best quality embryos transferred on day 3. With a universal blastocyst transfer policy, we would have been able to determine a more accurate blastocyst formation rate on a higher number of good quality day 3 embryos. However, this limitation affected both the overweight/obese and control patients equally.

This is the first study, to our knowledge, to examine blastocyst formation rate as the primary endpoint in an infertile overweight/obese population. All the embryos were cultured under the same conditions in the same laboratory during the same time period. The embryologists graded the embryos using standard morphologic criteria while blinded to a patient's BMI. The embryos were examined on day 3 and day 5 to give more information regarding implantation potential. It is evident that the ability of an embryo to reach the blastocyst stage is adversely affected in the overweight/obese population, suggesting that morphologic characteristics observed on day 3 do not represent the poor quality nature of embryos in patients with metabolic dysfunction.

In conclusion, obesity was shown to be associated with poor embryo progress as evidenced by lower blastocyst formation. Thus, embryonic arrest or dysfunction likely contributes to the increased risk of infertility, adverse pregnancy outcomes, and poor IVF outcomes seen in overweight and obese women [12, 31, 32]. Recently, our group showed that 10 % weight loss improves live birth rates in overweight/obese women [33]; however, it remains to be tested whether weight loss can improve blastocyst formation. Since we observed a similar decline in blastocyst formation in the overweight group with metabolic dysfunction as in those patients meeting obesity criteria, this may support the benefit of weight loss even in patients with borderline BMIs who can potentially reverse their weight-associated metabolic dysfunction. Further studies are needed to evaluate optimal interventions for the treatment of infertility in the setting of obesity.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required."

Conflict of interest The authors declare that they have no competing interests.

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