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The Effects of Oocyte Donor and Recipient BMI on Live Birth Rates and Pregnancy Outcomes following Assisted Reproduction

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By

Jiaxin Xu

B.S., Sun Yat-Sen University, 2018

Advisor: Audrey Jane Gaskins, Assistant Professor

An abstract of

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By Jiaxin Xu

Background. Excess body weight is a risk factor for impaired fertility in women conceiving both with and without medical assistance. However, whether excess body weight negatively influences female fertility on the level of the oocyte and/or uterine environment remains unclear. Vitrified donor oocyte ART offers an ideal model to study these effects.
Objective. To investigate the effects of oocyte donor and recipient BMI on outcomes of vitrified donor oocyte ART.
Design. Retrospective cohort study.
Setting. Reproductive Biology Associates, a private fertility center in Sandy Springs, Georgia, USA.
Patients. 338 oocyte donors and 932 recipients who underwent a total of 1651 embryo transfer cycles between 2008 and 2015.
Intervention(s). None.
Main outcome measure(s). Live birth, defined as the delivery of at least one live born infant per embryo transfer cycle. Secondary outcomes included positive pregnancy test, miscarriage, birth weight, and gestational length.
Results. There were no significant associations between donor BMI and probability of positive pregnancy test, miscarriage, and live birth. Recipients with a BMI ≥35 kg/m^2 had a significantly higher probability of pregnancy (RR 1.13, 95% CI 1.02, 1.25) and live birth (RR 1.26, 95% CI 1.07, 1.49) compared to normal weight recipients (p-trend=0.001 and 0.003, respectively). Among singleton live births, recipients with a BMI<18.5 kg/m^2 had a lower risk of delivery in a given week (HR 0.64 95% CI 0.43, 0.95) while women with a BMI ≥35 kg/m^2 had a higher risk of delivery in a given week (HR 1.45 95% CI 0.96, 2.20) compared to normal weight women. Obese recipients also had a higher risk of having a low birth weight baby (RR 1.76 95% CI 1.02, 3.02) compared to normal weight women. Donor BMI was not associated with birthweight or gestational length.
Conclusions. In the setting of vitrified donor oocyte ART, recipient BMI was positively associated with probability of live birth but negatively associated with gestational length and birthweight among singleton births. Our results suggest that impaired oocyte quality rather than endometrial receptivity may be the overriding factor influencing ART outcomes in obese women using autologous oocytes.

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Contents

Introduction

Infertility, the failure to conceive after one year of regular, unprotected sexual intercourse, affects 15-25% of couples in western countries [1, 2]. Assisted reproductive technologies (ART) have become one of the main treatment modalities for couples facing fertility problems. Since 2009, nearly 150,000 ART cycles have been performed yearly and are responsible for ~2% of live births nationwide [3, 4]. Excess body weight is one of the most consistent factors that has been related to impaired fertility in women conceiving both with and without medical assistance [5-7]. However, there is still controversy over whether excess body weight negatively influences female fertility on the level of the oocyte, embryo, and/or uterine environment.

Studies among women undergoing ART with oocyte donation represent a unique population where these questions can be further teased out. There have been a handful of previous studies focusing on obese donor oocyte recipients, but they have come to disparate conclusions regarding the effects of donor oocyte recipient obesity on ART outcomes. In a systematic review and meta-analysis conducted by Jungheim et, al., the authors reported that across 6 studies including a total of 4,758 women, no significant associations were observed between obesity and likelihood of implantation, pregnancy, miscarriage, or live birth among women using donor oocytes [8]. This suggests that female obesity may impact oocyte quality to a greater extent than the endometrium or uterine environment and may be the driving

factor underlying the observed associations between female obesity and reduced fertility [9]. An important limitation of this meta-analysis, however, was the limited number of small heterogeneous studies. To date, only two studies- one from Spain (n=1092 cycles) and one from the US (n=235 cycles), have investigated the influence of donor BMI on ART outcomes following oocyte donation with conflicting findings [10, 11]. The Spanish cohort found no associations between BMI in the donor or recipient and ART outcomes; however, the American cohort reported a reduced odds of clinical pregnancy and live birth with increasing donor BMI even after accounting for recipient BMI.

To expand on this existing literature, we used information from a large cohort of vitrified donor oocytes to investigate the influence of both oocyte donor and recipient BMI on outcomes of ART. Because vitrified oocytes are obtained from anonymous, young, healthy female donors, there is little to no correlation in BMI between the donor and the female recipient, which allows for the independent investigation of how excess body weight affects oocyte quality and endometrial function/receptivity independently. Moreover, due to the standardized ovarian stimulation and endometrial preparation protocols utilized in vitrified donor oocyte ART cycles, this limits confounding by clinical procedures, which can vary widely for donor oocyte ART cycles using fresh oocytes.

Materials and Methods

Study Design. Our study is a retrospective cohort of vitrified donor oocyte ART cycles conducted at Reproductive Biology Associates in Sandy Springs, Georgia, USA between 2008 and 2015. We included cycles in which all oocytes from an oocyte donor were cryopreserved via vitrification for use in an oocyte bank and later warmed in separate cohorts for recipients' use. Cycles in which gestational carriers were used or no embryos were transferred were excluded. After further excluding any donors and recipients who were missing data on body mass index (the primary exposure of interest), we had 338 oocyte donors and 932 unique recipients who underwent a collective total of 1651 embryo transfer cycles. This study was approved by the Emory Institutional Review Board prior to study initiation (IRB #80463).

Body weight assessment and covariate information. At the donor's and recipient's first visit to Reproductive Biology Associates, height and weight are measured with a standardized scale and stadiometer. We calculated body mass index (BMI) using the following formula: weight (in kg) divided by height (in m) squared. As expected, the range of BMIs among donors was much smaller than recipients given the strict inclusion criteria for becoming a donor. Therefore, donor BMI was divided into a three level categorical variable ($\leq$21, 21.1−24.9, $\geq$25) based on established cutoffs and the distribution in our cohort while recipient BMI was divided into five levels (<18.5, 18.5−24.9, 25−29.9, 30−34.9, $\geq$35) following WHO guidelines. At the initial visit, patients completed a questionnaire concerning

their demographics (e.g. age, race/ethnicity, smoking status) and reproductive history (e.g. gravidity, parity). Information on infertility diagnoses, among the recipients, are abstracted from the medical record according to SART guidelines. For each retrieval the donor undergoes, we collected ovarian reserve data (e.g. bilateral antral follicle count and anti-Müllerian hormone) and ovarian stimulation data (e.g. gonadotropin dose, number of days of stimulation, number of large follicles (>14mm) at trigger shot, peak estradiol levels, and trigger type). Among recipients, we collected information on the number of warmed donor oocytes and the number of embryos transferred and embryo stage at transfer for each ART cycle.

Recipient preparation and outcome assessment. In advance of oocyte warming, recipients were given a standard endometrial preparation of leuprolide acetate, estrogen, and progesterone. After sufficient endometrial development, the donor oocytes are warmed and two to three hours later the oocytes are fertilized via intracytoplasmic sperm injection (ICSI). The resulting embryos are then cultured in the lab until cleavage (day 3) or blastocyst stage (day 5/6). None of the embryos underwent pre-implantation genetic testing. Embryo transfer was performed in standard fashion. The highest quality embryo(s) were transferred first and the remaining embryos were cryopreserved for future use. Many recipients had one or more frozen embryo transfers from the initial cohort of warmed oocytes.

Live birth, defined as the delivery of at least one live born infant in a given embryo transfer cycle, was our primary outcome. Secondary outcomes included positive pregnancy test (defined as serum β- human chorionic gonadotropin (hCG) level >6 mIU/mL), pregnancy loss (defined as all positive pregnancy tests not resulting in live birth), and the proportion of warmed oocytes that: survived thaw, became fertilized, developed into useable embryos, and were cryopreserved. We also abstracted information on gestational age and birthweight among the ART cycles resulting in live birth. Gestational age less than 37 weeks was defined as preterm delivery and birth weight less than 2,500 grams was defined as low birth weight.

Statistical Analysis. Descriptive statistics were calculated across BMI categories for demographic, reproductive, and clinical characteristics of the donor and recipient. We tested for differences across BMI categories using Chi-Square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Log binomial regression with cluster weighted generalized estimating equations (GEE) was used to analyze the association between donor/recipient BMI and probability of live birth. Our weight was equal to the inverse of the cluster size (number of embryo transfer cycles) and was chosen to account for the fact that women with more severe infertility likely had a greater number of cycles. When cluster size is informative, using an unweighted approach in marginal analyses will over-weigh couples with the most severe infertility, leading to biased estimates. Donor BMI and recipient BMI were analyzed both as continuous and categorical variables. Risk ratios (RRs) were

calculated comparing the risk of live birth in a specific BMI category compared with the risk in the reference category (e.g. 21.1−24.9 kg/m^2 in donors and 18.5-24.9 kg/m^2 in recipients). Tests for linear trends were conducted using the median values of each category of BMI as continuous variables. We also examined the joint effect of donor and recipient BMI on the probability of live birth by cross-classifying donor/recipient pairs into BMI categories. Sensitivity analyses were conducted by restricting to only single embryo transfer, only blastocyst transfers, and only first embryo transfers.

To explore the associations between donor/recipient BMI and risk of positive pregnancy test (PPT) and risk of pregnancy loss we used cluster weighted GEE models; however, for the outcome of pregnancy loss, we restricted the analysis to only cycles in which a pregnancy was achieved. The association between donor BMI and secondary outcomes following oocyte warming (e.g. % survived, % fertilized, % usable embryos) were analyzed using GEE with binomial distribution. Data are presented as back transformed marginal percentages (95% CIs) at the mean level of continuous covariates and most common level of categorical covariates. Among singleton live births (N=670), we analyzed the association between BMI and length of gestation using a cluster weighted Cox proportional hazard model with a robust sandwich covariance estimate. A cluster weighted GEE with normal distribution and identity link function was used for birthweight analysis. For pre-term birth and low birthweight, a cluster weighted GEE with binomial distribution and logit link function was specified to

calculate the odds ratio (ORs) and 95% CIs. All of these models account for the multiple live births a woman could contribute to the analysis and the presence of non-ignorable cluster size by weighting each recipient inversely according to the number of live births they achieved.

Confounding factors were selected based on previous studies, a priori knowledge, and descriptive statistics from our cohort through the use of directed acyclic graphs (DAG). The final model retained the following variables: age, donor/recipient race (White, Black, Other), retrieval year (2008-2009, 2010-2011, 2012-2013, 2014-2015), uterine factor infertility, and PCOS. Since race was highly correlated between donors and recipients both variables could not be included in the final multivariable model. Therefore, donor race was considered as a confounder when the exposure was donor BMI and recipient race was considered as a confounder when the exposure was recipient BMI. All tests of statistical significance were two-sided and a significance-level of 0.05 was used. All data were analyzed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Our study population was comprised of 338 oocyte donors and 932 recipients. The mean (standard deviation) BMI of donors and recipients was 22.3 kg/m^2 (2.3 kg/m^2) and 24.5 kg/m^2 (4.7 kg/m^2), respectively. The prevalence of overweight (BMI>25 kg/m^2) was 17.8% in donors and 36.5% in recipients (**Tables 1 & 2**). The average age of donors at their first

retrieval was 25.5 years and the majority of donors were White (75%) with no prior birth history (78%). There were no statistically significant differences in demographic, reproductive history, or ovarian stimulation parameters across the donor BMI categories. The majority of recipients were over 40 years (68.5%), White (74%), with no prior births (73%). Recipients with higher BMIs tended, on average, to be older, of Black race, and were more likely to be diagnosed with tubal factor infertility, PCOS, or another ovulatory disorder. Recipients underwent a total of 1 (n=567, 60.8%), 2 (n=356, 38.2%), or 3 (n=9, 1.0%) embryo transfer cycles during follow-up. Among the 1651 embryo transfer cycles, 813 (49.2%) cycles resulted in a live birth. There was only a slight, positive correlation between donor and recipient BMI (r=0.16).

The percentage of oocytes that survived warming, successfully fertilized, developed into usable embryos, and were cryopreserved was not significantly different across donor BMI categories (**Table 3**). These was also no significant effect of donor BMI on the probability of positive pregnancy test (PPT), miscarriage, or live birth regardless of whether donor BMI was considered as a categorical or continuous variable (**Table 4**). In contrast, there was a statistically significant, positive association between recipient BMI and probability of PPT (RR 1.01 per 2 kg/m^2 increase in BMI, 95% CI 1.00, 1.02) and live birth (RR 1.02 per 2 kg/m^2 increase in BMI, 95% CI 1.00, 1.03). For both outcomes, recipients with a BMI $\geq$35 kg/m^2 had a significantly higher risk of PPT (RR 1.13, 95% CI 1.02, 1.25) and live birth (RR

1.26, 95% CI 1.07, 1.49) compared to normal weight recipients. Underweight recipients had a higher risk of PPT (RR 1.16, 95% CI 1.02, 1.31) compared to normal weight recipients; however, associations with live birth were attenuated. Results were similar when analyses were restricted to single embryo transfers, blastocyst transfers, first embryo transfers, recipients without tubal factor infertility, and recipients without PCOS or other ovulatory disorders (**Supplemental Table 1**). There was no indication of an interaction between donor and recipient BMI on probability of live birth (**Supplemental Table 2**).

In total, there were 670 singleton infants born among all embryo transfer cycles. After multivariable adjustment, there were no significant associations between continuous or categorical BMI among donors and length of gestation or birth weight (**Table 5**). Among recipients, there was an inverse association between BMI and gestational length (p-trend 0.003). Women with a BMI <18.5 kg/m^2 had a lower hazard of delivery in a given week (HR 0.64 95% CI 0.43, 0.95) while women with a BMI ≥35 kg/m^2 had a higher hazard of delivery in a given week compared to normal weight women (HR 1.45 95% CI 0.96, 2.20). Associations between recipient BMI and risk of preterm delivery were in a similar direction, although non-significant. There was a marginal, positive association between recipient BMI and risk of having a low birth weight baby (p-trend=0.05) such that women with a BMI ≥35 kg/m^2 had 1.76 times (95% CI 1.02, 3.02) the risk of delivering a low birthweight baby compared to normal weight women.

Discussion

In this large cohort of women donating and utilizing vitrified oocytes from a national oocyte bank, we found no association between donor BMI and ART outcomes but counter to our initial hypothesis, recipient BMI was positively associated with likelihood of positive pregnancy test and live birth. The positive association between recipient BMI and risk of live birth persisted after further adjustment and stratification for various demographic and reproductive characteristics namely, number of embryos transferred, stage of embryos transferred, as well as diagnosis of uterine factor infertility and PCOS. Despite enhanced fertility, recipients with higher BMI had significantly shorter gestational lengths and higher odds of having a low birthweight baby.

To date, numerous individual studies, reviews, and meta-analyses have documented an adverse effect of female overweight and obesity on outcomes of autologous ART[12-16]. In the most recent meta-analysis, which included 49 studies, the authors demonstrated that overweight (OR 0.92, 95% CI 0.86–0.97) and obese (OR 0.81, 95% CI 0.79–0.82) women undergoing ART had reduced live birth rates compared with females of normal BMI (<25 kg/m^2). Yet whether this association is due to an adverse effect of body weight on oocyte quality or the endometrium is still debated. In a meta-analysis of 6 studies evaluating ART outcomes among obese donor oocyte recipients, Jungheim and coauthors found no association between recipient obesity and clinical pregnancy (RR: 0.98, CI:0.83–1.15) or live

birth rate (RR: 0.91, 95% CI: 0.65–1.27) [8]; however, the authors noted that there was a high degree of heterogeneity across studies. Of the individual studies included in the meta-analysis, 2 found a mild negative effect [17, 18], 2 found no effect [19, 20], and 1 found a positive effect of recipient obesity on ART outcomes following oocyte donation [8]. An additional large study, not included in the meta-analysis, based on 2007–2008 data from the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System (n=9,366 fresh and 3,975 frozen donor egg cycles) also found inconsistent evidence for an association between recipient BMI and failure to achieve a clinical intrauterine gestation [21].

Based on this literature, our finding of a significant positive association between recipient BMI and live birth rate was unexpected and remains difficult to explain. While Jungheim and colleagues also found a positive association between recipient obesity and likelihood of livebirth following oocyte donation (OR 1.43 95% CI 1.04, 1.97) based on primary data from their fertility clinic in Missouri, these results were never published independent of the meta-analysis [8]. Some researchers have hypothesized that the accessibility of fat stores among obese women could support fetal development, which may explain the positive relationship, though direct evidence is lacking [22]. Two recent studies have documented increased endometrial thickness among obese women undergoing frozen embryo transfer compared to normal weight women which suggests that obese women may respond better to endometrial preparation protocols due to their hyperoestrogenic state [23, 24].

Yet whether small gains in endometrial thickness translates into clinical differences is less clear. The unexpected association between recipient obesity and higher probability of live birth could also be attributable to a type of selection bias due to clinic restrictions imposed on donor oocyte recipients. For instance, obese women with comorbidities may be more likely to be denied treatment and less likely to be represented in our data, which could lead to inflated success rates among the selected group of included obese recipients. That theory, however, does not coincide with the worse pregnancy and birth outcomes (e.g. shorter gestational ages and lower birthweights) we observed in our obese recipients.

As far as donor BMI is concerned, only two studies to date have considered the effect of donor BMI on live birth following oocyte donation ART and results have been conflicting [10, 11]. Similar to our results, a retrospective cohort study in Spain (n=1092 embryo transfer cycles) found that increasing oocyte donor BMI was not associated with likelihood of positive pregnancy [11]. In contrast, a retrospective cohort study from Massachusetts (n=235 fresh donor oocyte IVF cycles) found that oocyte donors with higher BMIs had reduced clinical pregnancy and live birth rates and this association persisted even after excluding known donors and those with a BMI $\geq$ 25 kg/m^2. The disparate findings may be due to differences in the criteria used to screen donors but at present this is hard to directly compare across studies.

Our study had several strengths. First, by utilizing data from a large vitrified donor oocyte bank we were able to ensure that all of our donors were anonymous and all the oocytes underwent a standard process of vitrification and later warming. This resulted in there being little to no correlation between donor and recipient BMI and controlled for many clinical factors by design. By focusing on a fertility center in Atlanta, GA, we also had a much higher proportion of racial/ethnic minorities than the typical fertility clinic which enhances our generalizability. Because we had comprehensive information on the BMI of donors and recipients, we were able to consider the joint effect of both donor and recipient BMI on ART outcomes, unlike many previous studies. We were also able to mutually adjust our statistical models for both donor and recipient BMI, which helped us delineate the independent impact of donor and recipient BMI on ART outcomes.

There were, however, serval limitations. Since we used data from an oocyte bank which has strict eligibility criteria for their donors, we had a limited range of donor BMIs. Moreover, the overweight donors we included in our analysis are most likely a highly selected sample of reproductive aged women with a BMI≥25 kg/m^2 given the extensive donor exclusion criteria. Therefore, it is possible that the effects of high donor BMI on ART outcomes are underestimated. While our sample size was large relative to many previous analyses, we only included 383 donors which limited our power to discern small, potentially meaningful, effects. As it was a retrospective cohort study, we also lacked information on

potential confounders of interest including socioeconomic status (SES). Among our oocyte recipients, SES is controlled for by design, as the ability to afford this type of infertility procedure (which is not often covered by insurance and costs a minimum of $19,000 per cycle) is limited. Among donors, however, there is likely more variation in SES, which may be related to BMI and fertility outcomes.

In conclusion, our study found that donor BMI had no significant impact on ART outcomes, while recipient BMI had a positive relationship with likelihood of positive pregnancy test and live birth. Our results support the conclusion that oocyte quality rather than endometrial receptivity may be the overriding factor influencing ART outcomes in obese women using autologous oocytes although further studies are warranted.

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Tables:

Table 1: Characteristics of Oocyte Donors by BMI, 2008-2015

		Donor BMI Categories (kg/m^2)			
	Total	≤ 21	$21.1 - 24.9$	≥ 25	p-value*
Number of women	338	97	181	60	
Age at first retrieval, years	25.5	25.0	26.0	26.0	0.79
	(23.0, 28.0)	(23.0, 28.0)	(23.0, 28.0)	(23.0, 28.0)	
Year of retrieval, n (%)					0.15
2008-2009	88 (26.0)	25 (25.8)	41 (22.7)	22 (36.7)	
2010-2011	107 (31.7)	31 (32.0)	57 (31.5)	19 (31.7)	
2012-2013	102 (30.2)	34 (35.1)	56 (30.9)	12 (20.0)	
2014-2015	41 (12.1)	7 (7.2)	27 (14.9)	7 (11.7)	
Race, n (%)					0.20
White	245 (74.7)	71 (75.5)	136 (76.8)	38 (66.7)	
Black	36 (11.0)	6 (6.4)	19 (10.7)	11 (19.3)	
Other	47 (14.3)	17 (18.1)	22 (12.4)	8 (14.0)	
Number of prior births, n (%)					0.76
0	263 (77.8)	74 (76.3)	144 (79.6)	45 (75.0)	
1	36 (10.7)	9 (9.3)	19 (10.5)	8 (13.3)	
≥2	39 (11.5)	14 (14.4)	18 (9.9)	7 (11.67)	
Anti-mullerian hormone, ng/mL	4.4	4.6	3.9	4.8	0.26
	(3.0, 6.6)	(3.4, 8.2)	(2.8, 6.5)	(2.7, 5.7)	
Antral follicle count, n	33.0	32.0	33.0	34.0	0.72
	(25.0, 41.5)	(25.0, 40.0)	(26.0, 41.5)	(23.5, 44.0)	
Gonadotropin total dose, IU	2400.0	2250.0	2400.0	2400.0	0.87
	(1950.0, 2850.0)	(1875.0, 2925.0)	(2025.0, 2850.0)	(1987.5, 2850.0)	
Days of stimulation, n (%)					0.78
8-9	88 (26.0)	23 (23.7)	47 (26.0)	18 (30.0)	
10-11	207 (61.2)	60 (61.9)	110 (60.8)	37 (61.7)	
12-13	43 (12.7)	14 (14.4)	24 (13.3)	5 (8.3)	
Follicles >14mm at trigger, n	20.0	20.0	20.0	20.0	0.99
	(16.0, 25.0)	(16.0, 24.0)	(16.0, 25.0)	(16.0, 25.0)	
Peak estradiol, pg/mL	2849.5	2979.0	2698.0	3247.5	0.48
	(1882.0, 4548.0)	(2009.0, 4479.0)	(1842.0, 4197.0)	(1950.5, 4749.0)	
Maturation trigger type, n (%)					0.81
hCG	125 (37.1)	36 (37.1)	64 (35.6)	25 (41.7)	
GnRH Agonist (Lupron)	212 (62.9)	61 (62.9)	116 (64.4)	35 (58.3)	

Data are presented as median (25^{th}, 75^{th} percentile) or n (%) unless otherwise noted. Amount of women with missing data: 10 for race, 203 for AMH (not routinely measured before 2012), 2 for AFC, 2 for maturation trigger type.

*p-values for differences across donor BMI categories were calculated using Chi-Square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Table 2: Characteristics of Oocyte Recipients by BMI, 2008-2015

		Recipient BMI					
	Total	<18.5	18.5 - 24.9	25 – 29.9	30 – 34.9	≥ 35	p-value*
Number of Women	932	15	577	218	82	40	
Age, years	42.0 (38.0, 44.0)	39.0 (37.0, 41.0)	42.0 (39.0, 44.0)	41.0 (38.0, 44.0)	42.0 (38.0, 44.0)	42.0 (40.0, 45.0)	0.02
Year of Embryo Transfer, n (%)							0.46
2008-2009	257 (27.6)	5 (33.3)	155 (26.9)	59 (27.1)	25 (30.5)	13 (32.5)	
2010-2011	298 (32.0)	4 (26.7)	188 (32.6)	68 (30.7)	25 (30.5)	14 (35.0)	
2012-2013	294 (31.6)	5 (33.3)	176 (30.3)	81 (37.6)	23 (28.1)	9 (22.5)	
2014-2015	83 (8.9)	1 (6.7)	58 (10.2)	10 (4.6)	9 (11.0)	4 (10.0)	
Race, n (%)							<0.001
White	683 (73.6)	11 (73.3)	438 (76.4)	152 (69.7)	56 (68.4)	26 (65.0)	
Black	121 (13.0)	0 (0.0)	45 (7.9)	45 (20.6)	20 (24.4)	11 (27.5)	
Other	124 (13.4)	4 (26.7)	90 (15.7)	21 (9.6)	6 (7.3)	3 (7.5)	
Current Smoking Status, n (%)							0.13
Yes	29 (3.1)	0 (0.0)	20 (3.5)	2 (0.9)	5 (6.1)	2 (5.0)	
No	903 (96.9)	15 (100.0)	557 (96.5)	216 (99.1)	77 (93.9)	38 (95.0)	
Number of prior births, n (%)							0.50
0	676 (73.3)	11 (73.3)	415 (71.9)	163 (74.8)	57 (69.5)	30 (75.0)	
1	179 (19.2)	3 (20.0)	115 (19.9)	39 (17.9)	13 (15.9)	9 (22.5)	
≥2	77 (8.3)	1 (6.7)	47 (8.2)	16 (7.3)	12 (14.6)	1 (2.5)	
Prior autologous IVF transfers, n (%)							0.12
0	485 (52.2)	3 (20.0)	295 (51.3)	127 (58.3)	43 (52.4)	17 (42.5)	
1	173 (18.6)	3 (20.0)	112 (19.5)	35 (16.1)	18 (19.5)	5 (12.5)	
2	113 (12.2)	4 (26.7)	68 (11.8)	24 (11.0)	10 (11.8)	7 (17.5)	
≥ 3	159 (17.1)	5 (33.3)	100 (17.4)	32 (14.7)	11 (17.4)	11 (27.5)	
Prior donor IVF transfers, n (%)							0.88
0	781 (84.0)	15 (100.0)	483 (84.0)	182 (83.4)	68 (82.9)	33 (82.5)	
1	94 (10.1)	0 (0.0)	61 (10.4)	21(10.1)	8 (9.8)	4 (10.0)	
≥2	55 (5.9)	0 (0.0)	32 (5.6)	14 (6.5)	6 (7.3)	3 (7.5)	
Uterine factor infertility, n (%)							0.01

Yes	151(16.2)	1 (6.7)	78 (13.5)	46 (21.1)	14 (17.1)	12 (30.0)	
No	781 (83.8)	14 (93.3)	499 (86.5)	172 (78.9)	68 (82.9)	28 (70.0)	
Recurrent pregnancy loss, n (%)							0.59
Yes	60 (6.4)	0 (0.0)	37 (6.4)	17 (7.8)	3 (3.7)	3 (7.5)	
No	872 (93.6)	15 (100.0)	540 (93.6)	201 (92.2)	79 (96.3)	37 (92.5)	
PCOS or other ovulatory dysfunction, n (%)							0.0004
Yes	27 (2.9)	1 (6.7)	14 (2.4)	2 (0.9)	5 (6.1)	5 (12.5)	
No	905 (97.1)	14 (93.3)	563 (97.6)	216 (99.1)	77 (93.9)	35 (87.5)	
Number of oocytes thawed, n (%)							0.17
≤5	158 (16.9)	6 (40.0)	96 (16.5)	36 (16.5)	14 (17.1)	7 (17.5)	
6	555 (59.6)	7 (46.7)	336 (58.4)	130 (59.6)	52 (63.4)	29 (72.5)	
≥7	219 (23.5)	2 (13.3)	145 (25.1)	52 (23.9)	16 (19.5)	4 (10.0)	
Number embryos transferred, n (%)							0.71
1	567 (60.8)	12 (80.0)	354 (61.4)	125 (57.3)	50 (61.0)	26 (65.0)	
2	356 (38.2)	3 (20.0)	216 (37.4)	91 (41.7)	32 (39.0)	14 (35.0)	
3	9 (1.0)	0 (0.0)	7 (1.2)	2 (0.9)	0 (0.0)	0 (0.0)	
Embryo stage at transfer, n (%)							0.49
Day 3	95 (10.2)	2 (13.3)	66 (11.4)	16 (7.3)	8 (9.8)	3 (7.5)	
Day 5	837 (89.8)	13 (86.7)	511 (88.6)	202 (92.7)	74 (90.2)	37 (92.5)	

Data are presented as median (25^{th}, 75^{th} percentile) or n (%) unless otherwise noted. Amount of women with missing data: 4 for race, 2 for prior autologous and donor IVF cycles.

*p-values for differences across recipient BMI categories were calculated using Chi-Square tests for categorical variables and Kruskal-Wallis tests for continuous variables

Table 3: Association between Donor BMI and early outcomes following oocyte thaw and fertilization (among 338 donors).

	Adjusted Percentage (95% CI)*			
	Surviving Oocytes	**Fertilized Oocytes**	**Usable Embryos**	**Cryopreserved Embryos**
Donor BMI				
≤ 21	91.5 (89.4, 93.3)	77.1 (74.0, 80.0)	51.1 (47.4, 54.8)	27.9 (24.3, 31.8)
$21 < BMI \leq 25$	92.4 (90.9, 93.6)	78.9 (76.8, 80.8)	52.4 (50.1, 54.8)	29.6 (27.3, 32.0)
> 25	92.4 (89.5, 94.6)	79.9 (76.8, 80.8)	53.3 (47.9, 58.6)	31.3 (25.9, 37.1)
P-trend†	0.29	0.26	0.26	0.26

*****The association between donor BMI and % oocytes surviving warm, % fertilized oocytes, % usable embryos, and % cryopreserved embryos were analyzed using generalized estimating equations with binomial distribution and log link function. Models are adjusted for donors' age, donors' race and retrieval year. The denominator for all percentages is the number of oocytes that were thawed.

†P-trend was calculated using the median values of each category of BMI as continuous variable

Table 4: Association between Donor BMI and Recipient BMI and probability of positive pregnancy test (PPT), miscarriage, and live birth (among 338 donors and 932 recipients who had a total of 1651 embryo transfer cycles).

	PPTs/Transfer Cycles (%)	Adjusted Risk Ratio of PPT (95% CI)*	Miscarriage/ PPTs (%)	Adjusted Risk Ratio of Miscarriage (95% CI)*	Live Births/ Transfer Cycles (%)	Adjusted Risk Ratio of Live Birth (95% CI)*
Donor BMI, per 2 kg/m^2		1.01 (0.99, 1.03)		1.02 (0.91, 1.14)		1.00 (0.96, 1.04)
Donor BMI						
< 21	340/497 (68.4)	0.96 (0.90, 1.02)	95/340 (27.9)	1.01 (0.79, 1.30)	244/497 (49.1)	0.97 (0.89, 1.07)
$21 - 24.9$	685/957 (71.6)	1.00 (ref)	202/685 (29.5)	1.00 (ref)	472/957 (49.3)	1.00 (ref)
≥ 25	135/197 (68.5)	0.96 (0.89, 1.04)	35/135 (25.9)	1.14 (0.75, 1.74)	97/197 (49.2)	0.93 (0.79, 1.08)
p-trend†		0.15		0.58		0.29
Recipient BMI, per 2 kg/m^2		1.01 (1.00, 1.02)		0.96 (0.92, 1.01)		1.02 (1.00, 1.03)
Recipient BMI						
<18.5	19/22 (86.4)	1.16 (1.02, 1.31)	5/19 (26.3)	1.18 (0.54, 2.58)	14/22 (63.4)	1.12 (0.83, 1.51)
18.5 - 24.9	717/1026 (69.9)	1.00 (ref)	209/717 (29.2)	1.00 (ref)	498/1026 (48.5)	1.00 (ref)
25 – 29.9	273/395 (69.1)	1.00 (0.93, 1.06)	80/273 (29.3)	1.00 (0.76, 1.30)	198/395 (48.4)	1.00 (0.91, 1.11)
30 – 34.9	104/150 (69.3)	1.03 (0.94, 1.13)	28/104 (26.9)	0.76 (0.50, 1.14)	74/150 (49.3)	1.08 (0.95, 1.24)
≥ 35	47/58 (81.0)	1.13 (1.02, 1.25)	10/47 (21.3)	0.62 (0.32, 1.19)	36/58 (62.1)	1.26 (1.07, 1.49)
p-trend		0.001		0.04		0.003

*Log binomial regression with cluster weighted generalized estimating equations was used to analyze the association between donor/recipient BMI and probability of PPT, miscarriage, and live birth. The weight was equal to the inverse of the number of embryo transfer cycles. Models for donor BMI are adjusted for donor's age and race, recipient's BMI and age, uterine factor infertility, and PCOS, and retrieval year. Models for recipient BMI are adjusted for donor's age and BMI, recipient's age and race, uterine factor infertility, add PCOS, and retrieval year.

†P-trend was calculated using the median values of each category of BMI as continuous variables.

Table 5. Association between donor BMI and recipient BMI and length of gestation and birthweight among donor oocyte recipient singleton live births (N=670).

		Length of Gestation			Birthweight		
	Number of Live Births	Mean Weeks/ % <37 weeks	Adjusted HR (95% CI)*	Adjusted OR of Pre-term (95% CI)†	Mean Grams/ % <2500g	Adjusted β (95% CI)‡	Adjusted RR of Low Birthweight (95% CI)†
Donor BMI, per 2 kg/m^2			1.01 (0.94, 1.08)	1.05 (0.89, 1.23)		25.1 (-26.3, 72.0)	0.98 (0.85, 1.14)
Donor BMI							
< 21	203	38.3 / 16.3	1.01 (0.84, 1.22)	0.84 (0.55, 1.28)	3197.7 / 11.3	-24.0 (-153.6, 105.5)	0.96 (0.65, 1.41)
$21 - 24.9$	384	38.4 / 15.6	1.00 (ref)	1.00 (ref)	3279.0/ 8.9	0 (ref)	1.00 (ref)
≥ 25	78	38.4 / 11.5	1.10 (0.84, 1.43)	0.79 (0.42, 1.48)	3394.1/ 9.0	60.7 (-131.9, 253.4)	0.94 (0.55, 1.60)
p-trend€			0.64	0.37		0.45	0.80
Recipient BMI, per 2 kg/m^2			1.04 (1.00, 1.08)	1.04 (0.96, 1.12)		-12.0 (-34.8, 10.8)	1.04 (0.99, 1.11)
Recipient BMI							
<18.5	11	39.5 / 9.1	0.64 (0.43, 0.95)	0.90 (0.28, 2.92)	3395.6 / 0.0	137.2 (-234.6, 509.0)	1.14 (0.41, 3.16)
18.5 - 24.9	409	38.4 / 15.7	1.00 (ref)	1.00 (ref)	3257.0/ 9.5	0 (ref)	1.00 (ref)
25 – 29.9	158	38.3 / 12.0	1.13 (0.90, 1.41)	0.79 (0.52, 1.19)	3309.3 / 10.8	11.4 (-136.5, 159.2)	0.98 (0.64, 1.48)
30 – 34.9	63	38.0 / 20.3	1.02 (0.77, 1.36)	1.02 (0.57, 1.83)	3173.5/ 11.1	-89.0 (-302.2, 124.1)	1.11 (0.63, 1.94)
≥ 35	25	38.0 / 20.8	1.45 (0.96, 2.20)	1.93 (0.78, 4.75)	3373.2 / 4.0	-138.2 (-409.3, 133.0)	1.76 (1.02, 3.02)
p-trend			0.003	0.08		0.08	0.05

All models for donor BMI are adjusted for donor's age and race, recipient's BMI and age, uterine factor infertility, and PCOS, and retrieval year. All models for recipient BMI are adjusted for donor's age and BMI, recipient's age and race, uterine factor infertility, add PCOS, and retrieval year.

*Analyses for gestational length were conducted using cluster weighted Cox proportional hazard and a robust sandwich covariance estimate to account for the multiple live births per woman in the presence of non-ignorable cluster size. Each observation was weighted inversely to the number of live births they contributed to the analysis.

†Analyses for pre-term birth and low birthweight were conducted using cluster weighted generalized estimating equations with binomial distribution and logit link function to account for within-person correlations in the presence of non-ignorable cluster size. Each observation was weighted inversely to the number of live births they contributed to the analysis.

‡Analyses for birthweight were conducted using cluster weighted generalized estimating equations with normal distribution and identity link function to account for within-person correlations in the presence of non-ignorable cluster size. Each observation was weighted inversely to the number of live births they contributed to the analysis.

€P-trend was calculated using the median values of each category of BMI as continuous variables.

Supplemental Table 1. Sensitivity analyses for the association between Donor BMI and Recipient BMI and probability of live birth**.**

	Adjusted Risk Ratio of Live Birth (95% CI)*				
	Single Embryo Transfer (N= 1,011 cycles)	**Only Blastocyst Transfers (N=1,514 cycles)**	**Only First Embryo Transfer (N= 901 cycles)**	**No Uterine Factor Infertility (N= 1,362 cycles)**	**No PCOS or other ovulatory disorder (N=1,560 cycles)**
Donor BMI					
< 21	0.95 (0.83, 1.08)	0.98 (0.89, 1.07)	1.03 (0.93, 1.14)	0.97 (0.88, 1.07)	0.97 (0.88, 1.07)
$21 - 24.9$	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥ 25	1.00 (0.81, 1.25)	0.89 (0.76, 1.06)	0.90 (0.75, 1.09)	0.96 (0.81, 1.13)	0.91 (0.77, 1.07)
p-trend†	0.42	0.19	0.18	0.46	0.23
Recipient BMI					
<18.5	1.04 (0.68, 1.59)	1.05 (0.75, 1.48)	0.96 (0.64, 1.43)	1.11 (0.80, 1.55)	1.21 (0.94, 1.57)
18.5 - 24.9	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
25 – 29.9	0.96 (0.85, 1.09)	0.99 (0.89, 1.10)	1.02 (0.91, 1.13)	1.01 (0.90, 1.12)	1.00 (0.91, 1.11)
30 – 34.9	1.08 (0.91, 1.30)	1.08 (0.94, 1.24)	1.08 (0.93, 1.24)	1.05 (0.91, 1.22)	1.08 (0.94, 1.24)
≥ 35	1.12 (0.87, 1.45)	1.28 (1.09, 1.51)	1.26 (1.10, 1.44)	1.30 (1.09, 1.54)	1.28 (1.08, 1.53)
p-trend	0.15	0.001	0.0005	0.0026	0.0009

*Log binomial regression with cluster weighted generalized estimating equations was used to analyze the association between donor/recipient BMI and probability of PPT, miscarriage, and live birth. The weight was equal to the inverse of the number of embryo transfer cycles. Models for donor BMI are adjusted for donor's age and race, recipient's BMI and age, uterine factor infertility, and PCOS, and retrieval year. Models for recipient BMI are adjusted for donor's age and BMI, recipient's age and race, uterine factor infertility, add PCOS, and retrieval year.

†P-trend was calculated using the median values of each category of BMI as continuous variables.

Supplemental Table 2. Joint effect of Donor BMI and Recipient BMI on probability of live birth (among 338 donors and 932 recipients who had a total of 1,651 embryo transfer cycles).

	Recipient BMI	Live Births/Transfer Cycles (%)	Adjusted Risk Ratio (95% CI)*	Adjusted Probability of Live Birth (95% CI)*
Donor BMI <25 kg/m^2	<25 kg/m2	460/944 (48.7)	1.00 (REF)	0.61 (0.57, 0.64)
	25-29.9 kg/m2	163/337 (48.4)	0.99 (0.88, 1.10)	0.60 (0.54, 0.66)
	≥30 kg/m2	88/164 (53.7)	1.11 (0.98, 1.26)	0.67 (0.60, 0.75)
Donor BMI ≥25 kg/m^2	<25 kg/m2	52/104 (50.0)	0.88 (0.70, 1.09)	0.53 (0.43, 0.66)
	25-29.9 kg/m2	23/49 (46.9)	0.97 (0.73, 1.29)	0.59 (0.44, 0.78)
	≥30 kg/m2	22/44 (50.0)	1.10 (0.86, 1.40)	0.67 (0.53, 0.84)

*Log binomial regression with cluster weighted generalized estimating equations was used to analyze the association between donor/recipient BMI and probability of PPT, miscarriage, and live birth. The weight was equal to the inverse of the number of embryo transfer cycles. Models were adjusted for donor age, donor race, recipient age, uterine, and year of retrieval.