Reproductive outcomes in oocyte donation cycles are associated with donor BMI

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STUDY QUESTION: When adjusting for recipient BMI, is donor body mass index (BMI) associated with IVF outcomes in donor oocyte IVF cycles?

SUMMARY ANSWER: Increasing oocyte donor BMI is associated with a reduction in clinical pregnancy and live birth rates.

WHAT IS KNOWN ALREADY: Increased BMI has been associated with suboptimal reproductive outcomes, particularly in assisted reproductive technology (ART) cycles. However, it remains unclear if this association implies an effect of BMI on oocyte quality and/or endometrial receptivity.

STUDY DESIGN, SIZE, DURATION: A retrospective cohort study of two hundred and thirty five consecutive fresh donor oocyte IVF cycles from 1 January 2007 through 31 December 2013 at the Massachusetts General Hospital (MGH) Fertility Center.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Analyses included a total of 202 oocyte donors and 235 total cycles. Following adjustments for recipient BMI, the relationship between donor BMI (categorized into quartiles) and IVF outcomes was assessed.

MAIN RESULTS AND THE ROLE OF CHANCE: In the entire (anonymous and known) donor population, a reduced odds of clinical pregnancy (P-trend = 0.046) and live birth (P-trend = 0.06) was observed with increasing BMI quartile. Compared with quartile 1 (BMI 17.8–21.1), odds ratio (OR) (95% CI) of clinical pregnancy was 0.9 (0.4–2.0), 0.5 (0.2–1.1) and 0.5 (0.2–1.1), and OR of live birth was 1.1 (0.5–2.6), 0.6 (0.3–1.2) and 0.6 (0.3–1.2) for quartiles 2 through 4 respectively. In anonymous donors only, the odds of clinical pregnancy (P-trend = 0.02) and live birth (P-trend = 0.03) also declined as BMI quartile increased. Compared with quartile 1 (BMI 17.8–21.1), odds ratio (OR) (95% CI) of clinical pregnancy was 0.7 (0.3–1.7), 0.5 (0.2–1.1) and 0.4 (0.1–0.9), and OR of live birth was 0.9 (0.4–2.2), 0.5 (0.3–1.2) and 0.4 (0.2–1.1) for quartiles 2 through 4 respectively.

LIMITATIONS, REASONS FOR CAUTION: Limitations include the retrospective design, sample size and data from a single institution. Clinical application may not be limited to oocyte donors, though caution should be used prior to applying these principles to the general population. Data should not be interpreted to mean that all oocyte donors should be restricted to a BMI of less than 21.2 kg/m².

WIDER IMPLICATIONS OF THE FINDINGS: Following adjustments for the respective BMI of the oocyte donor and recipient, this study demonstrates an association of preconception BMI with subsequent IVF outcomes. The observations of this study are consistent with prior animal studies, suggest a possible effect of BMI at the oocyte level prior to fertilization and implantation, and warrant further investigation.

STUDY FUNDING/COMPETING INTERESTS: None.

Key words: body mass index / obesity / oocyte / oocyte donor / in vitro fertilization / oocyte recipient / reproductive outcomes / oocyte quality
**Introduction**

Excess weight has a particularly deleterious impact in women, resulting in cardiometabolic health risks as well as adverse reproductive health outcomes (Practice Committee of American Society for Reproductive Medicine, 2008), of which most women are unaware (Cardozo et al., 2012, 2013). In addition to being a risk factor for infertility (Rich-Edwards et al., 1994), women who are overweight and obese undergoing assisted reproductive technologies (ART) require higher doses of gonadotrophins (Maheshwari et al., 2007), have fewer oocytes retrieved (Zhang et al., 2010), and have lower rates of fertilization (Zhang et al., 2010), implantation (Moragianni et al., 2012), and pregnancy (Wang et al., 2000; Loveland et al., 2001; Maheshwari et al., 2007; Rittenberg et al., 2011). While there are substantial data indicating that excess weight has a negative impact on the reproductive outcomes of ART cycles, it remains unclear if this effect is exerted at the level of the oocyte or the endometrium (Cardozo et al., 2011).

Classically, the oocyte donation model has been used to differentiate the effect of obesity on oocyte/embryo quality and endometrial receptivity; however, conflicting results remain. Several studies suggest that unfavorable ART outcomes in obese women are caused by subsoptimal oocyte quality (Cano et al., 1997; Wattanakumtornkul et al., 2003; Zenke and Chetkowski, 2004; Styne-Gross et al., 2005; Luke et al., 2011). In contrast, many investigators highlight the negative impact of obesity on endometrial receptivity (Beller et al., 2003, 2007, 2013; DeUgarte et al., 2010). These prior studies have assumed that donors have no comorbidities and have a normal body mass index (BMI), and have thus excluded the impact of the preconception environment by only accounting for the recipient BMI and not adjusting for donor BMI in their analyses.

Murine models demonstrate that obesity negatively impacts the quality and developmental competence of oocytes and embryos, and this effect of BMI persists even when the oocyte or embryo is removed from the obese host environment (Minge et al., 2008; Luzzo et al., 2012). Therefore, investigation of the potential impact of donor obesity on IVF outcomes in donor-recipient cohorts will provide invaluable insight into the possible effect of BMI prior to conception in humans. The objective of this study was to assess the association of BMI on donor oocyte in vitro fertilization (IVF) cycle outcomes by utilizing an oocyte donation model that accounts for the BMI of donor and recipient respectively.

**Materials and Methods**

**Study population**

Two hundred and forty-seven consecutive donor oocyte IVF cycles from 1 January 2007 through 31 December 2013 at Massachusetts General Hospital (MGH) Fertility Center were reviewed. All fresh donor oocyte cycles in which controlled ovarian hyperstimulation was initiated and had donor BMI data available, including subsequent fresh oocyte donation cycles by the same donor, were included. Of the 247 consecutive fresh donor oocyte cycles reviewed, analyses included a total of 202 oocyte donors and 235 total cycles.

Anonymous donors (unknown to the recipient) are selected by recipients via a third party agency and known donors (typically a relative or friend of the donor) are specifically selected by the recipient. All donors undergo a multidisciplinary medical and psychological evaluation to determine eligibility for donation as described previously (Practice Committee of American Society for Reproductive Medicine and Practice Committee of Society for Assisted Reproductive Technology, 2013).

**Stimulation protocols**

**Oocyte donors**

Oocyte donors underwent one of three stimulation protocols as previously described by our center (Styer et al., 2008, 2015; Cardozo et al., 2015): the long luteal phase GnRH agonist (GnRH-a) protocol (‘Low Dose Luteal Lupron’ or LDL), the follicular phase GnRH agonist (Flare) protocol, or the GnRH antagonist protocol.

**Recipients**

The programmed hormone replacement regimen consisted of oral contraceptive pill (OCP) pretreatment followed by pituitary down-regulation with daily Lupron™ (leuproide acetate, 0.5 mg/d SC; TAP Pharmaceuticals Inc., Lake Forest, IL, USA) starting the last 5 days of OCP use, followed by transdermal estradiol (Vivelle-Dot™; Novartis Pharmaceuticals, East Hanover, NJ, USA) for 2–3 weeks until the day of donor hCG trigger. On the day of donor oocyte retrieval, the recipient initiated i.m. micronized progesterone (50 mg daily; Progesterone in Sesame Oil; Watson Pharmaceuticals Inc., Parsippany, NJ, USA), vaginal micronized progesterone (100 mg per vagina twice daily; Endometrin; Ferring Pharmaceuticals, Tarrytown, NY, USA), and transdermal estradiol (0.2 mg every other day; Vivelle-Dot; Novartis Pharmaceuticals, East Hanover, NJ, USA) which was continued until 13 weeks gestation.

**Data collection and statistical analysis**

Data were collected through review of electronic medical record for all oocyte donors and donor oocyte recipients. Primary study outcomes were implantation (number of gestational sacs visualized per number of embryos transferred), clinical pregnancy (the presence of at least 1 gestational sac visualized at 6 weeks estimated gestational age), and live birth (birth of a viable infant on or after 24 weeks estimated gestational age) per cycle start. Secondary study outcomes included donor peak estradiol level, total number of oocytes retrieved from oocyte donor, number of mature oocytes retrieved, fertilization rate (defined as number of mature oocytes inseminated divided by number of two pronuclear embryos seen on the day following in vitro fertilization), and cleavage rate (percent of embryos demonstrating ≥2 blastomeres 2 days following in vitro fertilization).

Statistical analysis was performed using SAS Statistical software version 9.3 (SAS Institute, Cary, NC, USA). BMI of all donors was divided into quartiles. All data are presented by donor BMI quartile in order to understand the nature of the relationship between BMI and outcomes without assuming it is linear, as well as to detect odds ratios per group and not just per incremental BMI unit. Generalized linear mixed models were used to assess cycle characteristics and all results were adjusted for donor age, except for recipient lining and pattern, which were adjusted for recipient age. Results are presented as adjusted mean (95% confidence interval) or adjusted probability (95% confidence interval). Cycle outcomes were analyzed with logistic regression using generalized estimating equations (GEE) to take advantage of all available cycles while taking into account within-person correlations in cycle outcomes (controlling for repeated cycles) (Fitzmaurice et al., 2004) and presented as an adjusted odds ratio, with the exception of implantation rate which was analyzed using generalized linear mixed models and presented as an adjusted rate. Outcomes were adjusted for donor age, recipient age, recipient BMI, male factor, number of prior cycles in donor, donor antral follicle count, and donor status (known versus anonymous). The variables which were adjusted for were determined based on those that had P-values of less than or equal to 0.2 in univariate analysis (Table I), which included recipient BMI, male factor infertility, donor’s number of prior cycles, and donor status (known versus anonymous), as well as those
which are known to have an impact on IVF cycle outcomes based on previously published literature, including donor age (Barton et al., 2010), recipient age (Yeh et al., 2014), and donor antral follicle count (Vrontikis et al., 2010). A P-trend of <0.05 was considered significant.

### Ethical approval

This study was approved by the Partners Human Research Committee (Institutional Review Board of Partners HealthCare).

### Results

A total of 202 oocyte donors underwent 235 total cycles. Exclusion criteria included cancelation prior to cycle start, missing BMI data, and conversion to cryopreservation with no fresh embryo transfer. At the time of first donor oocyte cycle at MGH, the mean (range, SD) donor age (years) was 27.0 (21.6–42.3, 3.7) and the mean recipient age was 41.2 (29.9–49.7, 4.7). Mean (range, SD) donor BMI was 23.4 kg/m² (17.8–34.0, 3.1) and mean (range, SD) recipient BMI was 24.2 kg/m² (17.8–40.1, 4.3). The mean (range, SD) number of prior fresh cycles per donor at the time of their last cycle was 1.4 (0.0–5.0, SD 1.4). Of the 235 oocyte donation cycles, 230 (97.9%) used a low dose luteal down-regulation protocol, 3 (1.3%) used a GnRH antagonist down-regulation, and 2 (0.9%) used a GnRH flare. Total clinical pregnancy rate per cycle start (all cycles) was 61.7%, and overall live birth rate per cycle start was 54.9%.

The BMI of all donors was categorized into quartiles with approximately equal numbers of donors per quartile (at the boundaries there were several donors with the same BMI who could not be assigned to different groups), while recipient BMI remained a continuous variable. Subsequent analyses were subdivided into the following donor BMI quartiles: Q1 (17.8–21.1 kg/m²), Q2 (21.2–22.8 kg/m²), Q3 (22.9–25.2 kg/m²) and Q4 (25.3–34.0 kg/m²). Characteristics of donors and recipients at the time of donor’s first cycle, categorized by donor BMI quartile, are presented in Table I. Total number of previous cycles decreased with increasing BMI quartile (P = 0.02). Except for BMI, there were no differences in donor or recipient characteristics between quartiles. There was a positive correlation between donor BMI and recipient BMI for all cycles (R = 0.31, P < 0.01) and for anonymous cycles only (R = 0.26, P < 0.01). When each of the cycle characteristics listed in Table I were compared between known and anonymous donors, known donors were more likely to be older (P < 0.01), have a higher BMI (P < 0.01), have a higher day 3 FSH (P = 0.02), and completed fewer prior cycles (P > 0.01). All other cycle characteristics were similar between groups (data not shown). The odds ratios for clinical pregnancy and live birth of our covariates, which are included in the main model, are presented as Supplementary Table SI.

Additional cycle characteristics are presented in Table II. All results are adjusted for donor age, with the exception of recipient endometrial thickness and pattern, which are adjusted for recipient age, and use of ICSI, which is not adjusted for age. No difference was observed between quartiles with respect to total gonadotropin dose used, day of hCG administration, thickness or pattern of recipient lining on day of trigger injection, use of ICSI for insemination, fertilization rate, cleavage rate, number of embryos transferred, or likelihood of a Day 5 embryo transfer. A decrease in peak serum estradiol level was observed as BMI quartile increased (P-trend = 0.07), and mean number of eggs retrieved decreased with increasing BMI quartile (P-trend = 0.06) but neither reached statistical significance.

Nine cycles were canceled after stimulation start due to poor response. The median BMI for canceled cycles was 22.9 kg/m² versus 22.9 kg/m² for non-canceled cycles. Seventeen spontaneous abortions occurred in 235 cycles for a spontaneous abortion rate of 7.2%. There was no difference in median BMI for those who had a spontaneous abortion versus those who did not (22.9 kg/m², interquartile range 4.1 versus 23.5 kg/m², interquartile range 3.9; P = 0.81). Table III presents cycle outcomes by donor BMI quartile (Quartile 1 is the reference). Following adjustments for donor age, recipient age, recipient BMI, male factor infertility, donor’s number of prior IVF cycles, donor antral follicle count, and donor status (known versus anonymous), no difference was observed in implantation rate or

### Table I

Characteristics of donor and recipient at donor’s first cycle at MGH, by donor BMI quartile, mean (standard deviation) or percentage (frequency).

<table>
<thead>
<tr>
<th>BMI Quartile</th>
<th>Women (n)</th>
<th>Donor BMI (kg/m²)</th>
<th>Donor age (years)</th>
<th>Donor AFC</th>
<th>Donor D3 FSH (IU/l)</th>
<th>Total number of previous cycles*</th>
<th>Known donor, % (n)</th>
<th>Recipient age (years)</th>
<th>Recipient BMI (kg/m²)</th>
<th>Uterine factor, % (n)</th>
<th>Male factor, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 17.8–21.1</td>
<td>46</td>
<td>19.7 (0.9)</td>
<td>26.2 (3.3)</td>
<td>18.3 (5.7)</td>
<td>6.0 (1.5)</td>
<td>1.5 (1.4)</td>
<td>6.5% (3)</td>
<td>41.4 (4.9)</td>
<td>22.6 (2.8)</td>
<td>2.2% (1)</td>
<td>4.4% (2)</td>
</tr>
<tr>
<td>Q2 21.2–22.8</td>
<td>51</td>
<td>21.9 (0.5)</td>
<td>27.7 (4.1)</td>
<td>19.1 (6.4)</td>
<td>6.0 (1.6)</td>
<td>1.4 (1.4)</td>
<td>19.6% (10)</td>
<td>40.7 (4.7)</td>
<td>23.7 (3.8)</td>
<td>2.0% (1)</td>
<td>13.7% (7)</td>
</tr>
<tr>
<td>Q3 22.9–25.2</td>
<td>54</td>
<td>23.9 (0.7)</td>
<td>26.6 (3.0)</td>
<td>20.4 (7.9)</td>
<td>6.3 (1.6)</td>
<td>1.3 (1.5)</td>
<td>13.0% (7)</td>
<td>41.1 (4.6)</td>
<td>24.6 (4.7)</td>
<td>0.0% (0)</td>
<td>20.4% (11)</td>
</tr>
<tr>
<td>Q4 25.3–34.0</td>
<td>51</td>
<td>27.7 (2.0)</td>
<td>27.4 (4.3)</td>
<td>18.9 (7.7)</td>
<td>6.1 (1.7)</td>
<td>1.0 (1.2)</td>
<td>23.5% (12)</td>
<td>41.8 (4.7)</td>
<td>25.7 (5.0)</td>
<td>3.9% (2)</td>
<td>19.6% (10)</td>
</tr>
</tbody>
</table>

BMI, body mass index; AFC, antral follicle count; FSH, follicle stimulating hormone.

*Based on donor’s last cycle at MGH.
decrease in the odds of clinical pregnancy (anonymous donors (Table IV and Fig. 1), there was a statistically significant
change when the five patients who used a GnRH antagonist or flare protocol were omitted. A further sub-analysis of anonymous donors ex-
cluding recipients with BMI ≥25 showed the same trend toward lower
odds of clinical pregnancy and live birth with increasing BMI but did not reach statistical significance (Supplementary Table SII). Implantation
rates and birthweights were similar among quartiles for all donors and for anonymous donors only.

Cycle outcomes were also analyzed using donor BMI as a continuous variable instead of by quartile. A one-unit (1 kg/m²) increase in BMI is
associated with a 0.9 times lower odds of achieving a clinical pregnancy (OR 0.9 (0.82–1.02), P = 0.049). In addition, a one-unit (1 kg/m²) in-
crease in BMI is associated with a 0.9 times lower odds of achieving a live birth (OR 0.9 (0.82–1.02), P = 0.09, however this did not reach stat-
istical significance.

<table>
<thead>
<tr>
<th>BMI Q1</th>
<th>BMI Q2</th>
<th>BMI Q3</th>
<th>BMI Q4</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.8–21.1</td>
<td>21.2–22.8</td>
<td>22.9–25.2</td>
<td>25.3–34.0</td>
<td></td>
</tr>
<tr>
<td>Number of cycles</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>Total gonadotrophin dose (IU), mean</td>
<td>1845 (1625–2065)</td>
<td>1848 (1635–2061)</td>
<td>1900 (1709–2090)</td>
<td>2054 (1807–2300)</td>
</tr>
<tr>
<td>Peak E2 (pg/ml), mean</td>
<td>2680 (2349–3010)</td>
<td>2738 (2465–3010)</td>
<td>2482 (2186–2778)</td>
<td>2366 (2068–2663)</td>
</tr>
<tr>
<td>Day of donor hCG, mean</td>
<td>12.1 (11.2–13.1)</td>
<td>11.9 (11.0–12.8)</td>
<td>12.1 (11.3–13.1)</td>
<td>12.2 (11.3–13.2)</td>
</tr>
<tr>
<td>Recipient lining thickness on day of donor trigger (mm), mean</td>
<td>10.2 (9.6–10.8)</td>
<td>9.8 (9.1–10.5)</td>
<td>9.9 (9.3–10.4)</td>
<td>10.0 (9.2–10.7)</td>
</tr>
<tr>
<td>Recipient lining pattern, multilayered, %</td>
<td>94.2 (82.3–98.2)</td>
<td>96.3 (85.5–99.1)</td>
<td>96.6 (86.4–99.2)</td>
<td>92.9 (81.2–97.5)</td>
</tr>
<tr>
<td>Number of eggs retrieved, mean</td>
<td>15.1 (13.3–17.2)</td>
<td>14.8 (13.1–16.7)</td>
<td>13.8 (12.2–15.6)</td>
<td>12.9 (11.3–14.7)</td>
</tr>
<tr>
<td>ICSI, %</td>
<td>41.9 (29.1–55.9)</td>
<td>36.7 (25.1–50.2)</td>
<td>40.1 (28.4–53.0)</td>
<td>45.4 (32.3–59.3)</td>
</tr>
<tr>
<td>Fertilization rate (normal, 2PN), %</td>
<td>73.4 (68.1–78.2)</td>
<td>72.7 (67.6–77.1)</td>
<td>74.2 (69.2–78.7)</td>
<td>71.5 (65.7–76.6)</td>
</tr>
<tr>
<td>Cleavage rate, %</td>
<td>98.7 (96.7–99.5)</td>
<td>99.5 (98.2–99.9)</td>
<td>99.2 (97.7–99.7)</td>
<td>98.9 (96.9–99.6)</td>
</tr>
<tr>
<td>Number of embryos transferred, mean</td>
<td>1.7 (1.4–2.1)</td>
<td>1.8 (1.4–2.1)</td>
<td>1.6 (1.3–2.0)</td>
<td>1.6 (1.3–2.0)</td>
</tr>
<tr>
<td>Day 5 transfer (versus Day 2 or 3), %</td>
<td>62.9 (47.5–76.0)</td>
<td>53.4 (39.3–66.9)</td>
<td>58.0 (43.6–71.2)</td>
<td>62.2 (46.2–75.9)</td>
</tr>
</tbody>
</table>

E2, estradiol; hCG, human chorionic gonadotrophin; ICSI, intracytoplasmic sperm injection; 2PN, two pronuclear embryo observed on the day following in vitro fertilization (i.e. normal fertilization).

*Results are adjusted for age (donor or recipient as applicable). ICSI rate is not adjusted.

**Lightest infant included if multiple pregnancy. Birthweight is adjusted for multiple pregnancy in addition to other covariates.

Table III  Cycle outcome by donor BMI, adjusted OR (95% CI) or adjusted rate (95% CI).

<table>
<thead>
<tr>
<th>BMI Q1</th>
<th>BMI Q2</th>
<th>BMI Q3</th>
<th>BMI Q4</th>
<th>P-trend</th>
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<tbody>
<tr>
<td></td>
<td>Crude Multi variate</td>
<td>Crude Multi variate</td>
<td>Crude Multi variate</td>
<td>Crude Multi variate</td>
</tr>
<tr>
<td>Cycles (number)</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>Biochemical pregnancy</td>
<td>41 (74.5%)</td>
<td>Reference</td>
<td>46 (76.7%)</td>
<td>1.0 (0.4–2.5)</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>53.1%</td>
<td>52.9% (38.8–66.6)</td>
<td>55.0%</td>
<td>52.3% (39.6–64.8)</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>38 (69.0%)</td>
<td>Reference</td>
<td>41 (68.3%)</td>
<td>0.9 (0.4–2.0)</td>
</tr>
<tr>
<td>Live birth</td>
<td>34 (61.8%)</td>
<td>Reference</td>
<td>39 (65.0%)</td>
<td>1.1 (0.5–2.6)</td>
</tr>
<tr>
<td>Birthweight (g)**</td>
<td>3058 (2741–3375)</td>
<td>2994 (2638–3349)</td>
<td>3048 (2755–3340)</td>
<td>2764 (2215–3132)</td>
</tr>
</tbody>
</table>

*Results are adjusted for donor age, recipient age, recipient BMI, male factor, number of prior cycles in donor, donor antral follicle count, donor status (known versus anonymous).

**Lightest infant included if multiple pregnancy.
The results of a repeat analysis adjusting for total number of eggs retrieved (in addition to all other covariates previously controlled for including recipient BMI), indicated that a decrease in clinical pregnancy rate with increasing BMI persisted ($P$-trend $= 0.07$ for all donors, $P$-trend $= 0.04$ when excluding known donors). The trend toward lower live birth rate with increasing BMI also persisted when controlling for number of eggs retrieved ($P$-trend $= 0.06$ for all donors, $P$-trend $= 0.047$ when excluding known donors).

Discussion

In this retrospective cohort study, increasing donor BMI was associated with lower clinical pregnancy and live birth rates. Given the nature of this donor-recipient model, which controlled for recipient BMI, the findings of this study suggest an upstream effect of donor BMI prior to conception. To our knowledge, this is the first study using a donor-oocyte model that accounts for the BMI of the oocyte donor and recipient while studying the impact of BMI on clinical pregnancy and live birth outcomes. The observations of this study lend support to the hypothesis in animal models that there may be an effect of preconception BMI on the oocyte and subsequent IVF cycle outcomes.

In studies using the oocyte donation model, the association of BMI and IVF cycle outcomes is inconsistent. Several studies utilizing this model report no impact of BMI on clinical pregnancy rates (Bellver et al., 2003; Styne-Gross et al., 2005), while the majority have reported a decrease in pregnancy rates (Bellver et al., 2007, 2013; Dessolle et al., 2009; DeUgarte et al., 2010; Luke et al., 2011) and live birth rates (DeUgarte et al., 2010; Luke et al., 2011; Bellver et al., 2013) associated with increasing BMI. These variable results are difficult to interpret as each of these studies varies greatly in terms of size and methodology. However, adjustments for the BMI of the oocyte donor were not employed in these analyses. A systematic review and meta-analysis of
outcomes in obese donor oocyte recipients found no association between obesity and chance of implantation, pregnancy or live birth and noted that ‘oocyte quality rather than endometrial receptivity may be the overriding factor influencing IVF outcomes in obese women using autologous oocytes’ (Jungheim et al., 2013). The authors further acknowledge that only recipient BMI was collected and accounted for, and that donor BMI may in fact affect oocyte quality, and therefore could have biased the results of the meta-analysis (Jungheim et al., 2013). Therefore, the oocyte donation model, which adjusts for both donor and recipient BMI, of this study may provide a more clinically relevant approach to delineate factors impacting outcomes in donor oocyte IVF cycles.

An intriguing finding was the positive correlation between donor and recipient BMI, even when restricting to only anonymous cycles. One plausible explanation is that recipients emphasize having a donor with physical characteristics similar to their own over a donor with the healthiest possible BMI.

In this study, peak serum estradiol levels declined with increasing BMI, and may be explained by the declining numbers of oocytes aspirated with increasing BMI. Since this finding is consistent with existing literature (Zhang et al., 2010), it could be assumed that the decrease in clinical pregnancy rate and live birth rate with increasing BMI is a reflection of the smaller oocyte cohort associated with increasing BMI in this study. However, following adjustment for the number of oocytes retrieved (while still adjusting for recipient BMI and all other covariates), the observation of a decline in clinical pregnancy rate and live birth rate with increasing BMI persisted. These findings imply that these IVF cycle outcomes are independent of oocyte quantity, and may be most impacted by oocyte quality.

It is important to note that while cycle cancelations after stimulation start could be associated with BMI, the numbers were too small to assess for an association. These cycles are included as negative pregnancy outcomes to ensure that if BMI is associated with cycle cancelation, the pregnancy and live birth outcomes will not be biased.

It is also noteworthy that cycle outcomes such as clinical pregnancy rate and live birth rate, which trend toward or reach significance with all donors included, became statistically significant when known donors were excluded. One explanation for this finding is that known donors are not as rigorously screened (as evidenced by their older age, higher BMI and higher day 3 FSH compared with anonymous donors), and may have other underlying health issues and comorbidities. Since the overall trend toward worse IVF outcomes with higher donor BMI became more obvious with exclusion of known donors, results within the anonymous donor population may further delineate the impact of BMI in the ‘ideal’ donor population. Furthermore, the persistent trend toward lower odds of clinical pregnancy and live birth with increasing BMI seen in anonymous donors when excluding recipients with BMI ≥ 25 further emphasizes the impact of donor BMI, as the lack of statistical significance may reflect the very small sample size of this subpopulation.

When donor BMI was evaluated as a continuous variable, the finding that the odds of clinical pregnancy and live birth declined with increasing single units of BMI (1 kg/m²) is particularly intriguing, as this highlights the sensitivity of these outcomes to particularly small changes in BMI. The lack of statistical significance seen with live birth is likely a reflection of the relative clinical insignificance of a single-unit change in BMI. However, this also highlights the value of simultaneously examining data using donor BMI quartiles, as statistical significance is seen in declining odds of both clinical pregnancy and live birth with larger units of increase in donor BMI, increases which are also likely to be more clinically applicable.

The findings of this study are consistent with existing animal literature that suggests an impact of preconception obesity on reproductive outcomes. The altered maternal metabolic environment of obesity likely exerts a long-term impact on the oocyte and subsequent post-fertilization embryo, including delayed embryonic development, and the effect may persist when the oocyte or embryo is transferred to a metabolically normal host (Plenge et al., 2008; Robker, 2008; Wyman et al., 2008; Luzzo et al., 2012). Several mechanisms have been proposed to explain the impact of obesity on the preconception oocyte, with altered mitochondrial activity thought to be the primary underlying mechanism leading to poor oocyte quality and inferior reproductive outcomes. Since mitochondria are maternally inherited, do not begin to replicate until after implantation, play a major role in early embryonic development, and obesity results in abnormal mitochondria in oocytes and embryos (Igosheva et al., 2010), it has been proposed that mitochondrial dysfunction may impede early embryonic development (Cummins, 2004; Dumolland et al., 2007; Van Blerkom, 2008, 2011; Cardozo et al., 2011). Thus, reduced oocyte quality could result in downstream alterations of embryo quality and implantation potential, which may not be reflected by early embryo morphology prior to transfer. An alternate hypothesis of obesity’s impact on oocyte quality prior to conception involves substantially increased spindle and chromosome alignment defects in oocytes of obese mice compared with controls, which are thought to result in embryos with ‘massive aneuploidy’ (Luzzo et al., 2012).

The primary strength of this study is that our analysis models account for both donor and recipient BMI, and provide a comprehensive assessment of the impact of BMI prior to and subsequent to conception on reproductive outcomes. Moreover, the consistent use of protocols for donors and recipients was ideal to minimize variations in response. A limitation of this study is the relatively small sample size. Many of the results that are of borderline statistical significance demonstrate an notable trend but likely represent the relatively small sample size, and therefore larger future studies are needed. While the sample size is small, to our knowledge, this study still remains the largest to utilize the donor-recipient model to assess the impact of donor BMI, while controlling for recipient BMI, on IVF outcomes including clinical pregnancy and live birth rates. These findings provide a foundation for future research with larger numbers. Future larger studies may allow for the application of ROC curves based on donor BMI and clinical pregnancy and live birth rates, which could be used to determine an optimal cutpoint at which to consider limiting donors. An ideal future study would be an IRB approved randomized controlled trial using oocyte donors of variable BMI with normoweight recipients in order to compare IVF outcomes. However, given the significant emotional and financial burden of recipients undergoing oocyte donation cycles and desire to use the donor of their selection, enrollment and willingness to undergoing randomization may be a limiting factor. Since this study was completed at a single IVF program, some results may be reflective of treatment protocols and embryology laboratory techniques specific to our program. Future investigation should further explore the impact of small fluctuations in BMI on reproductive outcomes. A particularly intriguing future application of this study’s model would be to assess the association of
preconception weight loss on these same outcomes, and to investigate if the negative association of obesity on oocyte quality may be reversed with weight loss. How or if the findings of this study apply to women not undergoing IVF remains uncertain. Moreover, these data should not be interpreted to mean that all oocyte donors should be restricted to a BMI of less than 21.2 kg/m².

In summary, following simultaneous adjustments for oocyte donor and recipient BMI, we observed that increasing oocyte donor BMI is associated with worse IVF outcomes in donor-recipient IVF cycles, specifically a lower likelihood of clinical pregnancy and live birth. These findings imply that the negative impact of increasing BMI on IVF outcomes may occur at the level of the oocyte prior to fertilization. These observations are among the first in human studies to support the findings of prior animal studies, and warrant future investigation.

Supplementary data
Supplementary data are available at https://humrep.oxfordjournals.org/.

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Conflict of interest
None declared.

References
Barton SE, Missmer SA, Ashby RK, Ginsburg ES. Multivariate analysis of the association between oocyte donor characteristics, including basal follicle stimulating hormone (FSH) and age, and IVF cycle outcomes. Fertil Steril 2010;94:1292–1295.


Robker RL. Evidence that obesity alters the quality of oocytes and embryos. Pathophysiology 2008;15:115–121.


