Effect of Obesity on Oocyte and Embryo Quality in Women Undergoing In Vitro Fertilization

Divya K. Shah, MD, Stacey A. Missmer, ScD, Katharine F. Berry, MA, Catherine Racowsky, PhD, and Elizabeth S. Ginsburg, MD

OBJECTIVE: To estimate the effect of body mass index (BMI) on oocyte and embryo parameters and cycle outcomes in women undergoing in vitro fertilization (IVF).

METHODS: We evaluated a retrospective cohort of 1,721 women undergoing a first IVF cycle with fresh, autologous embryos between 2007 and 2010 in an academic infertility practice. Main outcome measures included number of mature and normally fertilized oocytes, embryo morphology, estradiol on the day of human chorionic gonadotropin administration, clinical pregnancy, spontaneous abortion, and live birth. We performed multivariable analyses, adjusting for potential confounders, including age at cycle start, infertility diagnosis, type of stimulation, total gonadotropin dose, use of intracytoplasmic sperm injection, and number of embryos transferred.

RESULTS: Compared with women of normal BMI, women with class II (BMI 35–39.9) and III (BMI 40 or higher) obesity had fewer normally fertilized oocytes (9.3 compared with 7.6 and 7.7, \( P < .03 \)) and lower estradiol levels (2,047 pg/mL compared with 1,498 and 1,361, \( P < .001 \)) adjusting for age and despite similar numbers of mature oocytes. Odds of clinical pregnancy (odds ratio [OR] 0.50, 95% confidence interval [CI] 0.31–0.82) and live birth (OR 0.51, 95% CI 0.29–0.87) were 50% lower in women with class III obesity as compared with women of normal BMI.

CONCLUSION: Obesity was associated with fewer normally fertilized oocytes, lower estradiol levels, and lower pregnancy and live birth rates. Infertile women requiring IVF should be encouraged to maintain a normal weight during treatment.

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LEVEL OF EVIDENCE: II

The increasing prevalence of obesity among children and adolescents has resulted in higher numbers of overweight and obese adults of reproductive age. The deleterious effects of obesity on spontaneous reproduction are well recognized, although the literature on obesity and assisted reproductive technology outcome remains heterogeneous and inconsistent. A 2007 review concluded that overweight and obese women with body mass indexes (BMI) 25 or greater have lower pregnancy rates after in vitro fertilization (IVF), require higher doses of gonadotropins to achieve sufficient ovarian response, and have higher miscarriage rates; however, the authors concluded that there was insufficient evidence regarding the effect of BMI on cycle cancellation, oocyte recovery, and live birth.

Little is known regarding the mechanisms by which obesity exerts its negative effect on reproductive outcome. Prior studies in women using donor oocytes have been inconsistent with most showing no change in pregnancy rate among obese recipients, but with others demonstrating a subtle decrease in the rate of ongoing pregnancy with increasing recipient BMI. Additionally, most studies exploring the effect of obesity on infertility have focused exclusively on clinical outcomes such as pregnancy rate or im-

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plantation rate rather than on oocyte or embryo quality, aspects of reproductive biology that are uniquely observable in the IVF population. We hypothesized that higher female BMI is associated with a reduced response to gonadotropins, fewer and poorer quality oocytes and embryos, and correspondingly lower pregnancy and delivery rates in women undergoing IVF.

MATERIALS AND METHODS

We conducted a retrospective cohort study of all women undergoing their first nondonor IVF or IVF with intracytoplasmic sperm injection cycle at Brigham and Women’s Hospital between January 2007 and December 2009. Birth outcomes from this patient population were followed through September 2010. Cycle information was obtained from Brigham and Women’s Hospital clinical IVF database and supplemented with review of patients’ medical records. Delivery data were obtained through direct written or phone communication with patients. Donor oocyte, gestational carrier cycles, cycles in which all embryos were cryopreserved without transfer, and cryopreserved embryo transfer cycles were excluded from the study population. Our standard time for embryo transfer is day 3 after oocyte retrieval based on our experience with increased rates of monochorionic twinning after transfer on day 5.11 The few patients undergoing day 5 transfers within the study period were excluded from the analysis, because the majority were cases of preimplantation genetic diagnosis. The study was approved by the Partners Healthcare institutional review board.

Body mass index was calculated as weight in kilograms over height in meters squared based on anthropometric measurements obtained at the first consultation visit. Based on World Health Organization cut points, BMI was categorized as underweight (18.4 or less), normal weight (18.5–24.9), overweight (25.0–29.9), or obese (30.0 or greater), which was further classified as class I (30.0–34.9), class II (35.0–39.9), and class III (40.0 or greater). Normal-weight women were used as the referent population for all comparisons.

Age at cycle start was categorized as younger than 35, 35–37, 38–40, 41–42, and older than 42 years according to Centers for Disease Control and Prevention and Society for Assisted Reproductive Technology cut points. Race was classified by the providing physician or nurse as white, African American, Hispanic, Asian, or Native American. Primary etiology of infertility and type of IVF stimulation were documented by the providing physician. Given the higher prevalence of polycystic ovary syndrome (PCOS) in obese women, PCOS was taken into consideration when stratifying women by primary infertility diagnosis (PCOS, male factor with no PCOS, female factor with no male factor or PCOS, and unexplained). The diagnosis of PCOS was based on the Rotterdam criteria and required two of the following three signs or symptoms: irregular or absent ovulation, clinical or biochemical signs of hyperandrogenism, and enlarged ovaries (more than 10 mL in volume), each containing at least 12 follicles under 10 mm in diameter.12 Stimulation regimens included: down-regulation protocols using gonadotropin-releasing hormone agonists,13 protocols using gonadotropin-releasing hormone antagonists,14 and poor responder protocols using low-dose gonadotropin-releasing hormone agonist flare or estradiol priming.15–17 Other variables included number of embryos transferred (categorized as 1, 2, 3, 4, and 5+), total gonadotropin dose (international units of follicle-stimulating hormone), and whether intracytoplasmic sperm injection was used.

Estradiol levels were recorded on the day of human chorionic gonadotropin administration. Oocytes were classified as germinal vesicle, metaphase I, metaphase II, or degenerated. At the fertilization check, oocytes were enumerated as normally fertilized (two pronuclei) or as having one pronuclei or three pronuclei. The quality of embryos was assessed morphologically on day 3 based on standard parameters, including cell number, degree of fragmentation, and cell symmetry.18 Percent embryo fragmentation was categorized as low (less than 10% fragmentation), moderate (10–25% fragmentation), or severe (greater than 25% fragmentation). Blastomere symmetry was described as high (perfect symmetry of all cells of the embryo), moderate (slight asymmetry), or low (severe asymmetry). Embryos with the highest implantation rates have eight cells, less than 10% fragmentation, and blastomeres of equal size and shape (ie, perfect symmetry).19 The number of embryos transferred was based on patient age and embryo quality as per the national guidelines of the Society for Assisted Reproductive Technologies.

The cancellation rate included women who began IVF stimulation with gonadotropins but did not undergo oocyte retrieval. Failed fertilization was defined as a lack of fertilization in a cycle with at least one mature oocyte. Clinical pregnancy denoted the presence of an intrauterine gestational sac on ultrasound examination and was expressed per cycle start as well as per embryo transfer. Spontaneous abortion was defined as the presence of an intrauterine gestational sac but no subsequent live birth.
Live birth was defined as the birth of a neonate at or beyond 24 weeks of gestation expressed per cycle start (first day of gonadotropin administration) and per embryo transfer.

We performed multivariable analyses, described in detail subsequently, adjusting for potential confounders, including the woman’s age at cycle start, infertility diagnosis, type of stimulation protocol, total dose of follicle-stimulating hormone administered, use of intracytoplasmic sperm injection, and number of embryos transferred. Other than age, which was included a priori, only those variables that resulted in a greater than 10% change in effect size of the BMI parameter estimates were identified as confounders and retained in the final models. Based on these criteria, only woman’s age at cycle start was included in the final regression models.

Analyses were performed using Statistical Analysis Software 9.1. Estradiol levels on the day of human chorionic gonadotropin administration were expressed as multivariable adjusted means with 95% confidence intervals (CIs) calculated using the least squares method. Multivariable adjusted Poisson regression was used to calculate the expected mean number of oocytes and embryos with 95% CI. Poisson regression was also used to examine the relation between BMI and markers of embryo morphology while adjusting for potential confounders. Multivariable-adjusted logistic regression models were used to estimate the association between BMI and dichotomous clinical outcomes such as failed fertilization, clinical pregnancy, and live birth. Results of the logistic regression analyses were expressed as adjusted odds ratios (ORs) with 95% CI using normal-weight women as the referent. To test for linear trend, models were run using an ordinal exposure, defined as the median BMI in each category. Effect modification was evaluated by comparing the likelihood ratios for the model with both main effects and interaction terms to the model with main effects only.

All P values were two-sided, and statistical significance was defined as P < 0.05. Graphs were produced using restricted cubic regression splines with knots specified at BMI cut points of 18.5, 24.9, 29.9, and 34.9.

RESULTS
A total of 1,721 women comprised the study population with each woman contributing a single IVF cycle to the analysis. Twenty percent of women were overweight and another 18% were obese with a 5% prevalence of class III obesity (Table 1). The mean age of the population at cycle start was 35.9 years (standard deviation 4.3, range 20.7–45.7 years). A majority of the study population was white followed

### Table 1. Characteristics by Body Mass Index of 1,721 Women Undergoing Their First In Vitro Fertilization Cycle

<table>
<thead>
<tr>
<th></th>
<th>Less Than 18.5 (n=47)</th>
<th>18.5–24.9 (n=1,023)</th>
<th>25–29.9 (n=341)</th>
<th>30–34.9 (n=145)</th>
<th>35–39.9 (n=79)</th>
<th>40 or Greater (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>34.9±4.5</td>
<td>35.8±4.2</td>
<td>36.2±4.4</td>
<td>36.1±4.6</td>
<td>36.4±4.4</td>
<td>35.5±4.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.7±0.7</td>
<td>21.9±1.7</td>
<td>27.1±1.4</td>
<td>32.3±1.4</td>
<td>37.4±1.3</td>
<td>44.4±3.7</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29 (72.5)</td>
<td>614 (79.5)</td>
<td>216 (81.5)</td>
<td>83 (78.3)</td>
<td>42 (70.0)</td>
<td>60 (81.1)</td>
</tr>
<tr>
<td>African American</td>
<td>0 (0.0)</td>
<td>24 (3.1)</td>
<td>25 (9.4)</td>
<td>13 (12.3)</td>
<td>12 (20.0)</td>
<td>11 (14.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (12.5)</td>
<td>94 (12.2)</td>
<td>14 (5.3)</td>
<td>7 (6.6)</td>
<td>3 (5.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Infertility diagnosis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>0 (0.0)</td>
<td>51 (5.0)</td>
<td>22 (6.5)</td>
<td>17 (11.9)</td>
<td>12 (15.2)</td>
<td>24 (27.9)</td>
</tr>
<tr>
<td>Male factor</td>
<td>12 (25.5)</td>
<td>290 (28.4)</td>
<td>100 (29.6)</td>
<td>47 (32.9)</td>
<td>22 (27.8)</td>
<td>23 (26.7)</td>
</tr>
<tr>
<td>Other female factor</td>
<td>20 (42.6)</td>
<td>416 (40.7)</td>
<td>143 (42.3)</td>
<td>49 (34.3)</td>
<td>35 (44.3)</td>
<td>26 (30.2)</td>
</tr>
<tr>
<td>Unexplained</td>
<td>15 (31.9)</td>
<td>264 (25.9)</td>
<td>73 (21.6)</td>
<td>30 (21.0)</td>
<td>10 (12.7)</td>
<td>13 (15.1)</td>
</tr>
<tr>
<td>Stimulation type†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Downregulation</td>
<td>36 (76.6)</td>
<td>756 (73.9)</td>
<td>254 (74.5)</td>
<td>107 (73.8)</td>
<td>56 (70.9)</td>
<td>64 (74.4)</td>
</tr>
<tr>
<td>Antagonist</td>
<td>2 (4.3)</td>
<td>90 (8.8)</td>
<td>33 (9.7)</td>
<td>19 (13.1)</td>
<td>4 (5.1)</td>
<td>9 (10.5)</td>
</tr>
<tr>
<td>Poor responder</td>
<td>9 (19.1)</td>
<td>177 (17.3)</td>
<td>54 (15.8)</td>
<td>19 (13.1)</td>
<td>19 (24.1)</td>
<td>13 (15.1)</td>
</tr>
<tr>
<td>Total FSH (international units)</td>
<td>3,208±2,090</td>
<td>3,493±2,173</td>
<td>3,89±2,085</td>
<td>3,805±2,224</td>
<td>4,353±2,450</td>
<td>3,884±1,820</td>
</tr>
</tbody>
</table>

BMI, body mass index; PCOS, polycystic ovarian syndrome; FSH, follicle-stimulating hormone.

Data are mean±standard deviation or n (%).

* Percentages may not sum to 100 as a result of other races or missing values.
† Numbers may not sum to the total sample size as a result of missing values.
‡ Downregulation=leutal gonadotropin-releasing hormone agonist protocols; poor responder=low-dose gonadotropin-releasing hormone agonist flare or estradiol patch priming protocols.
by 9% Asian and 6% African American. The prevalence of obesity was highest among African Americans (42%) and lowest among Asians (9%). Approximately 74% of women were stimulated with downregulation protocols, with antagonist and poor responder protocols used in the remaining 26%. The prevalence of PCOS increased with BMI, reaching 28% in morbidly obese women. Among women with normal BMI who started a cycle, the mean age was 35.8 years, 43% had a clinical pregnancy, and 34% had a live birth (data not shown).

Compared with women with low normal BMI, those with class I, II, and III obesity had significantly lower estradiol levels on the day of human chorionic gonadotropin administration (2,047 pg/mL compared with 1,756, 1,498, and 1,360, respectively, all two-tailed P<0.002). Class II and III obese women also had 18% and 17% fewer two pronuclei embryos than the normal referent population (9.3 compared with 7.6 and 7.7, P<0.03) (Table 2). Adjusting for infertility diagnosis (including presence of PCOS), total gonadotropin dose, or the type of stimulation protocol did not appreciably alter these results. None of the embryo morphology characteristics assessed differed across BMI categories.

A U-shaped association was observed between BMI and odds of failed fertilization (Table 3). Odds of failed fertilization appeared highest at both extremes of BMI; underweight women (OR 2.20, 95% CI 0.64–7.53) and those with class III obesity (OR 1.84, 95% CI 0.70–4.86) each had twice the odds of failed fertilization as the normal-weight referent. However, CIs were wide, likely as a result of small sample sizes within these extreme exposure categories.

The odds of clinical pregnancy were 33%, 44%, and 50% lower among women with class I, II, and III obesity, respectively, as compared with the normal referent population (Table 3). Underweight women also had 42% lower odds of clinical pregnancy, although the association was not statistically significant (95% CI 0.31–1.08). When depicted graphically using a cubic regression spline, an inverse U-shaped association was observed between BMI and PCOS, among women with normal BMI who started a cycle. The prevalence of PCOS increased with BMI, reaching 33% among underweight women, 44% among overweight women, and 50% lower among women with class I, II, and III obesity.

Table 2. Association Between Body Mass Index and Oocyte and Embryo Characteristics Among 1,721 Women Undergoing Their First In Vitro Fertilization Cycle*

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>No. of Total Oocytes†</th>
<th>No. of MII Oocytes†</th>
<th>No. of 2PN Embryos†</th>
<th>Embryo Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5 (n=47)</td>
<td>15.1 (12.7–18.0)</td>
<td>11.9 (9.9–14.3)</td>
<td>9.0 (7.2–11.2)</td>
<td>0.66 (0.44–1.00)</td>
</tr>
<tr>
<td>18.5–24.9 (n=1,023)</td>
<td>15.4 (13.0–18.2)</td>
<td>12.7 (10.8–15.1)</td>
<td>9.3 (7.4–11.5)</td>
<td>1.11 (0.82–1.48)</td>
</tr>
<tr>
<td>25–29.9 (n=341)</td>
<td>16.3 (15.1–17.6)</td>
<td>13.5 (12.5–14.6)</td>
<td>9.8 (9.9–10.7)</td>
<td>1.10 (0.82–1.32)</td>
</tr>
<tr>
<td>30–34.9 (n=145)</td>
<td>15.4 (13.8–17.1)</td>
<td>13.0 (11.6–14.6)</td>
<td>9.3 (8.0–10.7)</td>
<td>0.99 (0.79–1.23)</td>
</tr>
<tr>
<td>35–39.9 (n=79)</td>
<td>13.3 (11.4–15.4)</td>
<td>11.3 (9.7–13.2)</td>
<td>7.6 (6.4–9.0)</td>
<td>0.95 (0.75–1.27)</td>
</tr>
<tr>
<td>40 or Greater (n=86)</td>
<td>14.2 (12.3–16.4)</td>
<td>11.1 (9.5–13.0)</td>
<td>7.7 (6.4–9.1)</td>
<td>0.80 (0.59–1.08)</td>
</tr>
</tbody>
</table>

* All Poisson regression models are adjusted for age at cycle start (younger than 35, 35–37, 38–40, 41–42, older than 42 years).
† Expressed per cycle start.
‡ Results are expressed as adjusted relative risks (95% confidence interval).
§ Results are expressed as adjusted mean (95% confidence interval).

Table 3. Association Between Body Mass Index and Cycle Outcomes Among 1,721 Women Undergoing Their First In Vitro Fertilization Cycle*

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Failed Fertilization</th>
<th>Clinical Pregnancy</th>
<th>Spontaneous Abortion</th>
<th>Live Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5 (n=47)</td>
<td>2.20 (0.64–7.53)</td>
<td>1.00 (Referent)</td>
<td>0.29 (0.04–2.30)</td>
<td>0.76 (0.40–1.46)</td>
</tr>
<tr>
<td>18.5–24.9 (n=1,023)</td>
<td>1.00 (Referent)</td>
<td>0.90 (0.45–1.79)</td>
<td>0.91 (0.71–1.77)</td>
<td>0.76 (0.40–1.46)</td>
</tr>
<tr>
<td>25–29.9 (n=341)</td>
<td>1.04 (0.40–2.70)</td>
<td>0.95 (0.45–1.79)</td>
<td>0.97 (0.46–2.08)</td>
<td>0.75 (0.24–2.31)</td>
</tr>
<tr>
<td>30–34.9 (n=145)</td>
<td>1.58 (0.54–4.59)</td>
<td>0.94 (0.45–2.00)</td>
<td>0.75 (0.87–0.95)</td>
<td>0.66 (0.38–1.14)</td>
</tr>
<tr>
<td>35–39.9 (n=79)</td>
<td>1.84 (0.70–4.86)</td>
<td>0.87 (0.38–2.05)</td>
<td>0.70 (0.34–1.45)</td>
<td>0.51 (0.29–0.87)</td>
</tr>
<tr>
<td>40 or Greater (n=86)</td>
<td>1.65 (0.55–4.86)</td>
<td>0.89 (0.39–2.05)</td>
<td>0.70 (0.34–1.45)</td>
<td>0.51 (0.29–0.87)</td>
</tr>
</tbody>
</table>

* All Poisson regression models are adjusted for age at cycle start (younger than 35, 35–37, 38–40, 41–42, older than 42 years).
* Expresses as adjusted odds ratio (95% confidence intervals).
"Results are expressed as adjusted odds ratio (95% confidence intervals).
"Adjusted for other potential confounders including infertility diagnosis, type of stimulation protocol, total dose of follicle-stimulating hormone, the use of intracytoplasmic sperm injection, and the number of embryos transferred did not change the risk estimate by more than 10% and these variables were therefore not included in the final models."
Association between BMI and clinical pregnancy was seen (Fig. 1). No significant associations between BMI and the odds of spontaneous abortion were observed. All results remained consistent when analyses were conducted per cycle start (Table 3) and per embryo transfer (data not shown).

Women with class III obesity (BMI 40 or greater) also had a 49% lower odds of live birth (OR 0.51, 95% CI 0.29–0.87) as compared with those of normal weight (Table 3). A nonsignificant decrease in the odds of live birth was noted both among underweight women as well as women with class I or class II obesity, respectively (OR 0.76, 95% CI 0.40–1.46; OR 0.73, 95% CI 0.49–1.09; OR 0.66, 95% CI 0.38–1.14), suggesting an inverse U-shaped association between BMI and live birth (Fig. 2). The results were unchanged when data were analyzed per embryo transfer rather than per initiated cycle (data not shown). Additionally, both clinical pregnancy and live birth rates remained unchanged when the data were stratified based on age (all P values >.33 for tests for heterogeneity, data not shown).

DISCUSSION
Within a large cohort of infertile women undergoing IVF, we observed that female obesity is associated with fewer embryos, lower clinical pregnancy rates, and lower live birth rates compared with women of normal BMI. Odds of clinical pregnancy and live birth were up to 50% lower in women with class III obesity as compared with normal-weight control participants.

The existing literature is inconsistent as to whether obesity affects reproduction through an ovarian or uterine mechanism. A few studies have revealed small, nonsignificant decreases in pregnancy rates in obese recipients of donor eggs, thereby suggesting a subtle extraovarian mechanism. However, sample sizes were likely too low to identify a true effect. In contrast, a large analysis of 45,163 cycles from the Society for Assisted Reproductive Technology database found a significant inverse association between obesity and pregnancy rate with the use of autologous oocytes but no difference with the use of donor oocytes, suggesting an adverse effect of obesity on oocyte quality or number. In a small study, being overweight did not compromise pregnancy rates compared with normal-weight control participants when high-quality autologous embryos were transferred, further supporting the idea that the detrimental effect of body weight occurs at the level of the oocyte or embryo rather than the uterus. Recently published literature reviews of obesity and fertility suggest that the effect is likely mediated by molecular mechanisms acting at multiple levels of the reproductive process, including the oocyte, embryo, and endometrium.

Our data support an effect of female BMI on IVF outcome at the level of the ovary, because obese women had lower estradiol levels and fewer normally fertilized oocytes. We hypothesize that this may be the result of a decreased response to gonadotropins because adjusting for total gonadotropin dose did not appreciably change the result. In contrast, we found no association between obesity and morphologic characteristics of the embryo. This could either suggest that obesity may exert an effect on reproduction independent of embryo quality or the manner in which obesity affects embryo quality cannot be ascertained by morphologic grading of embryos. The decrease in pregnancy and live birth rates noted in obese women remained consistent regardless of whether data were analyzed per cycle started or per embryo transfer, suggesting that the negative effect of obesity on pregnancy also persists after the time of oocyte and embryo development.

We saw no difference in spontaneous abortion rates among BMI groups. Conflicting literature exists regarding the effect of obesity on first-trimester miscarriage, particularly in assisted reproductive technology cycles. A recent meta-analysis of 16 studies found
a higher odds of miscarriage among all women with a BMI 25 or greater but no association between BMI and spontaneous abortion when the analysis was restricted to women who had undergone IVF with intracytoplasmic sperm injection. A majority of the included studies, however, do not control for maternal age, a significant confounder in the relationship between BMI and spontaneous abortion.

Oocyte quality has only been directly assessed in four studies, each of which demonstrated some degree of reduction in quality, maturity, or size of oocytes with elevated BMI. There are equally few studies evaluating embryo quality in obese women, two of which suggested an adverse effect in women with a BMI 30 or greater and a third that did not. Although the large 2006 analysis by Dokras et al adjusted for age and presence of PCOS, the remainder of these studies were limited by small sample size, the relatively small proportion of obese women in the samples, and failure to adjust for confounders or were biased by including data contributed by the same woman across multiple cycle attempts.

In addition to confirming the adverse effect of obesity on female reproduction, our data also suggest lower odds of fertilization, pregnancy, and live birth among underweight women, although the number of women in this group was small and the associations were not statistically significant. Other epidemiologic studies examining the relation between BMI and the risk of ovulatory infertility have observed a similar U-shaped distribution with increased risk noted at both ends of the BMI spectrum.

The present study expands the existing body of literature in several ways. First, this study examines the effect of obesity on oocyte and embryo characteristics in a single IVF cohort. Second, the large sample size enabled construction of a valid multivariable model that accounted for potential confounders such as female age, infertility diagnosis, presence of PCOS, type of stimulation protocol, total gonadotropin dose, use of intracytoplasmic sperm injection, and the number of embryos transferred. Finally, because our hospital-based IVF program serves as a tertiary referral center for women with medical comorbidities including obesity, our study cohort contains the largest percentage of obese (18%) and morbidly obese (5%) women in the literature to date.

Several limitations are important to consider when interpreting our observations. First, despite the size and prevalence of obesity in our study population, we recognize that this study is underpowered to detect what may be a clinically important but mathematically small difference in live birth rate between women with class I and II obesity and normal-weight women. Because our routine collection of BMI data began in 2007, we could not increase our sample size. Our study nonetheless represents a single IVF cohort and uses the woman rather than the IVF cycle as the unit of measurement so that multiple cycles contributed by the same woman did not artificially increase the sample size.

Second, although this is one of the few studies to adjust for confounders when examining BMI and reproductive outcome, we lacked data for variables such as female smoking, weight of the male partner, medical comorbidities, or other lifestyle choices that may be correlated with BMI and associated with cycle outcomes. Because nearly 80% of our study population was white, the potential effect of race on BMI and IVF cycle outcome could not be assessed. Therefore, some residual confounding may remain.

Third, because our analysis was restricted to a single cycle per woman with height and weight measured only once, we cannot comment on the effect of changes in weight over time, a key unresolved clinical question regarding the benefit of postponing cycle initiation to allow for weight loss. Although the results of this study therefore cannot be used to counsel
women as to whether IVF outcomes improve with weight loss, these data add to the growing body of literature suggesting that the critical public health message—for assisted reproductive technology response as well as obstetric outcomes—is that it is always advisable that women maintain a normal weight before and while attempting to conceive. All obese patients in our practice undergo consultation with maternal–fetal medicine and are strongly encouraged to have bariatric surgery consultations before proceeding with IVF.

In conclusion, female obesity is associated with fewer embryos and lower live birth rates. This study suggests that obesity may affect reproduction both at the level of the ovary as well as after embryo transfer. The relatively small numbers of obese women undergoing IVF at any one institution complicates the large-scale study of reproductive outcomes related to BMI. Cooperative, multicenter investigations are needed to elucidate the biologic mechanisms through which BMI affects reproductive outcomes. Infertile women should be counseled that high, and possibly also low, extremes of BMI may negatively affect their likelihood of having a child from IVF treatment.

REFERENCES


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