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# Neutral effect of body mass index on implantation rate after frozen-thawed blastocyst transfer

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**Objective:** To examine the effects of body mass index (BMI) on implantation rate after uniform protocol frozen-thawed blastocyst transfer in women with a homogenous uterine environment.
**Design:** Retrospective cohort study.
**Setting:** Single IVF clinic at a large academic institution.
**Patient(s):** Four hundred sixty-one infertile women treated at a large academic institution from January 2007 to January 2014.
**Intervention(s):** All women underwent standardized slow frozen-thawed blastocyst transfers with good-quality day 5–6 embryos, following an identical hormonal uterine preparation, with comparison groups divided according to BMI category: underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), and obese ($\geq$30.0 kg/m$^2$).
**Main Outcome Measure(s):** Implantation rate.
**Result(s):** There were no statistically significant differences identified when comparing implantation rates among the four BMI cohorts. The implantation rate was 38.2% in normal weight patients, 41.7% in underweight patients, 45.1% in overweight patients, and 34.7% in obese patients. Adjusted odds ratios (OR) demonstrated no association between the main outcome, implantation rate, and BMI. Compared with the normal weight patients, the adjusted OR of implantation was 1.70 (95% confidence interval [CI], 0.40–7.72) for underweight patients, 1.61 (95% CI, 0.97–2.68) for overweight patients, and 0.92 (95% CI, 0.49–1.72) for obese patients. Secondary outcomes, including rates of miscarriage, clinical pregnancy, ongoing pregnancy, and live birth, were not significantly different between cohorts. While powered to detect a 16% difference between overweight and normal weight women, the study was underpowered to detect differences in the underweight and obese women, and no definitive conclusions can be drawn for these small cohorts. Patients with transfers that required the longest amount of time, greater than 200 seconds, had the highest average BMI of 27.5 kg/m$^2$.
**Conclusion(s):** Under highly controlled circumstances across 7 years of data from a single institution, using a uniform uterine preparation, following a precise transfer technique with high-quality day 5–6 slow frozen-thawed blastocysts, a BMI in the overweight range of 25–29.9 kg/m$^2$ is not associated with a poorer implantation rate or live-birth rate, nor is it associated with an increased risk of miscarriage when compared with a normal BMI range. The increased length of time required during transfer for women with higher BMI suggests body habitus may contribute to difficult transfers, although this may not translate into poorer implantation rates. By using a standardized protocol for slow freezing and thawing of embryos, using identical hormonal preparation and a uniform ET protocol, a homogenous uterine environment was created in this carefully selected cohort of women, thereby minimizing confounders and uniquely highlighting the neutral effect of overweight BMI on implantation rate. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
**Key Words:** Frozen-thawed embryo transfer, body mass index, implantation rate

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In the United States, nearly 25% of women in their reproductive years, ages 20–44, are overweight, and approximately 23% are obese (1, 2). As the proportion of overweight and obese women continues to increase, there has been mounting evidence that an elevated body mass index (BMI) contributes to poorer obstetric outcomes, including increased risk of miscarriage, preterm birth, gestational diabetes, gestational hypertension, and preeclampsia (3–7). Obesity has also been linked to increased risk of infertility as it has been shown to negatively affect ovulatory status and impair endometrial receptivity, leading many reproductive-age women with elevated BMIs to seek infertility care (8–12).

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The impact of elevated BMI on infertility outcomes is a growing area of interest and remains somewhat controversial, with large reviews demonstrating conflicting data (2, 13–16). The majority of studies include fresh ETs, with limited data available on frozen-thawed blastocyst transfers.

A recent retrospective review of 4,600 patients undergoing fresh ETs demonstrated poorer implantation rates, clinical pregnancy rates, and live-birth rates for obese women with BMI > 30 kg/$m^2$, and outcomes deteriorated with increasing BMI (14). A review of over 45,000 cycles from the Society for Assisted Reproductive Technology (SART) database, including fresh cycles (>80% of the study population) and frozen cycles, found that increasing BMI was associated with an increased risk of failure to achieve clinical pregnancy and failure to achieve a live birth (13). Outcomes were improved with the use of donor rather than autologous oocytes (13). Similarly, a review of 494,097 fresh cycles from the National Assisted Reproductive Technology Surveillance System confirmed that obesity increases the risk of miscarriage (adjusted relative risk, 1.23; 95% confidence interval [CI], 1.20–1.26) and has a negative impact on all cycle outcomes, including live-birth rate (3).

Because of the concern of obesity's impact on IVF cycle outcomes, some researchers and clinicians have recommended prohibiting IVF in women with a BMI above a certain threshold, ranging from 25 to 40 kg/$m^2$ (17, 18).

However, conflicting data exist on the association of BMI with IVF outcomes. A 2007 systematic review found there was a lack of sufficient data to support limiting IVF access for women over a specific BMI threshold. A subsequent updated 2011 systematic review including 14 studies concluded that IVF outcomes were only marginally affected by having a BMI in the overweight or obese range (19). This review reported a small association between overweight BMI and reduced live-birth rate with an OR of 0.90 (95% CI, 0.82–1.0), concluding that overweight women achieve reasonable success with IVF compared with normal weight women (19). While a study of 466 women undergoing hormonally substituted frozen-thawed ET (FET) demonstrated increased miscarriage rates in both underweight and obese women, a subsequent study including 318 hormonally substituted FET cycles, conducted by the same group, demonstrated only a minimal decrease in live-birth rate for women with elevated BMI (OR, 0.96; 95% CI, 0.92–0.99) (15, 16).

Thus, the immediate and long-term effects of BMI on FET cycles remain unclear. To that end, this study sought to primarily investigate the potential impact of BMI on implantation rate, particularly given the evidence that higher BMI may negatively affect endometrial receptivity (11, 13). We hypothesized that, among slow frozen-thawed blastocyst transfers in a group of women undergoing a universal uterine preparation over the course of 7 years within a single academic institution, elevated BMI would be associated with lower implantation rate. By creating a homogenous uterine environment with a uniform endometrial preparation, following a uniform slow freeze cryopreservation and thaw protocol and a uniform transfer technique, we controlled for a variety of confounders in an effort to more clearly isolate the potential effect of BMI.

## MATERIALS AND METHODS

Following study approval from the Partners Institutional Review Board, data from all consecutive frozen-thawed blastocyst transfer cycles conducted at the Massachusetts General Fertility Center between January 31, 2007, and January 31, 2014, were retrospectively reviewed. Of 590 frozen-thawed blastocyst transfer cycles initiated in this 7-year period, 13 were excluded due to cycle cancellation (embryos did not survive the thaw), two for unknown cycle outcomes, and six for incomplete cycle information. Only initial FET cycles were included, yielding 461 cycles of women undergoing cryopreserved blastocyst transfers from autologous or donor oocytes during the study period. After initial oocyte retrieval, all patients preserved day 5 or 6 blastocysts via a slow-freezing protocol.

### Slow-Freeze Cryopreservation

The slow-freeze cryopreservation technique used a phosphate-buffered saline–based medium with HSA protein supplementation. A two-step freeze protocol using glycerol and sucrose as cryoprotectants was used for blastocyst cryopreservation. First, a 10-minute incubation was performed in 5% glycerol, followed by a 5-minute incubation in a cryoprotectant solution of 10% glycerol and 0.2 mol/L sucrose solution. Individual blastocysts were loaded into Nunc cryovials, which contained 0.3 mL of cryoprotectant solution (10% glycerol/0.2 mol/L sucrose). A controlled rate Planer freezer was used to cool the vials at a rate of −2°C/minute until −7°C. After a 10-minute hold period, the vials were seeded. They were further cooled at a rate of −0.3°C/minute until −37°C. The cryovials were then plunged into liquid nitrogen as the final step in cryopreservation.

### Embryo Thaw

For blastocyst thawing, cryovials were removed from the cryotank and kept at room temperature for 1 minute. They were then immersed into a 30°C water bath for 2 minutes, followed by a four-step rehydration protocol. Embryos were first placed into a solution of 10% glycerol and 0.2 mol/L sucrose for 1 minute, followed by 5% glycerol solution for 3 minutes, followed by 0.2 mol/L sucrose solution for 2 minutes, followed by rinsing in the phosphate-buffered saline–based medium. The embryos were then cultured for either 24 hours (if frozen on day 5) or 4–5 hours (if frozen on day 6) in the 5% carbon dioxide incubator to allow for reexpansion.

### Uterine Preparation

Before blastocyst transfer, all women over the 7-year data collection period followed an identical preparatory protocol. Uterine preparation included the following protocol, as previously published: patients underwent pituitary down-regulation with a GnRH-agonist during the oral contraceptive pretreatment, with a baseline ultrasound (US) performed to confirm appropriate suppression, continued until midcycle (20). This was followed by sequential programmed hormone replacement, which included a 0.1 mg $E_2$ patch on days 1–5,