Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors

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Objective: To analyze the reproductive outcome of recipients of donated ova according to their body mass index (BMI).
Design: Twelve-year retrospective cohort analysis.
Setting: Fertility clinics.
Patient(s): 9,587 first cycles of ovum donation with ova from normoweight donors.
Intervention(s): Recipients divided according to their BMI to analyze IVF laboratory and outcome parameters: lean with BMI <20 kg/m^2 (n = 1,458; 15.2%); normoweight with BMI 20–24.9 kg/m^2 (n = 5,706; 59.5%), overweight with BMI 25–29.9 kg/m^2 (n = 1,770; 18.5%), and obese with BMI ≥ 30 kg/m^2 (n = 653; 6.8%).
Main Outcome Measure(s): Implantation, biochemical and clinical pregnancy, miscarriage, and live-birth rates.
Result(s): In vitro fertilization laboratory parameters did not differ according to BMI. However, implantation, pregnancy, clinical pregnancy, twin pregnancy, and live-birth rates were significantly reduced as BMI increased. In the lean, normoweight, overweight, and obese groups, the implantation rate was 40.4%, 39.9%, 38.5%, and 30.9%, clinical pregnancy rate was 56.9%, 55.9%, 54.3%, and 45.3%, and live-birth rate was 38.6%, 37.9%, 34.9%, and 27.7%, respectively. However, clinical miscarriage rates were similar in all the groups.
Conclusion(s): Female obesity impairs the reproductive outcome of ovum donation probably as a result of reduced uterine receptivity. (Fertil Steril® 2013;100:1050–8. ©2013 by American Society for Reproductive Medicine.)
Key Words: Female obesity, live birth, ovum donation, pregnancy, uterus

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Obesity has increased sharply in both developed and developing countries, leading to higher morbidity and mortality rates, social stigmatization, and significant direct and indirect economic burdens on society (1–4). Recent statistics show that 68% of the adult population are overweight (body mass index [BMI] ≥ 25 kg/m^2), and around 36% are obese (BMI ≥ 30 kg/m^2) in the United States (5, 6).

Although the deleterious effect of female obesity on human reproduction was initially a subject of controversy (7), most recent studies have shown that obese women present an increased risk of subfecundity and infertility (8–11) even when they ovulate regularly (12), and they have decreased conception rates (implantation and pregnancy rates) (7). Miscarriage rates and pregnancy complications are also higher in this population (13–15). Poor reproductive outcomes in obese women seem to apply to all modes of conception—natural, ovulation induction, in vitro fertilization–intracytoplasmic sperm injection (IVF-ICSI), and ovum donation (16–21)—and this is especially the case in women with higher BMIs, central distribution of fat, or an association with polycystic ovary syndrome (PCOS) (22–24). However, how female

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weight excess affects each component of the reproductive system (oocyte, embryo, and uterus) is not entirely clear, as information regarding this subject is often scarce or obtained from animal models (25–28).

Concerning the endometrium, the first clinical studies performed in humans with the ovum donation model provided conflicting results regarding implantation, pregnancy, and miscarriage rates (29–31), which has lead to a scientific debate (32, 33). More recent research has pointed to a relationship between recipient BMI and poor reproductive outcome that may be mediated by a reduction in uterine receptivity (18, 34, 35). Moreover, gene expression analysis during the window of implantation has revealed endometrial dysregulation in obese women versus normoweight controls, particularly when PCOS is associated (36). However, not all studies have reported similar results (20). Moreover, methodologic problems in patient selection, inadequate description of cases, or the retrospective nature of the scientific design have been frequently being blamed for the lack of consensus on this issue (37, 38).

The aim of the present study was to assess the reproductive outcome in a large sample of well-characterized first-time recipients of donated ova obtained from normoweight donors, according to their BMI, in order to clinically ascertain the association between female obesity and endometrial receptivity.

MATERIALS AND METHODS

Study Population

Our previous study (18) analyzed a database of 2,656 first ovum donation cycles registered during a 4.5-year period in IVI-Valencia. The current analysis uses the same database enlarged to include 9,587 first ovum donation cycles performed between January 1, 2000, and December 31, 2011, in three different settings: IVI Valencia, Madrid, and Barcelona. In both studies, the BMI of the recipients was known, and any recipients with uterine pathologic conditions (submucous or >4 cm intramural fibroids, polyps, adhesions, adenomyosis, or müllerian defects) or a clinical history of recurrent miscarriage (with the exception of cases of known maternal chromosomal abnormality) were excluded. The uterine assessment was routinely performed by two-dimensional vaginal ultrasonography. When a uterine condition was suspected, three-dimensional ultrasound or a hysteroscopy was performed to confirm the diagnosis or treat the condition. Cycles were included in the analysis when oocytes were provided by donors with a BMI <25 kg/m^2; we discarded any older cycles in which overweight donors were accepted for the program. Pregnancies were followed until the time of delivery to determine the live-birth rates (rather than to the 20th week of gestation, as in our previous report).

We divided the 9,587 cycles into four groups according to the BMI (weight /height^2) of the recipient to analyze the IVF laboratory and outcome parameters: lean with BMI <20 kg/m^2 (n = 1,458; 15.2%); normal with BMI 20–24.9 kg/m^2 (n = 5,706; 59.5%), overweight with BMI 25–29.9 kg/m^2 (n = 1,770; 18.5%), and obese with BMI $\geq$ 30 kg/m^2 (n = 653; 6.8%). The study was approved by the institutional review board and the ethics committee.

Ovarian Stimulation in Donors

In Spain, ovum donation is anonymous. Donors must be between 18 and 35 years old, be healthy with no family history of inherited or chromosomal conditions, and have normal gynecologic examination results and a negative screening for infectious diseases. Karyotyping and a psychological examination are routinely performed in our center.

The protocols for ovarian stimulation and oocyte pickup have been described elsewhere (18, 39). In brief, controlled ovarian stimulation (COS) was performed after a long or short protocol. In the long protocol, gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate (Procrin; Abbott) or nafarelin acetate (Synarel; SEID S.A.) was employed for pituitary desensitization at a dosage of 1 mg or 800 μg per day, respectively, from the midluteal phase of the preceding cycle until ovarian quiescence was confirmed by ultrasound after menstruation. The GnRH-agonist dosage was then halved and maintained until the day of human chorionic gonadotropin (hCG) administration.

In the short protocol, a 0.25 mg dose of GnRH antagonist (Cetrotide; Merck-Serono; or Orgalutran; MSD) was given daily from day 6 of COS until the day of hCG administration. Ovarian stimulation was performed using 150–225 IU/day of recombinant follicle-stimulating hormone (Gonal-F; Merck-Serono) or recombinant follicle-stimulating hormone plus human menopausal gonadotropin (hMG) (Menopur; Ferring Pharmaceuticals), according to the woman's age, basal hormone values, ovarian pattern at ultrasound, and BMI. Gonadotropins were administered from day 3 of menstruation. Serial transvaginal ultrasound examinations and serum estradiol (E_2) determinations were initiated on day 5 of COS and were repeated every 48 hours to monitor the ovarian response. We administered hCG (Ovitrelle; Merck-Serono) subcutaneously when at least two leading follicles had reached a mean diameter $\geq$18 mm.

Since 2009, in our short protocol, two ampules (0.2 mg) of the GnRH-agonist triptorelin (Decapeptyl; IpsenPharma) are administered for final oocyte maturation and pickup in many of our donors. This approach is based on the studies showing a 100% reduction in the incidence of ovarian hyperstimulation syndrome and no oocyte quality or pregnancy outcome impairment in comparison with the conventional hCG protocol (40). Transvaginal oocyte retrieval under ultrasound guidance was scheduled 36 hours after hCG or triptorelin administration.

Endometrial Preparation in Recipients

The protocol for endometrial preparation in oocyte recipients has also been described elsewhere (18). In short, pituitary desensitization is achieved by a single intramuscular ampule administration of 3.75 mg of triptorelin (Decapeptyl depot 3.75; Ipsen Pharma) in the midluteal phase of the preceding cycle in recipients with ovarian function. Hormone replacement therapy is initiated after ultrasound