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ARTICLE

High-quality embryos retain their implantation capability in overweight women

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Abstract To assess the effect of obesity on implantation rate, pregnancy rate and course of pregnancy in young women undergoing IVF in whom only high-quality embryos were transferred, a cohort study included women attending the IVF unit in 2006–2007 with favourable parameters to achieve pregnancy (<38 years, fewer than three IVF cycles, transfer of two high-quality embryos), grouped by body mass index (BMI). Of 230 women, 160 had a BMI $\leq$25 kg/m^2 (mean 21.6 ± 2.2) and 73 had BMI >25 kg/m^2 (mean 29.5 ± 3.7). The overweight group had a higher consumption of gonadotrophins during stimulation. There were no between-group differences in treatment protocols, duration of gonadotrophin stimulation, maximal oestradiol concentrations, endometrial thickness and number of oocytes retrieved/fertilized, or in rates of pregnancy (51.3%, 52.1%), implantation (34.5%, 37.5%), multiple pregnancy, and abortion. Rate of gestational diabetes or pregnancy-induced hypertension was higher in the overweight group (23.3%, 8.2%; $P = 0.045$). Within the overweight group, those with multiple pregnancies were at highest risk (31.3%, 6.9%; $P = 0.031$). In conclusion, implantation and pregnancy rates are not compromised in overweight women when high-quality embryos are transferred. However, in overweight women, pregnancy complications remain high, mainly in those with multiple pregnancies.

KEYWORDS: BMI, implantation, IVF, overweight, pregnancy complications

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Introduction

Obesity is associated with impaired reproductive outcome in patients undergoing IVF treatment. Specifically, an increase in cycle cancellation (Spandorfer et al., 2004), decreased implantation and clinical pregnancy rates (Loveland et al., 2001), increased spontaneous abortion rates (Fedorcsak et al., 2004; Wang et al., 2002), lower ongoing pregnancy rates (Loveland et al., 2001) and lower live birth rates (Fedorcsak et al., 2004) have been reported. Suggested mechanisms include a direct adverse effect of overweight or obesity on endometrial receptivity (Metwally et al., 2007a) and a direct or indirect effect on oocyte/embryo quality; the latter, however, is still controversial. Some authors noted a lower number of mature oocytes (Dokras et al., 2006), poorer oocyte quality, lower fertilization rates (Krizanovska et al., 2002; van Swieten et al., 2005) and lower embryo quality (Metwally et al., 2007b) in obese or overweight patients, whereas others failed to support these findings (Bellver et al., 2007; Lashen et al., 1999; Lewis et al., 1990; Nichols et al., 2003; Wang et al., 2000). The relative value of the endometrial factor and of the embryonic factor on impaired implantation in overweight women has not been separately assessed.

The aim of the present study was to further assess the effect of overweight on endometrial receptivity and implantation. To control for the embryo factor, a study population in whom only high-quality embryos were transferred and no other factors known to impair implantation coexisted was selected.

Materials and methods

Patient selection

All IVF cycles performed in the IVF unit of a tertiary university-affiliated medical centre in 2006 and 2007 were retrospectively analysed. Only patients with favourable parameters were included in the study: patient age <38 years, transfer of two high-quality embryos (defined below) and fewer than three previous IVF attempts. Exclusion criteria were any known factor that could affect implantation, such as hydrosalpinx, fibroid uterus and congenital uterine anomaly, and any known factor that could affect the course of pregnancy, such as chronic illness (diabetes, hypertension, autoimmune disease). For patients who met the inclusion criteria and had more than one cycle, only the data for the first cycle were included. The study was approved by the local institutional review board.

Protocol for ovarian stimulation

The gonadotrophin-releasing hormone long protocol consisted of daily injections of Decapeptyl 0.1 mg (Ferring, Germany) or a depot injection of Decapeptyl 3.75 mg at the early follicular or midluteal phase. Down-regulation was confirmed after 13–15 days (no ovarian cysts >18 mm, oestradiol <74 pmol/l) and was followed by gonadotrophin stimulation. The gonadotrophin-releasing hormone short protocol consisted of daily injections of Decapeptyl 0.1 mg starting on day 2 or 3 of the menstruation, followed by gonadotrophin stimulation from day 4 or 5 of menstruation. The antagonist protocol consisted of daily gonadotrophin stimulation from day 3 or 4 of menstruation followed by daily injections of Cetrotide 0.25 mg (Serono, Switzerland) or Orgalutran 0.25 mg (Organon, The Netherlands), from the point at which the leading follicle reached 14 mm to the day of human chorionic gonadotrophin injection. In all treatment protocols, gonadotrophin stimulation consisted of recombinant FSH (Gonal F; Serono; or Puregon; Organon). The choice of protocol for ovarian stimulation was based on patient characteristics or response during previous IVF cycles or ovulation induction if available.

During treatment, the ovarian response was monitored by vaginal ultrasound measurements of follicular growth and serum oestradiol concentration every 1–3 days, starting on day 5 or 6 of stimulation and the FSH dosage was adjusted accordingly. Human chorionic gonadotrophin (Ovitrelle, 250 μg; Serono, Italy) was administered when at least two leading follicles measured 17 mm or more. After retrieval, oocytes were fertilized by standard insemination or intracytoplasmic sperm injection, depending on sperm parameters or previous IVF performance. Embryos were transferred on day 2 or 3. The luteal phase was supported by daily vaginal progesterone (Utrogestan 600 mg/day; Besins International Laboratories, France; or Endometrin, 200 mg/day; Ferring). A serum pregnancy test was performed 12 days after embryo transfer. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with a fetal pole with documented heart rate on ultrasound scan 4 weeks after the embryo transfer.

Embryo quality

Embryos were graded by their morphological appearance under light microscopy at 48 or 72 h after oocyte collection, using the system of Staessen et al. (1992): grade I: even and homogeneous blastomeres without fragmentation; grade II: even and homogeneous blastomeres with <20% fragmentation; grade III: uneven and nonhomogeneous blastomeres with 20–50% fragmentation; grade IV: uneven and nonhomogeneous blastomeres with >50% fragmentation. This study included only cycles in which two top-quality embryos were transferred: two 4-cell grade I embryos for day-2 transfers and two 6–8-cell grade I embryos for day-3 transfers.

Data collection

The following data were collected from the patient files: baseline clinical parameters: patient age, day-3 FSH concentration, cause of infertility, duration of infertility; IVF cycle parameters: cycle number, type of protocol, number of oocytes retrieved, number of mature oocytes, fertilization rate, embryo quality and implantation rate. The following data were prospectively collected by phone questionnaire: course of pregnancy, pregnancy complications, hospitalizations, mode of delivery, delivery complications and infant's birthweight. The patients were divided by BMI for comparison of the findings: group 1: BMI $\leq$25 kg/m^2; group 2: BMI >25 kg/m^2.

Table 1 Clinical parameters: comparison between groups.

Characteristic	*BMI ≤25 kg/m²*	*BMI >25 kg/m²*	*P-value*
No. of patients	160	73	
BMI (kg/m²)	21.6 ± 2.2	29.5 ± 3.7	<0.001
Age (years)	30.7 ± 4.3	31.9 ± 4.5	0.038
IVF cycle number	1.8 ± 1.0	2.4 ± 1.5	0.004
Cause of infertility			0.020
PCOS	14 (8.8)	9 (12.3)	
Male	83 (51.9)	34 (46.6)	
Unexplained	53 (33.1)	17 (23.3)	
Mechanical	5 (3.1)	7 (9.6)	
Combined	5 (3.1)	6 (8.2)	
Primary infertility	77 (48.1)	49 (67.1)	0.007

Values are mean or number (%) unless otherwise stated.
BMI = body mass index; PCOS = polycystic ovary syndrome.

Statistical analysis

Statistical Package for Social Sciences version 15.0 for Windows (SPSS, USA), was used for data management and analysis. The analyses performed included *t*-test for continuous data and chi-squared test for categorical data. Differences were considered significant when *P* was less than 0.05.

Results

During the study period, 2135 IVF cycles were performed in 1020 patients. A total of 233 patients (233 cycles) met the inclusion criteria. Division by BMI yielded 160 patients in group 1 (mean BMI 21.6 ± 2.2 kg/m²) and 73 in group 2 (mean BMI 29.5 ± 3.7 kg/m²). Seventy-five percent of the patients had a BMI 26 kg/m² or less (75th percentile). Within the group of overweight patients ($n = 73$), 18 (24.7%) patients were obese (BMI 30–35 kg/m²) and seven patients (9.6%) were morbidly obese (BMI >35 kg/m²). The patients' characteristics are presented in **Table 1**. The overweight group was characterized by older age, higher incidence of primary infertility and higher IVF cycle number.

The IVF cycle characteristics are presented in **Table 2**. There was no difference between groups in the distribution of treatment protocols, duration of gonadotrophin stimulation, maximal oestradiol concentrations, endometrial thickness and number of oocytes retrieved and fertilized. The overweight group had a higher consumption of gonadotrophin during stimulation. Pregnancy and implantation rates were similar in the two groups. Moreover, mean BMI was similar between pregnant and non-pregnant patients (24.3 ± 4.1 versus 23.7 ± 4.9 kg/m²). On receiver–operating characteristic curve analysis for prediction of pregnancy, BMI was not a significant variable (area under the curve0.567, 0.492–0.641). On multiple logistic regression analysis, with BMI, age, primary versus secondary infertility, treatment protocol and cycle number as predictors of pregnancy, only age was a significant variable (OR0.931, 0.874–0.992, $P = 0.027$).

Table 2 IVF cycle characteristics and outcome.

	BMI ≤25 kg/m²	*BMI >25 kg/m²*
No. of cycles	160	73
Protocol type		
Long	91 (56.9)	36 (49.3)
Short	28 (17.5)	15 (20.5)
Antagonist	41 (25.6)	22 (30.1)
Total FSH dose for stimulation[a]	2085 ± 1032	2462 ± 1219
Days of stimulation	10.3 ± 2.5	10.9 ± 5.9
Maximal oestradiol concentration (pmol/l)	7069 ± 3667	6999 ± 3729
Endometrial thickness (mm)	10.2 ± 2.2	10.8 ± 2.3
No. of oocytes retrieved	12.3 ± 6.0	12.9 ± 6.7
No. of oocytes fertilized	7.2 ± 3.8	7.8 ± 4.5
Fertilization rate (%)	62.5 ± 21.5	64.7 ± 21.9
No. of embryos transferred	322	144
Pregnancies (pregnancy rate)	82 (51.3)	38 (52.1)
Implantation rate/embryo transferred	34.5% (111/322)	37.5% (54/144)
OHSS, moderate and severe	6 (3.8)	2 (2.7)

Values are number (%) or mean unless otherwise stated.
BMI = body mass index; OHSS = ovarian hyperstimulation syndrome.
[a]FSH consumption was significantly higher in the BMI >25 kg/m² group ($P = 0.015$).

Pregnancy course, outcome and complications are presented in **Table 3**. Rates of multiple pregnancies and abortions were similar in the two groups. There was no significant between-group difference in newborn weight in either singleton or multiple pregnancies. Overall, the incidence of gestational diabetes or pregnancy-induced hypertension was higher in the overweight group (23.3% versus 8.2%, $P = 0.045$). Furthermore, when the whole population was stratified by singleton or multiple pregnancies, the risk was highest for those with multiple pregnancies (31.3% versus 6.9%, $P = 0.031$).

Discussion

This study sought to determine the effect of overweight on endometrial site in terms of implantation potential. A young study population was carefully selected with the highest probability to achieve pregnancy except for BMI and divided them into two groups according to BMI below or above

Table 3 Pregnancy outcome and complications.

	BMI ≤25 kg/m²	*BMI >25 kg/m²*	*P-value*
No. of cycles	160	73	
No. of pregnancies	82	38	
Multiple pregnancies	29 (35.4)	16 (42.1)	NS
Abortions	21 (25.6)	8 (21.1)	NS
Live birth/cycle	61 (38.1)	30 (41.1)	NS
Mean weight at delivery			
Singletons	3239 ± 483	2955 ± 562	NS
Twins	2288 ± 368	2247 ± 479	NS
No. of pregnancy complications/all completed pregnancies (%)[a]	5/61 (8.2)	7/30 (23.3)	0.045
No. of pregnancy complications/completed singleton pregnancies (%)[a]	3/32 (9.4)	2/14 (14.3)	NS
No. of pregnancy complications/completed multiple pregnancies (%)[a]	2/29 (6.9)	5/16 (31.3)	0.031

Values are number (%) or mean unless otherwise stated.
NS = not statistically significant.
[a]Gestational diabetes and pregnancy-induced hypertension.

25 kg/m^2. No deleterious effect of BMI was found on rates of implantation (with high-quality embryos only), pregnancy, abortion or multiple pregnancies. However, the overweight women had a higher rate of pregnancy complications than the normal-weight women.

Obesity is associated with impaired reproductive outcome. In a prospective cohort of 3029 consecutive subfertile couples and ovulatory,van der Steeg et al. (2007) evaluated the time to spontaneous ongoing pregnancy within 12 months. They found that the probability of a spontaneous pregnancy declined linearly with a BMI over 29 kg/m^2 and concluded that obesity is associated with lower pregnancy rates in subfertile ovulatory women. In another study, Thomson et al. (2009) studied 52 overweight and obese women with polycystic ovary syndrome and reproductive impairment who underwent a 20-week weight loss programme. They concluded that this intervention resulted in improvements in reproductive function but no change in anti-Müllerian hormone concentrations.

To determine the extra-ovarian effect of excess body weight on pregnancy outcome in patients undergoing IVF treatment, Bellver et al. (2007) included a large cohort (n = 2656) of first-time donation cycles in which only good-quality oocytes from normal-weight women were used, thereby eliminating the effect of obesity on oocyte development. Standardized stimulation and endometrial preparation protocols were applied in all cases and oocytes from women with uterine defects or a history of recurrent miscarriage were excluded. The women were divided into four groups by BMI (lean, normal, overweight, obese). The authors found no difference in rates of implantation, pregnancy, miscarriage and ongoing pregnancy among the groups. Like in the present study, the high quality of the embryos apparently overcame the lower implantation rate and higher abortion rate expected in the obese women.

The mechanisms by which obesity exerts a negative effect on reproduction are not yet fully understood. Obesity is known to have profound effects on sex hormone secretion and metabolism, leading to a modification in the concentration of bioavailable oestrogen and androgens. This and other endocrine disruptions contribute to the infertile phenotype (Pasquali, 2006). It has become increasingly clear that an abnormal endocrine milieu may lead to impaired folliculogenesis and follicular atresia as a result of hypersecretion of luteinizing hormone (Balen, 1993), hyperinsulinaemia (Poretsky et al., 1985), increased insulin-like growth factor (IGF)-1 production (Adashi et al., 1985) and increased androgen ratio (Hsueh et al., 1994). Obese women also exhibit an altered ovarian follicular environment, particularly increased metabolite, C-reactive protein and androgen activity concentrations, which may be associated with poorer reproductive outcomes (Robker et al., 2009). Hyperinsulinaemia has been associated with disruptions in at least two key proteins in the endometrium: reduced glycodelin, which is involved in recurrent pregnancy loss, and decreased IGF-1 protein, which interferes with adhesion at the maternal–fetal interface (Carrington et al., 2005). Moreover, studies have shown that visceral adipose is a key regulator of the interrelated network of factors that increase insulin resistance, inflammation, coagulation and fibrinolysis (Yudkin et al., 1999) and that obese subjects have higher-than-normal concentrations of acute phase proteins and adipose-tissue-derived proinflammatory cytokines (Hotamisligil et al., 1995), such as interleukin-6, plasminogen activator inhibitor type-1 and tumour necrosis factor-α, which are thought to exert a negative effect on implantation and early embryonic development (Gosman et al., 2006). The peripheral role of the adipocyte-derived hormone leptin in implantation is under investigation (Cervero et al., 2004). In two comprehensive reviews, Mitchell et al. (2005) and Budak et al. (2006) describe the possible influence of the adipokines leptin, adiponectin, ghrelin, PYY3–36 and resistin on energy homeostasis and female fertility.

If obesity does indeed adversely influence the outcome of assisted conception cycles, the next question to address is its specific target, namely the endometrium (Bellver et al., 2007) or the developing embryo. Several studies have

investigated the possible effect of obesity on embryo quality (Bellver et al., 2010; Dechaud et al., 2006; Fedorcsak et al., 2000, 2004; Metwally et al., 2007b; Spandorfer et al., 2004; Wittemer et al., 2000). Wittemer et al. (2000) noted a significantly poorer oocyte quality in obese women than in women with a normal BMI and Metwally et al. (2007b), in a study of young women undergoing IVF/intracytoplasmic sperm injection, found that obesity apparently had an adverse effect on embryo quality, but not on oocyte quality. In a recent study, Bellver et al. (2010) reported that female obesity impairs IVF outcome, but embryo quality is not affected, suggesting that the culprit is an alteration in the uterine environment. In a recent study in female mice, Minge et al. (2008) demonstrated that peri-conception treatment with insulin-sensitizing pharmaceuticals can directly influence ovarian functions and exert positive effects on oocyte developmental competence. They also noted that improved blastocyst quality in obese females treated with rosiglitazone before mating indicates that peroxisome proliferator-activated receptor γ is a key target for metabolic regulation of ovarian function and oocyte quality. Since the present study focused on the influence of obesity on endometrial receptivity, while eliminating embryo quality as a possible confounding factor, a possible effect of obesity on the oocyte/embryo quality cannot be excluded.

Besides its direct effect on pregnancy, obesity is an independent risk factor for maternal complications of pregnancy, such as pre-eclampsia and gestational diabetes (ACOG, 2005; Leddy et al., 2008). Additionally, obese women are more likely to have delivery complications, including preterm delivery, fetal macrosomia, increased need for induction of labour, greater use of instrumental delivery and a higher risk of emergency Caesarean delivery (ACOG, 2005). In the present study, as expected, the overall incidence of these obesity-related pregnancy complications was higher in the overweight group, especially in the overweight women with multiple pregnancies.

In summary, the current results suggest that transferring good-quality embryos overcomes the negative effect of obesity on implantation and pregnancy rates in patients undergoing IVF treatment. This finding implies that the endometrium plays a minimal role in the mechanism underlying the discouraging IVF results reported in obese patients. Nevertheless, the negative impact of obesity on fertility is further extended to the pregnancy state. Given the higher risk of pregnancy complications in obese women, clinicians should continue to counsel patients on the health consequences of obesity and further encourage them to aggressively pursue weight reduction prior to conception.

References

ACOG Committee Opinion No. 315, 2005. Obesity in pregnancy. American College of Obstetricians and Gynecologists. Obstet. Gynecol. 106, 671—675.

Adashi, E.Y., Resnick, C.E., D'Ercole, A.J., Svoboda, M.E., Van Wyk, J.J., 1985. Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. Endocr. Rev. 6, 400—420.

Balen, A.H., 1993. Hypersecretion of luteinizing hormone and the polycystic ovary syndrome. Hum. Reprod. 8, 123—128.

Bellver, J., Melo, M.A.B., Bosch, E., Serra, V., Remohí, J., Pellicer, A., 2007. Obesity and poor reproductive outcome: the potential role of the endometrium. Fertil. Steril. 88, 446—451.

Bellver, J., Ayllón, Y., Ferrando, M., et al., 2010. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil. Steril. 93, 447—454.

Budak, E., Fernández Sánchez, M., Bellver, J., Cerveró, A., Simón, C., Pellicer, A., 2006. Interactions of the hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. Fertil. Steril. 85, 1563—1581.

Carrington, B., Sacks, G., Regan, L., 2005. Recurrent miscarriage: pathophysiology and outcome. Curr. Opin. Obstet. Gynecol. 17, 591—597.

Cervero, A., Horcajadas, J.A., MartIn, J., Pellicer, A., Simón, C., 2004. The leptin system during human endometrial receptivity and preimplantation development. J. Clin. Endocrinol. Metab. 89, 2442—2451.

Dechaud, H., Anahory, T., Reyftmann, L., Loup, V., Hamamah, S., Hedon, B., 2006. Obesity does not adversely affect results in patients who are under going in vitro fertilization and embryo transfer. Eur. J. Obstet. Gynecol. Reprod. Biol. 127, 88—93.

Dokras, A., Baredziak, L., Blaine, J., Syrop, C., Van Voorhis, B.J., Sparks, A., 2006. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet. Gynecol. 108, 61—69.

Fedorcsak, P., Storeng, R., Dale, P., Tanbo, T., Abyholm, T., 2000. Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta Obstet. Gynecol. Scand. 79, 43—48.

Fedorcsak, P., Dale, P.O., Storeng, R., et al., 2004. Impact of overweight and underweight on assisted reproduction treatment. Hum. Reprod. 19, 2523—2528.

Gosman, G.G., Katcher, H.I., Legro, R.S., 2006. Obesity and the role of gut and adipose hormones in female reproduction. Hum. Reprod. Update 12, 585—601.

Hotamisligil, G.S., Arner, P., Caro, J.F., Atkinson, R.L., Spiegelman, B.M., 1995. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J. Clin. Invest. 95, 2409—2415.

Hsueh, A.J., Billig, H., Tsafriri, A., 1994. Ovarian follicle atresia: a hormonally controlled apoptotic process. Endocr. Rev. 15, 707—724.

Krizanovska, K., Ulcova-Gallova, Z., Bouse, V., Rokyta, Z., 2002. Obesity and reproductive disorders. Sb. Lek. 103, 517—526.

Lashen, H., Ledger, W., Bernal, A.L., et al., 1999. Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. Hum. Reprod. 14, 712—715.

Leddy, M.A., Power, M.L., Schulkin, J., 2008. The impact of maternal obesity on maternal and fetal health. Rev. Obstet. Gynecol. 1, 170—178.

Lewis, C.G., Warnes, G.M., Wang, X.J., Matthews, C.D., 1990. Failure of body mass index or body weight to influence markedly the response to ovarian hyperstimulation in normal cycling women. Fertil. Steril. 53, 1097—1099.

Loveland, J.B., McClamrock, H.D., Malinow, A.M., Sharara, F.I., 2001. Increased body mass index has a deleterious effect on in vitro fertilization outcome. J. Assist. Reprod. Genet. 18, 382—386.

Metwally, M., Tuckerman, E.M., Laird, S.M., Ledger, W.L., Li, T.C., 2007a. Impact of high body mass index on endometrial morphology and function in the peri-implantation period in women with recurrent miscarriage. Reprod. Biomed. Online 14, 328—334.

Metwally, M., Cutting, R., Tipton, A., Skull, J., Ledger, W.L., Li, T.C., 2007b. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod. Biomed. Online 15, 532—538.

Minge, C.E., Bennett, B.D., Norman, R.J., Robker, R.L., 2008. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. Endocrinology 149, 2646—2656.

Mitchell, M., Armstrong, D.T., Robker, R.L., Norman, R.J., 2005. Adipokines: implications for female fertility and obesity. Reproduction 130, 583—597.

Nichols, J.E., Crane, M.M., Higdon, H.L., Miller, P.B., Boone, W.R., 2003. Extremes of body mass index reduce in vitro fertilization pregnancy rates. Fertil. Steril. 79, 645—647.

Pasquali, R., 2006. Obesity and androgens: facts and perspectives. Fertil. Steril. 85, 1319—1340.

Poretsky, L., Grigorescu, F., Seibel, M., Moses, A.C., Flier, J.S., 1985. Distribution and characterization of insulin and insulin-like growth factor I receptors in normal human ovary. J. Clin. Endocrinol. Metab. 61, 728—734.

Robker, R.L., Akison, L.K., Bennett, B.D., et al., 2009. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. J. Clin. Endocrinol. Metab. 94, 1533—1540.

Spandorfer, S.D., Kump, L., Goldschlag, D., Brodkin, T., Davis, O.K., Rosenwaks, Z., 2004. Obesity and in vitro fertilization: negative influences on outcome. J. Reprod. Med. 49, 973—977.

Staessen, C., Camus, M., Bollen, N., et al., 1992. The relationship between embryo quality and the occurrence of multiple pregnancies. Fertil. Steril. 3, 626—630.

Thomson, R.L., Buckley, J.D., Moran, L.J., et al., 2009. The effect of weight loss on anti-Müllerian hormone levels in overweight and obese women with polycystic ovary syndrome and reproductive impairment. Hum. Reprod. 24, 1976—1981.

van der Steeg, J.W., Steures, P., Eijkemans, M.J., et al., 2007. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum. Reprod. 23, 324—328.

van Swieten, E.C., van der Leeuw-Harmsen, L., Badings, E.A., van der Linden, P.J., 2005. Obesity and clomiphene challenge test as predictors of outcome of in vitro fertilization and intracytoplasmic sperm injection. Gynecol. Obstet. Invest. 59, 220—224.

Wang, J.X., Davie, M.J., Norman, R.J., 2000. Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study. BMJ 321, 1320—1321.

Wang, J.X., Davies, M.J., Norman, R.J., 2002. Obesity increases the risk of spontaneous abortion during infertility treatment. Obes. Res. 10, 551—554.

Wittemer, C., Ohl, J., Bailly, M., Bettahar-Lebugle, K., Nisand, I., 2000. Does body mass index of infertile women have an impact on IVF procedure and outcome? J. Assist. Reprod. Genet. 17, 547—552.

Yudkin, J.S., Stehouwer, C.D., Emeis, J.J., Coppack, S.W., 1999. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler. Thromb. Vasc. Biol. 19, 972—978.

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