Impact of overweight and underweight on assisted reproduction treatment

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BACKGROUND: Underweight and overweight may affect reproduction and interfere with treatment of infertility. The purpose of this report is to describe the independent effect of body weight on treatment with IVF and ICSI.

METHODS: Records of 5019 IVF or ICSI treatments in 2660 couples were reviewed. The influence of body mass index (BMI) on treatment outcome was examined, after accounting for differences in age and infertility diagnosis.

RESULTS: The cumulative live birth rate within three treatment cycles was 41.4% [95% confidence interval (CI) 32.1–50.7] in obese women with BMI ≥ 30 kg/m² and 50.3 (95% CI 47.0–53.7) in normal weight women with BMI 18.5–24.9 kg/m². Obesity was associated with an increased risk of early pregnancy loss occurring before 6 weeks gestation. Positive correlation between BMI and gonadotrophin requirement during stimulation and negative correlation between BMI and number of collected oocytes were observed. Underweight (BMI < 18.5 kg/m²) was not related to an impaired outcome of IVF or ICSI. CONCLUSIONS: Obesity is associated with lower chances for live birth after IVF and ICSI and with an impaired response to ovarian stimulation.

Key words: body mass index/insulin resistance/IVF/PCOS

Introduction

Initiation and maintenance of reproductive functions are related to an optimal body weight in women. Underweight [body mass index (BMI) < 18.5 kg/m²], as well as overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²) are associated with an increased risk of anovulatory infertility (Rich-Edwards et al., 2002). Reduced fecundity of underweight and overweight women is probably related to multiple endocrine and metabolic alterations, which include—but are not limited to—effects on steroid metabolism and altered secretion and action of insulin and other hormones, such as leptin, resistin, ghrelin or adiponectin. These alterations can affect follicle growth, embryo development and implantation (Poretsky et al., 1999; Moschos et al., 2002; Tanbo, 2002; Pasquali et al., 2003), and it is therefore of concern that being underweight or overweight may interfere with treatment of infertility with IVF and ICSI.

Clinical observations on the effects of body weight during IVF and ICSI are conflicting. In overweight/obese compared with normal weight women, increased FSH requirement during ovarian stimulation, fewer collected oocytes, decreased serum estradiol concentrations, frequent cycle cancellations and low pregnancy rate have been observed (Crosignani et al., 1994; Homburg et al., 1996; Soderstrom-Antila et al., 1996; Wang et al., 2000; Wittemer et al., 2000; Carrell et al., 2001; Loveland et al., 2001; Mulders et al., 2003; Nichols et al., 2003). It has also been reported that obese women are at increased risk of miscarriage after IVF or ICSI, an association not fully explained by the high prevalence of polycystic ovary syndrome (PCOS), which is itself related to miscarriage, among obese infertile women (Fedorcsak et al., 2000b; Wang et al., 2001, 2002). Confirming the harmful effect of obesity, weight loss was found to improve the outcome of assisted reproduction treatment in obese women (Clark et al., 1998).

Other studies, however, find no significant effect of obesity on response to ovarian stimulation (Lewis et al., 1990; Lashen et al., 1999; Loh et al., 2002) or on pregnancy rate and outcome of pregnancies conceived by IVF and ICSI (Lewis et al., 1990; Lashen et al., 1999; Wittemer et al., 2000; Winter et al., 2002). It has also been suggested that abdominal fatness has a more important impact on IVF outcome than obesity itself (Wass et al., 1997). This controversy among various reports, which is partly caused by the varying focus of investigators, differences in study designs and low sample size of some reports, led us to examine the impact of underweight and overweight on IVF and ICSI treatment in a large cohort of women.

Patients and methods

The subjects of this retrospective study were all the 2660 infertile couples who underwent a total of 5019 treatments of IVF or ICSI...
between September, 1996 and May, 2002 in our department. All treatments were preceded by downregulation with a GnRH agonist (Synarel, Pfizer, USA, or Suprefact, Hoechst, Germany) from the mid-luteal phase of the previous menstrual cycle. Ovarian stimulation was achieved by recombinant FSH (Gonal F, Serono, Switzerland, or Puregon, Organon, The Netherlands), using a protocol described earlier (Fedorcsák et al., 2000b). As a rule, the starting daily FSH dose was 150 IU, with the exception of women older than 35 years and those with BMI > 35 kg/m² who received 200–225 IU, and women with polycystic ovaries who received 75–150 IU starting FSH dose. Ovulation was induced with 10000 IU of HCG (Profasi, Serono or Pregnyl, Organon) when at least one follicle had reached a diameter of >17 mm. Oocytes were retrieved 34–38 h later by guidance of vaginal ultrasound.

Gamete handling, fertilization and embryo culture were performed according to standard IVF procedures. Briefly, Universal IVF medium (Medi-Cult, Copenhagen, Denmark) was used during oocyte insemination and embryo culture. In ICSI cycles, only ejaculated spermatozoa were microinjected. Embryos were scored from grade 1 (high quality) to grade 4 (poor quality) according to the number, size and shape of blastomeres and degree of fragmentation, using previously described criteria (Van den Abbeel et al., 1988). Embryos were transferred on day 3, except in cases with few embryos (≤2), which were transferred on day 2. As a rule, and when available, two embryos were transferred. However, during the period 1996–1997, transfer of three embryos was sometimes allowed in selected older women (>35 years) with multiple prior unsuccessful cycles, after counselling the patient on the risks of multiple gestation. Luteal phase support up to 14 days after oocyte retrieval consisted of either daily i.m. injection of 25 mg progesterone in oil, Crinone® vaginal gel (90 mg, Serono) or intravaginal Progestan® (600 mg, Nourypharma, Germany) capsules.

The serum concentration of βHCG was measured on day 14 after oocyte retrieval and, in the case of concentrations above 20 UI/L, which indicated pregnancy, an ultrasound scan was performed 3–4 weeks later to verify the viability of pregnancy and count gestational sacs. Early pregnancy loss was defined as biochemical pregnancy (< 20 UI/L; HCG was measured on day 14 after oocyte retrieval) without subsequent ultrasound signs of viable pregnancy. The implantation rate was calculated as the ratio of the number of gestational sacs over the number of transferred embryos. Pregnancies were followed to term by general practitioners or obstetricians at the patients’ local hospitals. Every pregnant woman was contacted on pregnancy outcome, and copies of original medical records were obtained.

Weight and height of women were measured with a calibrated balance and height rod at the first visit, a median 80 days before the first IVF or ICSI cycle. The main cause of infertility, as determined by the physician, was categorized as male factor (assessed by sperm analysis), tubal factor (assessed by hysterosalpingogram or laparoscopy), endometriosis (laparoscopy), PCOS (defined by polycystic ovaries on ultrasound scan, and two or more of the following criteria: oligo/amenorrhoea, hirsutism and hyperandrogenism), other specific diseases or unexplained infertility.

Data analysis

Data with normal distribution are presented as mean (SD); data with log-normal distribution are presented as geometric mean [95% confidence interval(CI)]. Data for IVF and ICSI cycles were analysed and compared for the following strata of BMI (kg/m²): underweight, BMI < 18.5; normal weight, 18.5–24.9; overweight, 25.0–29.9; and obesity, ≥ 30.0. Generalized linear models were used to assess linear association between classes of BMI and continuous variables. In these analyses, age and main infertility diagnosis were included as covariates, to examine the independent effect of BMI. $x^2$ test for linear trend was used to assess linear association between classes of BMI and rate variables. Logistic regression was used to calculate odds ratios for live birth and for miscarriage, using BMI classes, age and infertility diagnosis as explanatory variables. The fit of logistic models was assessed with Hosmer-Lemeshow test. Cumulative live birth rates were calculated by the Kaplan–Meier method, and were compared across BMI classes with the log rank test for trend. SPSS version 10 (SPSS Inc., Chicago, IL) was used for data analysis. $P < 0.05$ was considered statistically significant.

Results

During a period of 6 years, 2660 couples participated in our IVF programme. According to classification by BMI, 2.9% of women were underweight (BMI < 18.5 kg/m²) and 9.0% were obese (BMI ≥ 30.0 kg/m²). Significant positive correlation was observed between BMI and body weight ($r = 0.92, P < 0.001$), indicating that increased body weight was secondary to obesity and not tall stature. Obese women (BMI ≥ 30.0 kg/m²) were significantly younger than women with normal BMI (18.5–24.9 kg/m²; Table I). Positive correlation was observed between BMI and incidence of PCOS, and negative correlation between BMI and incidence

### Table I. Clinical characteristics of women according to BMI

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>No. of women</th>
<th>Body weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Age (years)</th>
<th>Duration of infertility (years)</th>
<th>Main cause of infertility</th>
<th>Tubal factor</th>
<th>Male factor</th>
<th>Endometriosis</th>
<th>Unexplained infertility</th>
<th>PCOS</th>
<th>Other causes</th>
<th>P</th>
<th>Linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td>76</td>
<td>50 (SD 4)</td>
<td>17.7 (SD 0.6)</td>
<td>31.7 (SD 3.7)</td>
<td>5.0 (SD 2.4)</td>
<td>Tubal factor</td>
<td>23 (30%)</td>
<td>19 (25%)</td>
<td>20 (26%)</td>
<td>11 (15%)</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
<td>$&lt; 0.05$</td>
<td>0.93</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>1839</td>
<td>62 (SD 6)</td>
<td>21.8 (SD 1.7)</td>
<td>32.5 (SD 3.7)</td>
<td>5.3 (SD 3.1)</td>
<td>Male factor</td>
<td>614 (33%)</td>
<td>547 (30%)</td>
<td>309 (17%)</td>
<td>290 (16%)</td>
<td>65 (4%)</td>
<td>14 (1%)</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>504</td>
<td>26.9 (SD 1.4)</td>
<td>26.3 (SD 3.6)</td>
<td>5.4 (SD 2.4)</td>
<td>Tubal factor</td>
<td>163 (32%)</td>
<td>163 (32%)</td>
<td>57 (11%)</td>
<td>74 (15%)</td>
<td>40 (8%)</td>
<td>7 (1%)</td>
<td>7 (1%)</td>
<td>&lt; 0.001</td>
<td>0.17</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>241</td>
<td>33.3 (SD 2.8)</td>
<td>31.7 (SD 3.9)</td>
<td>5.3 (SD 2.9)</td>
<td>Male factor</td>
<td>59 (25%)</td>
<td>80 (33%)</td>
<td>13 (5%)</td>
<td>29 (12%)</td>
<td>57 (24%)</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 by post hoc comparison (Bonferroni) between groups.
of endometriosis or tubal factor as leading causes of infertility (Table I).

Results of IVF and ICSI treatment

A total of 5019 IVF or ICSI cycles were initiated; the mean number of initiated cycles per patient (1.9, SD 0.9) did not differ significantly among BMI classes. Linear association was observed between higher BMI and longer stimulation with FSH, requirement for increased total doses of FSH, increased frequency of cycle cancellations due to insufficient follicular development and lower number of collected oocytes (Table II). BMI was not significantly related to diploid fertilization rate either by IVF or by ICSI (Table II). The quality and number of cells of transferred embryos were not significantly different among classes of BMI. No significant association was observed between BMI and implantation rate of transferred embryos (Table II). The quality and number of cells of transferred embryos were not significantly different among classes of BMI. No significant association was observed between BMI and implantation rate of transferred embryos (Table II).

Linear association was observed between higher BMI and lower incidence of embryo transfer and lower mean number of transferred embryos (Table II). The quality and number of cells of transferred embryos were not significantly different among classes of BMI. No significant association was observed between BMI and implantation rate of transferred embryos, or BMI and (biochemical) pregnancy rate (Table II). We found that increased BMI is related to a lower live birth rate in obese women (BMI ≥30.0 kg/m²) compared with women with normal weight (BMI 18.5–24.9 kg/m²).

Treatment outcome in the first IVF or ICSI cycle

During the first IVF or ICSI cycles of the treated couples (n = 2660), a positive correlation was observed between BMI and total FSH dose and between BMI and frequency of cycle cancellations. Negative correlation was observed between BMI and the number of collected oocytes. No significant association was observed between BMI and pregnancy rate, but increased BMI was associated with higher incidence of early pregnancy loss and, although not statistically significant (P = 0.09), with a lower live birth rate (Table III).

Discussion

We found that increased BMI is related to a lower live birth rate and a higher incidence of early pregnancy loss among women undergoing IVF or ICSI. Furthermore, increased BMI was related to an increased FSH requirement, longer period of stimulation, increased risk of insufficient follicle development and fewer obtained oocytes.

Compared with women with normal weight, obese women achieved on average 3.9 (95% CI 0.3–7.6) fewer live births per 100 started IVF and ICSI cycles. As a cumulative effect, 41 of 100 obese women gave birth to living newborn(s)
within three treatment cycles, compared with 50 of 100 women who had normal body weight. Of the 3.9 ‘missing’ live births per 100 started cycles, ~3.2 could be attributed to an increased incidence of early pregnancy loss in obese women (Figure 1). These findings agree with earlier observations that overweight and obesity are related to lower chances of live birth due to an increased risk of miscarriage of early pregnancies conceived in vitro (Fedorcsak et al., 2000b; Wang et al., 2002). Miscarriage in obese women is probably not caused by the IVF procedure itself, since obesity also increases miscarriage rate in recipients of donated oocytes (Bellver et al., 2003) and during natural conception (Hamilton-Fairley et al., 1992). The cause of early pregnancy loss in obese women is not identified in this report, as we did not observe statistically significant differences in fertilization rate, cleavage stage and morphology of transferred embryos, or in implantation and biochemical pregnancy rates among women with different BMI. Other studies, however, suggest that obesity and the associated endocrine alterations may affect corpus luteum function (Sherman and Korenman, 1974; Fedorcsak et al., 2000a), early embryo development (Kawamura et al., 2002; Fedorcsak and Storeng, 2003), trophoblast function (Castellucci et al., 2000) and endometrial receptivity (Alfer et al., 2000; Gonzalez et al., 2000).

The foregoing calculations would predict that the most effective strategy to improve the outcome of IVF and ICSI in obese women is to reduce the incidence of early pregnancy loss and miscarriage. However, the best way to achieve this end has not yet been found. Both weight loss (Clark et al., 1998) and metformin treatment, at least in women afflicted with PCOS (Jakubowicz et al., 2002), were claimed to reduce the incidence of miscarriage, but the true clinical efficacy of these methods remains to be established in controlled studies. It is also unknown whether early pregnancy loss could be

Table III. Characteristics of IVF and ICSI treatment in the first cycle of the couples

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>No. of started cycles</th>
<th>Total FSH dose (IU)*</th>
<th>No. of cancelled cycles</th>
<th>No. of oocytes collected*</th>
<th>No. of embryo transfers</th>
<th>No. of biochemical pregnancies</th>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤18.5</td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
<td>≥30.0</td>
<td>Linear trend</td>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>1839</td>
<td>504</td>
<td>241</td>
<td>–</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1906 (1752–2073)</td>
<td>1857 (1826–1890)</td>
<td>1902 (1842–1966)</td>
<td>2337 (2229–2451)</td>
<td>0.008</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>2 (2.6%)</td>
<td>64 (3.5%)</td>
<td>25 (5.0%)</td>
<td>16 (6.6%)</td>
<td>0.008</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>8.1 (6.9–9.5)</td>
<td>7.6 (7.4–7.9)</td>
<td>7.0 (6.6–7.4)</td>
<td>7.0 (6.4–7.7)</td>
<td>0.03</td>
<td>0.03</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>71 (93.4%)</td>
<td>1569 (85.3%)</td>
<td>416 (82.5%)</td>
<td>202 (83.8%)</td>
<td>0.06</td>
<td>0.06</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>24 (31.6%)</td>
<td>553 (30.1%)</td>
<td>150 (29.8%)</td>
<td>70 (29.1%)</td>
<td>0.06</td>
<td>0.06</td>
<td>0.68</td>
</tr>
</tbody>
</table>

P.Fedorcsak et al.

Figure 1. Flow chart of the outcome of IVF and ICSI treatment in women with normal weight (NW; BMI 18.5–25.0 kg/m²) and in obese women (OB; BMI ≥ 30.0 kg/m²). Numbers indicate percentage of 100 who started IVF and ICSI cycles based on the data of Table II.

*aGeometric mean (95% CI) adjusted for age.
prevented by a more vigorous luteal phase support in obese women. We observed an association between increased BMI and increased FSH requirement, fewer collected oocytes and increased risk of insufficient follicle development during ovarian stimulation for IVF and ICSI, suggesting that the response to FSH stimulation is attenuated by overweight and obesity. Although the starting dose of FSH was not fixed in this report, the correlation between BMI and length of stimulation suggests that the differences in FSH requirement were not caused solely by a deliberate prescription of higher FSH doses in obese women. Furthermore, the analysis of the 2600 first treatment cycles (one cycle per couple) yielded similar results to those obtained with all cycles, indicating that the association of increased BMI and increased FSH requirement was not due to a dose adjustment in successive cycles of the same couple.

During ovarian stimulation with FSH, selection of multiple growing follicles requires that the serum FSH concentration exceeds a ‘threshold’ (Hillier, 2000). In obese women, the threshold effect of exogenous FSH is reduced (Imani et al., 2000), which consequently may lead to fewer selected follicles, fewer collected oocytes and a requirement for larger FSH doses for stimulation, as observed in the present analysis.

To what extent this impaired response to stimulation contributes to the reduced live birth rate in obese women is uncertain. The contribution of increased cycle cancellations is probably small: assuming that cancelled cycles would have resulted in a similar live birth rate to non-canceled cycles, the ~3.6 excess cancellations per 100 started cycles would account for ~0.8 of the 3.9 ‘missing’ live births in obese women (Figure 1). Furthermore, although obese women had fewer oocytes collected, fewer embryos to select for transfer and fewer cycles that proceeded to embryo transfer, pregnancy and implantation rates were similar in obese and normal weight women. Consequently, alternative stimulation regimens that increase the number of available oocytes and reduce cancellation rate in obese women—assuming that oocyte quality and endometrial receptivity are not compromised and the risk of hyperstimulation is not increased—may bring about only a marginal improvement of live birth rate after IVF and ICSI in obese women.

It has been suggested that the association of body weight and IVF outcome is of an ‘inverted U shape’, implicating that underweight has as deleterious an effect on IVF outcome as overweight and obesity (Wang et al., 2000; Winter et al., 2002). Our data do not reveal a significant impact of underweight on clinical pregnancy rate or live birth rate during IVF. It remains to be examined whether differences between our study and Australian reports (Wang et al., 2000; Winter et al., 2002) are caused by true biological differences among patient populations or statistical phenomena due to frequency of underweight.

In summary, we found that obesity is associated with a lower live birth rate after IVF and ICSI treatment, mainly because of an increased risk of early pregnancy loss in obese women. An impaired response to ovarian stimulation in obese women was also observed. Underweight was not related to an impaired outcome of IVF or ICSI in this analysis.

References


Body weight and ART

2527


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