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ARTICLE

Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples

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Abstract This study investigated the impact of women's body mass index (BMI) on the outcome after consecutive IVF/intracytoplasmic sperm injection cycles in 487 patients initiating treatment with 5-year follow-up. The total number of cycles was 1417. In total 103 (21.1%) were overweight (BMI 25–29.9 kg/m^2) and 59 (12.1%) were obese (BMI ≥30 kg/m^2). Number of initiated cycles/woman ($P = 0.01$), number of cancelled cycles/woman ($P < 0.01$) and the total dose of gonadotrophin used/cycle ($P < 0.01$) rose with increasing BMI. A negative linear association between BMI and the number of retrieved oocytes ($B = -0.243$, $P < 0.001$) and an inverse U-shaped relationship between BMI and the number of developed embryos was seen, with less embryos available among underweight and obese women ($P = 0.03$). The number with positive serum human chorionic gonadotrophin/cycle decreased significantly with increasing BMI ($P < 0.01$). The ongoing pregnancy rate/cycle among the obese women was lower (20.8% versus 28.3% in normal-weight women; $P = 0.04$). Live-birth rate per cycle was 15.2% versus 21.5%. Multiple logistic regression analysis showed that the only independent predictors of live birth were women's age ($P = 0.037$), women's BMI ($P = 0.034$) and men's age ($P = 0.040$).

KEYWORDS: body mass index, IVF outcome, live-birth rate, obesity, overweight

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Introduction

In the developed countries, increased health risks, including declining fertility rates, are a consequence of the global obesity epidemic. According to the body mass index (BMI) definitions of the World Health Organization (WHO), 35% of Danish women aged 25–44 are overweight (BMI $\geq$ 25 kg/m^2) or obese; in women aged 16–24 years, the corresponding figure reaches 18% (Ekholm et al., 2006). The proportion of obese individuals (BMI $\geq$ 30 kg/m^2) has more than doubled in 18 years from 1987 to 2005 from 5.5% to 11.4% in Denmark, and for women this increase was most pronounced for the fertile age groups (women aged 16–44 years; http://www.si-folkesundhed.dk). Similar figures are seen throughout Europe (James et al., 2004). The WHO predicts that the obesity epidemic will continue and that 60–70% may be obese in Europe in 2030. Both male and female overweight has a negative influence on the reproductive system (James et al., 2004; Maheshwari et al., 2007). In overweight women, an altered secretion of pulsatile gonadotrophin-releasing hormone results in altered endocrinological profiles of ovarian and adrenal androgens and LH, resulting in oligo- or anovulation. Mild to moderate weight loss in anovulatory women is associated with the return of spontaneous ovulation and a reduction of the need for ovulation induction (Clark et al., 1995, 1998).

In a systematic review on the effect of overweight and obesity on assisted reproduction treatment, Maheshwari et al. (2007) stated that women with BMI $\geq$25 kg/m^2 have a lower chance of pregnancy following IVF, require higher doses of gonadotrophins and have increased miscarriage rates. According to the same review there was insufficient evidence on the effect of BMI on live birth, cycle cancellation, oocyte recovery and ovarian hyperstimulation syndrome. Only 11 out of 21 included studies had predefined cut-off values for BMI and considerable heterogeneity was displayed between the studies. Meta-analyses showed that when normal-weight women (BMI 20–25 kg/m^2) were compared with women with BMI $\geq$25 kg/m^2, the chance of pregnancy per woman was higher with an odds ratio (OR) 1.40 (95% confidence interval (CI) 1.22–1.60). Further, the OR for pregnancy was 1.47 (95% CI 1.20–1.80) for a woman with a BMI $<$30 kg/m^2 compared with women with BMI $\geq$30 kg/m^2 (Maheshwari et al., 2007). Regarding overweight and delivery rates it was not possible to generate a funnel plot because of the paucity of studies, as only three were found and only one study from Sweden reported live-birth rates (Dokras et al., 2006; Fedorcsak et al., 2004; Wittemer et al., 2000). Fedorcsak et al. (2004) included all women undergoing assisted reproduction treatment over a 6-year period in one clinical centre (n = 2660 couples) and found cumulative live-birth rates within three treatment cycles to be similar (41.4% in women with BMI $\geq$ 30 kg/m^2 versus 50.3% in normal-weight women).

The effect of female obesity on many assisted reproduction treatment outcomes is still only insufficiently described. Studies are heterogeneous regarding BMI categories, inclusion and exclusion criteria and analytic approach (per patient or per cycle) and results are inconsistent. The purpose of this study was to investigate the impact of female BMI on IVF/intracytoplasmic sperm injection (ICSI) outcomes including live-birth rates after consecutive cycles with adjustment for important covariates.

Methods

Participants were included in the Copenhagen Multi-centre Psychosocial Infertility (COMPI) Research Programme from four different public fertility clinics (Herlev University Hospital; Fertility Clinic, Rigshospitalet, Copenhagen University Hospital; Odense University Hospital; Regional Hospital Braedstrup) (Pinborg et al., 2009; Schmidt, 2006). All new Danish-speaking couples received a questionnaire for both partners prior to their first treatment attempt (n = 1372 couples) consecutively from January 2000 to August 2001 and a second questionnaire by mail after 12 months. In 878 couples both spouses responded to the two questionnaires (878/1372, 64%). To make the sample more homogenous, the study excluded collection of clinical data for those couples already having a child after fertility treatment prior to inclusion in COMPI, couples who had adopted a child in the 12-month follow-up period and couples who had had no treatment during the first 12 months of follow-up. Thus data was collected from clinical files on 808 couples in 2005–2006. The study was able to identify clinical files for 799 of the 808 couples (98.9%) and collect detailed 5-year follow-up data regarding each initiated treatment cycle including BMI (**Figure 1**).

During the COMPI study inclusion period, the fertility clinics initiated systematic collection of pre-treatment information on women's weight and height. The study population with data on women's BMI consisted of 487 couples

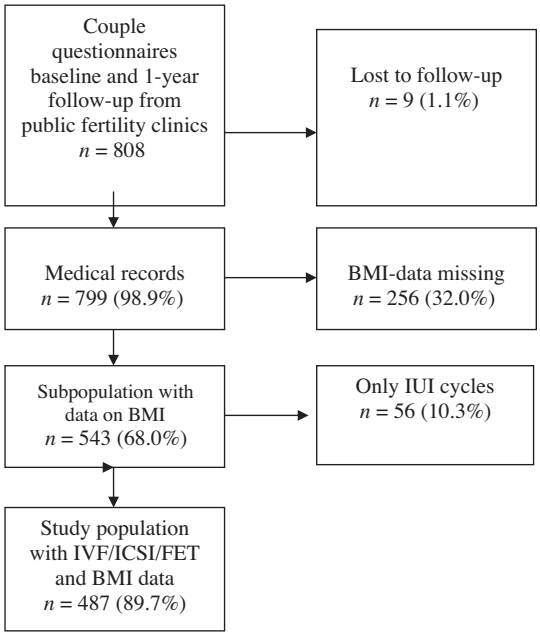

Figure 1 Flow chart of the study population (487 couples). BMI = body mass index; FET = frozen-embryo transfer; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination.

treated with IVF, ICSI or frozen-embryo transfer (FET). Couples only undergoing intrauterine insemination cycles were excluded in this study.

The COMPI study contains numerous variables based on self-reported questionnaires, clinical files and national register data. Only data relevant for the present study are described. Socio-demographic and medical information (age, occupational social class, years trying to conceive prior to study inclusion, reproductive events prior to study inclusion, fertility treatment prior to study inclusion) were obtained from the baseline questionnaire immediately before the couples initiated a treatment period at one of the clinics involved in COMPI.

Infertility diagnoses were obtained from the clinical records and categorized in one main cause for each couple: (i) tubal obstruction and other female infertility causes; (ii) anovulation or irregular ovulation only; (iii) male factor infertility only; (iv) male and female infertility; (v) unexplained infertility; and (vi) other causes. Women's height and weight were obtained and used for BMI calculations. BMI was categorized according to the WHO recommendations (2000): underweight ($<$18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese ($\geq$30 kg/m^2). Women's smoking was assessed by number of cigarettes per day and categorized as yes/no.

For each IVF/ICSI treatment cycle during the 5-year follow-up period, data was collected on: (i) type of treatment (IVF, IVF with donor spermatozoa, ICSI, FET); (ii) down-regulation prior to gonadotrophin stimulation (yes/no); (iii) total dose of gonadotrophins; (iv) cycle cancellation (yes/no) and if yes, the reason for cancelling (poor stimulation response/no eggs retrieved/no fertilization/other reasons); (v) number of oocytes retrieved; (vi) total number of fertilized embryos; (vii) total number of embryos for cryopreservation; (viii) positive serum human chorionic gonadotrophin (HCG) (yes/no); (ix) vaginal ultrasound examination at gestational week 7 (gestational sac, viable fetus (yes/no), ectopic pregnancy); and (x) pregnancy outcome (biochemical pregnancy, miscarriage, ectopic pregnancy, live birth, stillbirth).

Statistical analysis

Statistical analyses were performed in SAS version 9.2 (Statistical Analysis Software) for Windows XP. For differences between means of continuous data of all four BMI groups, one-way analysis of variance (ANOVA) was displayed. Subanalyses on differences between means of normal-weight (BMI 18.5–24.99 kg/m^2) versus obese (BMI $\geq$ 30 kg/m^2) women were performed with Student's *t*-test. Differences

Table 1 Clinical characteristics of the study population (n = 487) according to body mass index (BMI).

Variable	*Body mass index (kg/m^2)*				*P-value*[a,b]
	<18.5	*18.5–24.9*	*25.0–29.9*	*≥30.0*	
Women	20 (4.1)	305 (62.6)	103 (21.1)	59 (12.1)	–
Bodyweight (kg)	50.5 ± 3.7	62.7 ± 6.4	77.4 ± 6.5	94.3 ± 13.3	–
BMI (kg/m2)	17.9 ± 0.4	21.9 ± 1.7	27.2 ± 1.5	33.3 ± 2.9	–
Women's age (years)	32.0 ± 3.4	32.1 ± 3.5	31.7 ± 3.7	31.4 ± 3.7	NS (NS)
Men's age (years)	34.9 ± 5.5	34.1 ± 5.0	34.2 ± 5.0	35.2 ± 6.5	NS (NS)
Smoker	10/15 (66.7)	71/228 (31.1)	22/76 (28.9)	12/41 (29.3)	NS (NS)
Social class[c]					0.02 (<0.01)
I + II	7 (35.0)	57 (18.7)	20 (19.4)	5 (8.5)	–
III + IV	9 (45.0)	183 (60.0)	59 (57.3)	38 (64.4)	–
V + VI	4 (20.0)	35 (11.5)	18 (17.5)	9 (15.3)	–
Student	0	30 (9.8)	4 (3.9)	5 (8.5)	–
Total	20 (100)	305 (100)	101 (98.1)	57(96.6)	–
Years of infertility	4.2 ± 2.1	3.9 ± 2.0	4.1 ± 2.1	4.7 ± 2.8	NS (0.04)
Ever pregnant prior to inclusion	5 (25.0)	101 (33.1)	29 (28.2)	14 (23.7)	NS (NS)
Fertility treatment prior to inclusion	12 (60.0)	185 (60.7)	62 (60.2)	34 (57.6)	NS (NS)
Main cause of infertility					<0.01 (<0.01)
Tubal[d]	6 (30.0)	79 (25.9)	31 (30.1)	14 (23.7)	–
Irregular ovulation or anovulation	1 (5.0)	9 (3.0)	0	8 (13.6)	–
Male factor	8 (40.0)	117 (38.4)	39 (37.9)	16 (27.1)	–
Unexplained	5 (25.0)	58 (19.0)	18 (17.5)	6 (10.2)	–
Other diagnoses	0	14 (4.6)	3 (2.9)	5 (8.5)	–
Mixed factor (female + male)	0	26 (8.5)	12 (11.7)	9 (15.3)	–

Values are *n* (%), mean ± standard deviation, or *n*/total (%). NS = not statistically significant.
[a]Comparisons of all four groups. For mean values of quantitative data ANOVA was used and for categorical data chi-squared test was used.
[b]Values in parentheses are comparisons of normal BMI (18.5–24.9 kg/m^2) with obese ($\geq$30 kg/m^2). For mean values Student's t-test was used and for differences between categorical variables chi-squared test was used.
[c]Social class is defined in Hansen (1984).
[d]Combination of women with only tubal obstruction and women with both tubal obstruction and irregular ovulation or anovulation.

Table 2 Total number of IVF, intracytoplasmic sperm injection (ICSI) and frozen-embryo transfer (FET) cycles (n = 1417) and mean number of treatments per women according to body mass index.

Treatment cycles	*Body mass index (kg/m²)*				P-*value*[a]
	<18.5	*18.5–24.9*	*25.0–29.9*	*≥30.0*	
Treatment cycles (IVF + ICSI + FET)	51	842	319	205	NS
IVF cycles	30 (58.8)	455 (54.0)	160 (50.2)	116 (56.6)	–
ICSI cycles	14 (27.5)	247 (29.3)	97 (30.4)	62 (30.2)	–
FET cycles	7 (13.7)	140 (16.6)	62 (19.4)	27 (13.2)	–
Cancelled cycles	10 (19.6)	72 (8.6)	26 (8.2)	39 (19.0)	<0.01
Treatment cycles per woman (mean ± standard deviation)					
All treatment cycles/woman	2.6 ± 1.2	2.8 ± 1.6	3.1 ± 1.8	3.5 ± 2.1	0.01
IVF cycles/woman	1.5 ± 1.1	1.5 ± 1.4	1.6 ± 1.4	2.0 ± 1.8	–
ICSI cycles/woman	0.7 ± 0.9	0.8 ± 1.3	0.9 ± 1.4	1.1 ± 1.5	–
FET cycles/woman	0.4 ± 0.6	0.5 ± 0.8	0.6 ± 0.9	0.5 ± 0.7	–
Cancelled cycles	0.5 ± 1.0	0.2 ± 0.5	0.3 ± 0.5	0.7 ± 1.4	<0.01

Values are n, % and mean ± standard deviation, NS = not statistically significant.
[a]Comparisons of all four groups. For mean values of quantitative data ANOVA was used and for categorical data chi-squared test was used.

between distributions for both comparisons of all four BMI groups and comparisons between normal-weight and obese women were assessed using chi-squared test. A P-value <0.05 was considered statistically significant.

Univarate and multiple linear regression analyses on first cycle were performed for the association between BMI and the quantitative variables number of aspirated oocytes, number of embryos, smoking, years of infertility, women's age and the categorical variables pregnancy prior to inclusion (yes/no) and fertility treatment prior to inclusion (yes/no). The study also explored whether the association between the determinant BMI and the outcome number of embryos developed was linear, quadratic or cubic. Multiple logistic regression analyses were performed to identify predictors of achieving a live birth and to take into account that most couples underwent more than one treatment cycle by using the SAS Glimmix procedure (Larsen et al., 2000). Women's and men's ages, women's BMI, duration of infertility prior to treatment, infertility diagnosis and social class were included in the model. Although smoking is a risk factor, this variable was not included as the study did not have smoking data on all participants. Multilevel logistic regression analyses with interaction terms of women's BMI and women's age (≤25, 26–30, 31–35, >35 years) were performed to evaluate the women's age cut-off at which weight loss is no longer relevant.

Results

The total number of overweight and obese women (BMI >25 kg/m²) eligible for the study was 162 (33.3%), out of whom 59 (12.1%) were obese (BMI > 30 kg/m²). The clinical characteristics of the study population are given in **Table 1**. All four BMI groups differed significantly regarding social class and main cause of infertility (P = 0.02 and P < 0.01, respectively). In analyses comparing only normal weight (BMI 18.5–24.9 kg/m²) with obese (BMI > 30 kg/m²), the obese group had a significantly longer mean period of infertility (P = 0.04), more women with anovulatory infertility (P < 0.01) and fewer women belonging to the higher social classes (P = 0.007). Regarding women's and men's age, smoking and fertility treatment prior to public treatment, no differences were observed between the normal-weight and obese groups.

The 487 infertile couples underwent a total of 1417 treatment cycles (IVF, ICSI or FET) with no differences in the distribution of treatment modality between groups (**Table 2**). There were a higher proportion of cancelled cycles in the underweight and the obese group (19–20%) versus 8–9% in the normal-weight and overweight groups. The number of initiated treatment cycles per woman during the 5-year follow-up period increased with increasing BMI and was highest among the obese women. Furthermore, there was a significantly higher mean number of cancelled cycles per woman among the obese and the reasons for cancelling a cycle differed significantly, with 'no fertilization' as the main cause in the high BMI group, while 'poor ovarian response' was the major factor among normal-weight women (P < 0.01; **Table 2**).

Table 3 shows the per-cycle-based outcomes of all 1181 fresh IVF and ICSI cycles. The total dose of gonadotrophin used, number of collected oocytes, number of embryos, number of cancelled cycles and number of cycles resulting in a positive serum HCG differed significantly between the four BMI groups (all P < 0.01) with the poorest outcome observed among the obese women. Regarding ongoing pregnancy and live-birth rates, no significant differences were seen between the four groups. Comparisons of normal-weight versus obese women showed ongoing pregnancy rates of 28.3% versus 20.8% (P = 0.04) and live-birth rates of 21.5% and 15.2% (p = 0.06) respectively.

To eliminate the decreasing probability of achieving pregnancy after repeated treatment cycles in the same couple, characteristics of only the first IVF or ICSI cycle in each couple were studied (Table 4). For first IVF or ICSI cycle, the mean number of oocytes retrieved and the mean number of embryos per cycle differed significantly between the four BMI groups (P < 0.01 and P = 0.01, respectively). Regarding

Table 3 Per-cycle-based characteristics of all fresh IVF and intracytoplasmic sperm injection treatments ($n = 1181$) according to body mass index (BMI).

Variable	*Body mass index (kg/m²)*				P-*value*[a,b]
	<18.5	18.5–24.9	25.0–29.9	≥30.0	
Started cycles	44	702	257	178	–
Total dose gonadotrophin (IU, median, range)	1950 (900–6075)	2025 (162–7075)	2250 (300–5800)	2400 (300–5850)	<0.01
Cancelled cycles	9 (20.5)	57 (8.1)	22 (8.6)	32 (18.0)	<0.01
Reason for cancellation					0.02
Poor response to stimulation	1 (11.1)	18 (36.7)	3 (14.3)	5 (16.1)	–
No eggs retrieved	0 (0.0)	14 (28.6)	6 (28.6)	12 (38.7)	–
No fertilization	8 (88.9)	17 (34.7)	12 (57.1)	14 (45.2)	–
Total	9	49	21	31	–
Oocytes collected	9.6 ± 6.1	9.9 ± 5.3	9.4 ± 5.1	8.3 ± 5.8	<0.01
Embryos	6.2 ± 5.5	6.2 ± 4.0	6.0 ± 4.4	4.7 ± 3.7	<0.01
Pregnancy outcome					
Positive HCG	14 (31.8)	221 (31.5)[b]	75 (29.2)	43 (24.2)[b]	<0.01 (NS)[b]
Biochemical pregnancy	0 (0.0)	10 (1.4)	4 (1.6)	1 (0.6)	NS
Ectopic pregnancy	0 (0.0)	5 (0.7)	3 (1.2)	3 (1.7)	NS
Ongoing pregnancy[c]	14 (31.8)	199 (28.3)[b]	68 (26.5)	37 (20.8)[b]	NS (0.04)[b]
Miscarriage	1 (2.3)	24 (3.4)	8 (3.1)	9 (5.1)	NS
Live birth	9 (20.5)	151 (21.5)[b]	45 (17.5)	27 (15.2)[b]	NS (0.06)[b]
Lost to follow-up	4 (9.1)	31 (4.4)	15 (5.8)	3 (1.7)	–

Values are *n* (%) or mean ± standard deviation, unless otherwise stated. HCG = human chorionic gonadotrophin; NS = not statistically significant.
[a]Comparisons of all four groups. For mean values of quantitative data ANOVA was used and for categorical data chi-squared test was used.
[b]Values in parentheses are comparisons of normal BMI (18.5–24.9 kg/m²) with obese (≥30 kg/m²). Chi-squared test was used.
[c]Ongoing pregnancy was defined as at least one fetus with fetal heartbeat verified by ultrasound in week 7.

differences in pregnancy outcomes, no statistically significant differences between the four BMI groups were found. However, comparing first cycle of only normal-weight and obese women found ongoing pregnancy rates of 31.5% versus 22.0% and live-birth rates 24.6% versus 16.9% in the two groups, respectively, but the differences were not statistically significant (Table 4).

Multiple linear regression analysis including only the first IVF or ICSI cycle showed a significant negative association between the number of collected oocytes and continuous BMI ($P < 0.001$, $B = -0.243$, standard error (SE) = 0.059) and women's age ($P = 0.014$, $B = -0.179$, SE = 0.073). Smoking, years of infertility, pregnancy or fertility treatment prior to inclusion were not statistically significant in the univariate analyses and thus not included in the final multiple regression model. **Figure 2** illustrates the expected number of oocytes collected related to women's BMI and age based on the final linear regression model.

The association between BMI and the number of developed embryos did not show a linear relationship but fitted a model with a quadratic association with an inverse U-shaped curve with less developed embryos in the low-weight and obese women ($P = 0.03$, $B = -0.018$, SE = 0.008; **Figure 3**). Thus both low BMI and obesity were negative predictors of the number of developed embryos in the first IVF or ICSI cycle, with BMI approximately 22 kg/m² as the most optimal for ovarian response (**Figure 3**).

Multilevel logistic regression analysis was conducted on predictors of live birth in consecutive treatment cycles, taking into account that the same couple could have had more than one treatment cycle. These analyses were conducted separately for all consecutive IVF/ICSI/FET cycles and in a separate analysis for fresh IVF/ICSI cycles only. The following potential covariates were included; women's BMI, women's age, men's age, duration of infertility prior to study inclusion, infertility diagnosis and social class. The final model for all consecutive IVF/ICSI/FET cycles showed that women's age, men's age and women's BMI were independent predictors of live birth (**Table 5**). For each increase in women's BMI of 1 kg/m² and for each 1-year increase in women's age and men's age, the probability of achieving a live birth was significantly reduced ($P = 0.034$, $P = 0.037$ and $P = 0.04$, respectively; **Table 5**). In the analyses only including fresh cycles, men's age was no longer statistically significant. The impact of an increase in women's BMI on reduced probability of a live birth was identical when comparing the estimates based on all treatment cycles including frozen embryos and on fresh cycles only.

To determine the women's age, where a weight reduction to increase the chance of pregnancy is no longer clinically relevant, interaction terms of women's age and BMI in the logistic regression analyses were included. These results showed that BMI had the highest impact in the youngest age group, ≤25 years (OR 0.93, 95% CI 0.87–0.98) with less

Table 4 Characteristics of first-cycle fresh IVF and intracytoplasmic sperm injection treatments (n = 487) according to body mass index.

Variable	*Body mass index (kg/m²)*				*P-value*[a,b]
	<18.5	*18.5–24.9*	*25.0–29.9*	*≥30.0*	
Started cycles	20	305	103	59	–
Total dose gonadotrophin (IU)	2008 ± 922	1987 ± 705	2153 ± 748	2176 ± 659	NS
Cancelled cycles	2 (10.0)	29 (9.5)	12 (11.7)	10 (17.0)	NS
Reason for cancellation[b]					NS
Poor response to stimulation	0	4	1	2	–
No eggs retrieved	0	5	4	3	–
No fertilization	2	15	7	5	–
Missing	0	5	0	0	–
Total	2	29	12	10	–
Oocytes retrieved	9.9 ± 6.2	10.5 ± 5.5	9.6 ± 5.2	7.6 ± 4.7	<0.01
Embryos	6.0 ± 5.2	6.5 ± 4.2	6.1 ± 4.5	4.4 ± 3.5	0.01
Pregnancy outcome					
Positive HCG	6 (30.0)	107 (35.1)	33 (32.0)	16 (27.1)	NS (NS)
Biochemical pregnancy	0	4 (1.3)	2 (1.9)	2 (3.4)	–
Ectopic pregnancy	0	1 (0.3)	0	0	–
Ongoing pregnancy[c]	6 (30.0)	96 (31.5)	30 (29.1)	13 (22.0)	NS (NS)
Miscarriage	1 (5.0)	10 (3.3)	2 (1.9)	3 (5.1)	–
Live birth	4 (20.0)	75 (24.6)	24 (23.3)	10 (16.9)	NS (NS)
Lost to follow-up	1 (5.0)	17 (5.6)	5 (4.9)	1 (1.7)	–

Values are n (%) or mean ± standard deviation, unless otherwise stated. HCG = human chorionic gonadotrophin; NS = not statistically significant.
[a]Comparisons of all four groups. For mean values of quantitative data ANOVA was used and for categorical data chi-squared test was used.
[b]Values in parentheses are comparisons of normal BMI (18.5–24.9 kg/m²) with obese (≥30 kg/m²). Chi-squared test was used.
[c]Ongoing pregnancy was defined as at least one fetus with fetal heartbeat verified by ultrasound in week 7.

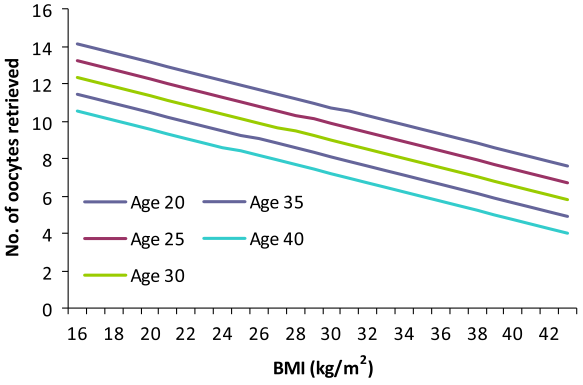

Figure 2 The expected number of oocytes retrieved related to women's body mass index (BMI) and female age. Multiple linear regression analysis only including the first IVF or intracytoplasmic sperm injection cycle showed a significant negative association between the number of collected oocytes and BMI ($P < 0.001$, $B = -0.243$, SE = 0.059) and women's age ($P = 0.014$, $B = -0.179$, SE = 0.073).

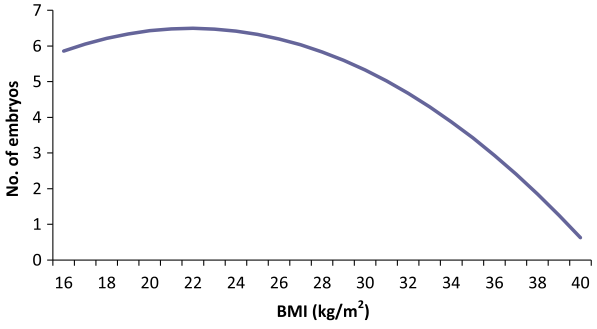

Figure 3 The expected number of embryos related to women's body mass index (BMI). The association between BMI and the number of embryos showed a quadratic relationship with an inverse U-formed curve with fewer embryos among the low-weight and the obese women ($P = 0.03$, $B = -0.018$, SE = 0.008).

impact with women's age 26–30 years (OR 0.96, 95% CI 0.93–1.00), 31–35 years (OR 0.96, 95% CI 0.93–1.00) and ≥36 years (OR 0.96, 95% CI 0.92–1.01), where results were no longer statistically significant.

Discussion

The major findings of this study of 1417 consecutive IVF/ICSI cycles in 487 couples initiating public fertility treatment were: (i) the number of cancelled cycles per woman was significantly higher in the obese group; (ii) positive serum HCG

Table 5 Multilevel logistic regression analysis on predictors of a first live birth in all IVF, intracytoplasmic sperm injection and frozen-embryo transfer treatment cycles and in all fresh IVF/intracytoplasmic sperm injection cycles.

Variable	*All treatment cycles (n = 1334)*	P-value[a]	*All fresh cycles (n = 1164)*	P-value[a]
Female BMI	0.96 (0.93–1.00)	0.034	0.96 (0.93–0.99)	0.024
Female age	0.95 (0.90–1.00)	0.037	0.93 (0.89–0.98)	0.011
Male age	0.96 (0.93–1.00)	0.040	0.97 (0.94–1.01)	NS

Results are presented as odds ratios (95% confidence interval) per year and kg/m^2. The following potential covariates were included; women's BMI, women's age, men's age, duration of infertility prior to study inclusion, infertility diagnosis and social class.
[a]For each increase in women's BMI of 1 kg/m^2 and for each 1-year increase in women's age and men's age. BMI = body mass index; NS = not statistically significant.

decreased with increasing BMI; and (iii) ongoing pregnancy was lower among obese versus normal-weight women. Live-birth rate appeared to be lower in obese than in normal-weight women, but the difference did not reach statistical significance. Increasing women's age and also rising men's age and women's BMI were significant negative predictors of live birth.

The strengths of the study are the long follow-up period of 5 years including specific information on all consecutive IVF/ICSI and FET cycles, which made it possible to adjust for relevant confounders such as social class and length of infertility. Both per patient and per cycle analyses as well as a multiple logistic regression analyses were performed to take into account that most couples underwent more than one treatment cycle.

One limitation of this study is the questionnaire design, where 64% of the initial 1372 couples responded to both the baseline and the 1-year questionnaire. A response rate of 64% in a survey with two questionnaires with a time interval of 1 year is considered good, but gives rise to concern of possible selection bias. However, there are no reasons to believe that BMI should have a skewed distribution between responders and non-responders and with an equal distribution of BMI there is no risk of bias according to the association between BMI and pregnancy outcome. Data on women's height and weight was missing in 32% of the cases in the clinical files. This lack of BMI can be explained by the new implementation of recording of BMI during the study period at Danish Fertility Clinics. Before the year 2000 BMI was considered of no relevance for assisted reproduction treatment outcome and was not recorded. Thus participants included at the beginning of the study period lacked data on BMI in their clinical files. The date of starting recording of BMI differed between the four participating fertility clinics. The risk of collection bias is considered to be limited, as there was no systematic lack of BMI recording. Lack of BMI data was solely related to the time period of inclusion in the study. Women's height and weight was only recorded at the first admission to the fertility clinics and no further recording of BMI was performed; hence the data could not be analysed for effects of changes in BMI over time. As the COMPI cohort was planned as a follow-up survey to explore many IVF outcomes including psycho-social effects of treatment and as BMI was not the primary endpoint, no power calculation was performed on BMI at study initiation.

The presence of polycystic ovary syndrome (PCOS) may have an independent effect on pregnancy rates (Wang et al., 2000). PCOS was not explicitly reported in the medical files and therefore the current data were based on the questionnaires, where the diagnostic category included 'irregular ovulation or anovulation'. As WHO type II anovulatory infertility is due to PCOS in 85–90% of the patients, it is believed that the vast majority of the patients reporting anovulation in this study have PCOS. Similarly, there was no specific differentiation of endometriosis patients. Irregular ovulation or anovulation was rarely reported in the normal-weight and overweight BMI groups, but in the obese group 13.6% of the patients reported anovulatory infertility. In Denmark, fertility specialists outside the University Hospital clinics treat most PCOS patients. This probably explains the modest number of patients with anovulation in the present trial. The primary treatment is ovulation induction with clomiphene citrate followed by low-dose recombinant FSH step-up protocols and a total of 6–9 cycles are offered. Thus, as IVF is only offered if pregnancy is not obtained following ovulation induction, there may be a negative selection of anovulatory patients belonging to the poorest prognosis group in the study material.

Comparison with other studies

Approximately one-third of the women in the study population had BMI $\geq$25 kg/m^2, which reflects the known distribution of high BMI in the general Danish population of women in the fertile age groups (Ekholm et al., 2006). Women's BMI was a significant negative predictor of live birth in the current multiple logistic regression analyses, but the sample size was too limited to draw firm conclusions regarding specific differences in live-birth rates between BMI groups. This may be because the vast majority of the high BMI group belonged to the overweight (BMI 25–29.9 kg/m^2) group and that the obese (BMI $>$ 30 kg/m^2) group consisted of only 59 patients, with a mean BMI 33.3 $\pm$ 2.9 kg/m^2, which is not very high. The results may have been different if the mean BMI had been 38 kg/m^2 or more.

Unlike women's age, BMI has only very recently been routinely recorded in the National Danish IVF register and is not yet recorded in other European national databases such as the Human Fertilisation and Embryology Authority (HFEA,

UK) (Maheshwari, 2010). The advantage of large individual datasets compared with meta-analyses is that the individual datasets are homogeneous and allow adjustment for relevant confounders. In the systematic review by Maheshwari et al. (2007), it was stated that sufficient knowledge on the impact of BMI on IVF live-birth rates, cancelled cycles and the reason for cancelling, collected oocytes, developed embryos and surplus embryos for freezing is still only weakly understood and documented. The systematic review revealed that BMI $\geq$25 kg/m^2 decreases the chance of pregnancy following assisted reproduction treatment (Maheshwari et al., 2007). In agreement, the current study found that women's BMI influences the chance of assisted pregnancy; however, the BMI cut-off was higher, namely 30 kg/m^2, than in the systematic review.

Regarding overweight and delivery rates, it was not possible to generate a funnel plot because of paucity of studies, as only three were found (Maheshwari et al., 2007), and further only one study from Sweden was found to report live-birth rates (Dokras et al., 2006; Fedorcsak et al., 2004; Wittemer et al., 2000). The Swedish study included all women undergoing assisted reproductive technology over a 6-year period in one clinical centre (2660 couples and 5019 IVF and ICSI cycles) and found a non-statistically significant difference in cumulative live-birth rates within three treatment cycles 41.4% in women with BMI $\geq$ 30 kg/m^2 versus 50.3% in normal-weight women (Fedorcsak et al., 2004). Wittemer et al. (2000) included 398 couples but excluded women with a poor prognosis and with PCOS. A decrease in the delivery rate per attempt was observed with increasing BMI values (20.8%, 15.2% and 14.3%, respectively, for BMI <20 kg/m^2, 20–25 kg/m^2 and >25 kg/m^2), but without reaching statistical significant difference (Wittemer et al., 2000). Dokras et al. (2006) included 1293 women less than 38 years of age and found no significant differences in first-cycle pregnancy rate in four different BMI groups.

In a very recent study of the 2007 US assisted reproduction treatment patient population including over 45,000 embryo transfers, it was found that increasing BMI was associated with significantly greater odds of failure to achieve a clinical intrauterine pregnancy per treatment cycle (Luke et al., 2011). This adverse effect was greater among women aged <35 years than in women aged $\geq$35 years, using their own (autologous) oocytes. Owing to small numbers, the effect of the use of donor oocytes with increasing BMI was analysed only among women aged $\geq$35 and it was not significant. The odds of failure to achieve a live birth significantly increased with older age and higher BMI when using autologous oocytes. The US results were per-cycle based and cannot be directly extrapolated to the Danish population as in the US population 40.0% had BMI >25 kg/m^2 and 6.4% had BMI >35 kg/m^2, while in the Danish population 33% had BMI >25 kg/m^2, indicating more severe adiposity in the US population. Further, in the US study 40% of the embryo transfers were with three or four embryos, with higher clinical gestation rates and a multiple birth rate of more than 30%, while the vast majority in Denmark were double-embryo transfer with lower multiple birth rates (Luke et al., 2011).

This study's findings of BMI as a significant independent predictor of live birth after consecutive IVF/ICSI cycles is in agreement with Swedish and recent US findings that obesity is associated with lower chances of pregnancy and live birth after IVF and ICSI (Fedorcsak et al., 2004; Luke et al., 2011). Additionally a recent review stated that observations from fertility clinics indicate that obese women may have altered oocyte developmental competence and sub-optimal early embryo development that may influence the pregnancy rates (Robker, 2008). This is supported by recent findings in their own laboratory, which demonstrate that diet-induced obesity in mice impairs oocyte developmental competence. This theory is consistent with the finding of increased very early miscarriages in obese women with the majority of studies describing pregnancy loss by 6–7 weeks of gestation, as detected by ultrasound (Fedorscak et al., 2000, 2004; Lashen et al., 2004).

The current study observed that men's age had an independent effect on live-birth rates in multilevel logistic regression analyses. This is in accordance with a recent systematic review, which concluded that increased paternal age has an influence on DNA integrity and telomere length in spermatozoa and is suggested to have epigenetic effects (Sartorius and Nieschlag, 2010). The authors speculated that these changes might, at least in part, be responsible for the association of paternal age over 40 years with reduced fertility, an increase in pregnancy-associated complications and adverse outcome in the offspring. Sartorius and colleagues highlighted that not only higher maternal age but also increasing paternal age (at least over 40 years) is associated with lower fertility, an increase in pregnancy-associated complications such as miscarriage, pre-eclampsia, possibly uteroplacental bleeding disorders, preterm birth and surgical deliveries. Two other studies, with spontaneous conceptions (de la Rochebrochard and Thonneau, 2002) and 17,000 intrauterine inseminations (Belloc et al., 2008), have shown that paternal age above 35–40 years after adjustment for maternal age is associated with significantly higher miscarriage rates. In the light of the current findings, the influence of paternal age should be considered in all future studies on assisted reproduction outcome, but it is impossible to provide any recommendations for clinical practice based on this study alone.

In coherence with previous studies (McClure et al., 1992; Mulders et al., 2003), the current study observed a significantly higher number of cancelled cycles in obese versus normal-weight women. Additionally, this study found more cancelled cycles in the underweight group. The two previous studies found that higher cancellation rates combined with substantially higher miscarriage rates led to lower live-birth rates per initiated cycle in obese women. In this study, 'no collected oocytes' was a more frequent reason for cancellation among obese women than in any of the other BMI groups. The reasons for the higher number of cancelled cycles that did not reach embryo transfer could be because of two factors. One is that technical difficulties in obese women, where the ultrasound-guided follicle puncture and flushing, may be more difficult. The other reason could be that in the obese group fewer follicles are present probably because of under-dosage of gonadotrophins, e.g. because the obese women may have a higher FSH threshold for multiple follicular growth. This is in accordance with a previous study (Nyboe Andersen et al., 2008) showing that the individual threshold dose for ovulation induction in anovulatory women can be predicted

based on menstrual cycle history; mean ovarian volume and, BMI.

Denmark has the highest availability of medically assisted reproductive treatments per woman of fertile age in Europe, and 7.9% of the national birth cohort in 2008 was born after medically assisted reproduction (both assisted and non-assisted reproduction treatments) (de Mouzon et al., 2010; http://www.fertilitetsselskab.dk). Infertile couples are offered three fully reimbursed IVF or ICSI transfer cycles with fresh embryos, but if live birth is obtained after the first or second fresh treatment cycle, no more fresh cycles are offered. There are no restrictions regarding the number of reimbursed FET and intrauterine insemination cycles, but only women aged below 40 years can be referred to public fertility treatment. As overweight and obese women are more likely to experience less successful assisted reproduction treatment, it is relevant to consider an upper BMI threshold for public IVF treatment or a certain required weight loss before treatment starts. The current results estimate that weight loss is relevant in the younger age groups and that women in older age groups do not benefit from weight loss. It is clinically relevant to raise the question of a women's age cut-off, where weight loss is no longer clinically relevant to enhance the chance of pregnancy, but it is difficult to identify a specific women's age cut-off, as the odds ratios lie very close. This cut-off value should be identified in future larger studies. Further, there are other concerns when treating women with high BMI, e.g. complications in relation to oocyte collection. Therefore the maximum BMI for allowing women to receive treatment set by the individual clinics cannot be altered by the current results, but it is sensible to consider women's age where weight loss no longer has a consequence for the treatment outcome. In the absence of complete Danish IVF datasets it is difficult to justify a specific cut-off to access treatment. Some healthcare settings include strict upper limits for BMI (Maheshwari, 2010). In New Zealand more drastic prioritization for fertility treatment has been achieved by the development of clinical priority access criteria (CPAC) in the mid-1990s. Seven separate criteria were developed for CPAC to provide a rationing basis for public access to treatment for couples who were most in need but balanced by those who would benefit most from treatment (Gillet et al., 2006). Only women within the BMI range 18–32 kg/m^2 applied to the CPAC and women outside this range were only accepted on the basis that they had undergone weight reduction to within the agreed range. Gillet et al. (2006) showed that 38% of women with BMI $>$32 kg/m^2 had a birth from conceiving a treatment-related pregnancy or spontaneous pregnancy, compared with 52% of women with BMI $<$32 kg/m^2. Weight loss allowed women in the BMI group 32–35 kg/m^2 to access treatment, but women in the higher BMI groups were nevertheless less successful.

Apart from the obesity-related fertility problems, there is indisputable evidence that pregnancy in overweight and obese women is associated with an increased risk of complications, leading to higher maternal and neonatal morbidity and mortality and increased costs (Cedergren, 2004; Denison et al., 2008; Linné, 2004; Sebire et al., 2001). Despite concerns regarding costs, there are few studies on economics of infertility treatment in overweight and obese women (Koning et al., 2010; Maheshwari et al., 2009). In a recent paper, Koning et al. (2010) described a framework for evaluating costs and outcomes of fertility care with regard to the economic consequences of overweight and obesity in infertility. For a hypothetical cohort of 1000 women separated in anovulatory and ovulatory groups based on extensive literature searches, they concluded that there is an increased cost per live birth through the path of infertility treatment for overweight and obese women when compared with those with normal BMI with the costs being the highest in the anovulatory group (Koning et al., 2010). In an editorial, Maheshwari (2010) stated that the findings of Koning et al. (2010) should be taken cautiously, as the model was based on data from varied observational studies with inherent bias despite robust methodology. Both authors agreed that reduced effectiveness of treatment is not a reason to withhold treatment, but there may be a case for rationing where public funding is available; rationalization for a specific cut-off value is questionable.

The current results confirm that treating women in the higher BMI ranges is a challenge and that these women are at a disadvantage compared with their normal-weight counterparts. Women should be counselled of the negative implications of increased BMI on reproductive outcome and general health. Weight loss with regard to women's age should be encouraged in those undergoing fertility treatment for both the overweight and obese, of course under consideration of the women's age cut-off, where weight loss no longer counts. Hence, it is timely that public funding of intervention strategies and weight-reduction programmes should be a major focus and first-choice treatment for certain patient groups in reproductive health care.

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