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Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women

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BACKGROUND: Obesity is increasing rapidly among women all over the world. Obesity is a known risk factor for subfertility due to anovulation, but it is unknown whether obesity also affects spontaneous pregnancy chances in subfertile, ovulatory women. METHODS: We evaluated whether obesity affected the chance of a spontaneous pregnancy in a prospectively assembled cohort of 3029 consecutive subfertile couples. Women had to be ovulatory and had to have at least one patent tube, whereas men had to have a normal semen analysis. Time to spontaneous ongoing pregnancy within 12 months was the primary endpoint. RESULTS: The probability of a spontaneous pregnancy declined linearly with a body mass index (BMI) over 29 kg/m^2. Corrected for possible related factors, women with a high BMI had a 4% lower pregnancy rate per kg/m^2 increase [hazard ratio: 0.96 (95% CI 0.91–0.99)]. CONCLUSIONS: These results indicate that obesity is associated with lower pregnancy rates in subfertile ovulatory women.

Keywords: obesity; subfertility; pregnancy chance; spontaneous conception

Introduction

The use of assisted fertility techniques has increased tremendously in the past three decades (Society for Assisted Reproductive Technology and American Society for Reproductive Medicine, 2002). Although this may be due to better availability of the wide range of current technologies, an increased demand for fertility care may play a role as well. This increased demand may be due to an increased incidence of Chlamydia trachomatis and increased maternal age (Martin, 2000; Coombes, 2004). Additionally, obesity is expected to be a potential cause for an increase in subfertility in the near future (Bolúmar *et al*., 2000).

Obesity is increasing rapidly all over the world, affecting more than one billion people worldwide (Haslam and James, 2005). The World Health Organization (WHO) considers a body mass index (BMI) as abnormal if BMI is over 25.0 kg/m^2 and defines obesity as a BMI over 30.0 kg/m^2 (World Health Organisation, 1995). More women of reproductive age are becoming overweight and obese. Nowadays, the incidence of obesity in women of child bearing age is 12% in Western Europe and 25% in North America (Butler, 2004; Linné, 2004; Haslam and James, 2005; Watson, 2005). The main adverse consequences are cardiovascular disease, type 2 diabetes and cancer. Overall, it is thought to be the sixth most important risk factor for mortality and morbidity (Allison *et al*., 1999). Furthermore, obesity is a known risk factor for anovulation, which may lead to subfertility (Rogers and Mitchell, 1952; Hartz *et al*., 1979; Norman and Clark, 1998; Moran *et al*., 1999).

Current NICE fertility guidelines recommend that all obese women, regardless of their cycle characteristics, should be informed that they are likely to take longer to conceive (National Institute for Clinical Excellence, 2004). This recommendation is based on three studies. Two studies analysed the relationship between BMI and time to pregnancy in women who were pregnant or had delivered a child (Jensen *et al*., 1999; Bolúmar *et al*., 2000), whereas the third study analysed fat distribution and the chance of conceiving in women in a donor insemination programme (Zaadstra *et al*., 1993). All studies reported a negative effect of obesity on the chance of pregnancy in these potentially fertile women.

However, evidence that obesity also affects the chance of spontaneous pregnancy in subfertile ovulatory women is still lacking. The aim of this study was to determine whether obesity in subfertile ovulatory women is associated with a decreased chance of spontaneous pregnancy.

Materials and Methods

Between January 2002 and February 2004, we included consecutive subfertile couples that had not been evaluated previously for subfertility, in a prospective cohort study. The study was performed in 24 hospitals in the Netherlands. The detailed study protocol has been documented in a previous publication (van der Steeg *et al*., 2007).

In short, all couples underwent a fertility work-up consisting of: a fertility history, including details about height and weight, smoking habits, assessment of ovulation, assessment of tubal patency and semen analysis (Dutch Society of Obstetrics and Gynaecology, 2004). Duration of subfertility and female and male age were set at the end of the infertility assessment. Subfertility was considered to be secondary if a woman had conceived in the current or in a prior partnership, regardless of the pregnancy outcome. The BMI was calculated as the weight in kilograms divided by the square of the height in meters, both self-reported during the first visit. BMI of the men as well as timing and frequency of intercourse were not documented.

Fertility work-up of the female partner

Ovulation was assessed by means of a basal body temperature chart, measurement of mid-luteal serum progesterone or by sonographic monitoring of the cycle. The menstrual cycle was considered regular if the duration of the cycle was between 23 and 35 days, with an inter-cycle variation of less than 8 days, during the past year (Munster *et al*., 1992). Tubal pathology was assessed by a chlamydia antibody test (CAT), hysterosalpingography (HSG) or laparoscopy. Those with a positive CAT subsequently went on to have further investigation with a HSG or laparoscopy (Mol *et al*., 1997). Couples, in whom the female partner was diagnosed with anovulation or with two-sided tubal pathology, were excluded from the analysis.

Fertility work-up of the male partner

Semen analysis was performed at least once according to the WHO guidelines, including semen volume, concentration, morphology and motility (World Health Organisation, 1999). Couples in whom the man had a total motile sperm count (TMC) $<3 \times 10^6$ were excluded from the study.

Follow-up

After completion of the fertility work-up, the probability of a spontaneous pregnancy within 1 year, leading to live birth, was calculated with a validated prediction model (http://www.freya.nl/probability.php) (Hunault *et al*., 2004; van der Steeg *et al*., 2007). Depending on that probability couples were counselled for expectant management or fertility treatment according to the national fertility guidelines (Dutch Society of Obstetrics and Gynaecology, 1998; Dutch Society of Obstetrics and Gynaecology, 2000). The exact study flow has been reported in a previous paper (van der Steeg *et al*., 2007). Couples were followed prospectively from the completion of the fertility work-up until pregnancy or start of treatment within 12 months. The primary endpoint was time to conception without treatment, resulting in an ongoing pregnancy and counted in calendar time used in a continuous way. Couples who did not conceive were censored when treatment started or at the last date of contact during follow-up.

Analysis

We first assessed the relation between BMI and probability of pregnancy through spline functions. By visual inspection, it was determined whether BMI behaved as a linear or non-linear function in relation to the probability of spontaneous pregnancy, and whether cut-off values for optimal BMIs could be observed. Non-linearity was tested with ANOVA analysis (Harrell *et al*., 1988).

We then analysed the predictive capacity of BMI as hazard ratios (HR) by Cox proportional hazard analysis of the time to spontaneous ongoing pregnancy. The proportional hazards assumption was evaluation with S-plus (Grambsch and Therneau, 1994). Lastly, we repeated the analysis correcting for possibly related factors in a multivariable hazards regression model. Potential related factors were female age, duration of subfertility, previous pregnancy, referral status, semen motility and current smoking of the female and male partner (Bolúmar *et al*., 2000; Hunault *et al*., 2004).

In all analyses, a *P*-value of 0.05 was used to indicate significance. Calculations were performed with SPSS® 12.0 (SPSS Inc., Chicago, IL, USA) and S-plus® 6.0 (MathSoft Inc., Seattle, WA, USA) programs.

Ethical approval

The study was approved by the local ethics committee of each participating centre.

Results

In total, 6035 subfertile couples that had completed their fertility work-up were registered. Of these, 379 (6.3%) couples with a duration of subfertility less than 1 year, 692 (12%) couples with anovulation, 211 (3.5%) couples with two-sided tubal pathology and 699 (12%) couples with severe male factor were excluded (Fig. 1). In 1025 (17%) couples the BMI was not reported. Therefore, 3029 couples were included in the analysis. Follow-up was completed for 2793 couples (92%). Of all couples, 529 (17%) had a spontaneous ongoing pregnancy within 1 year (Fig. 1). In 17 women, pregnancy outcome was unknown. There were 47 women (7.8% of all pregnancies) who miscarried and four women (0.7% of all pregnancies) who had an ectopic pregnancy. Within 12 months,

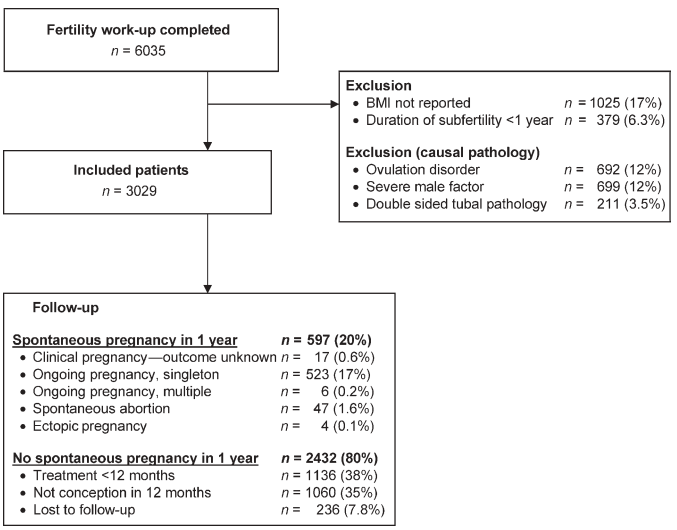

Figure 1: Flow chart

1136 (38%) couples started treatment, whereas 1060 (35%) neither started treatment nor became pregnant. Median length of follow-up was 28.1 weeks (fifth to 95th percentile: 2–134 weeks), 18.5 weeks (1–100 weeks) for those who conceived and 31.5 weeks (2–146 weeks) for those without a pregnancy.

Baseline characteristics are represented in the Table I. The median BMI was 22.9 kg/m^2 (5–95th percentile: 19–33 kg/m^2). A BMI below 18.5 kg/m^2 was found in 3.7% of the women, between 18.5 and 25 in 67%, between 25 and 30 in 19%, between 30 and 35 kg/m^2 in 6.7%, and $\geq$35 kg/m^2 in 3.8%. Couples, in whom the BMI was not documented, were on average older, more often secondary subfertile and more often referred by a gynaecologist (ANOVA statistics, $P < 0.05$), although differences were small. Other baseline characteristics were comparable between the groups. The spline analysis showed that BMI had an inversed U-shaped relationship with the probability of pregnancy, although this was not statistically significant over the whole range (Fig. 2) (ANOVA $P = 0.4$). From this spline function, two thresholds were derived at 21 and 29 kg/m^2. Women with a BMI between 21 and 29 were defined as the reference group. The univariable analysis showed that BMI, female age, duration of subfertility, secondary subfertility, referral status and semen motility were statistically significantly related to the probability of a spontaneous ongoing pregnancy (Table II). A BMI above 29 kg/m^2 was associated with a statistically significant lower probability of spontaneous ongoing pregnancy than the reference group [HR 0.95 per kg/m^2 above 29 kg/m^2 (95% CI 0.91–0.99)]. A BMI below 21 kg/m^2 was associated with a lower probability of spontaneous ongoing pregnancy than the reference group, but was not statistically significant [HR 0.97 per kg/m^2 below 21 kg/m^2 (95% CI

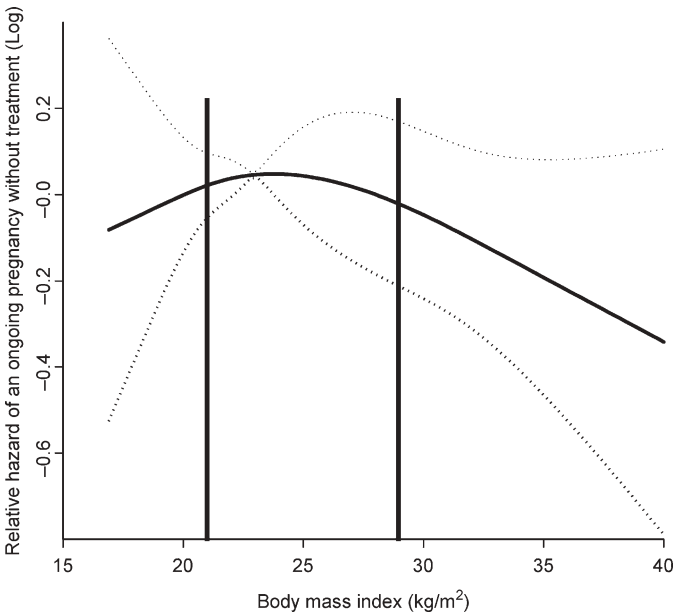

Figure 2: Spline function of the BMI in relation to time to spontaneous ongoing pregnancy.
Relative hazard~HR. Dotted lines represent 95% confidence intervals. Vertical lines show the thresholds of 21 and 29 kg/m^2. BMIs above 29 kg/m^2 were significantly associated with a decreased fecundity, whereas there was a trend below 21 kg/m^2

Table I. Baseline characteristics.

	BMI available $n = 3029$		BMI missing $n = 1025$		*P*-value[a]
	Mean	5–95th percentile	Mean	5–95th percentile	
Female age (year)	32.1	25–39	32.9	26–40	<0.01
Male age (year)	34.9	27–44	35.7	28–46	<0.01
Duration of subfertility (year) (median)	1.5	1.0–4.0	1.5	1.0–4.3	0.41
BMI (kg/m^2)	22.9	19–33	—	—	—
Subfertility, primary (%)	73		66		<0.01
Subfertility, secondary (%)	27		34		—
Referral status (second care)	92		86		<0.01
Referral status (third care)	7.8		14.1		—
Semen—TMC[b] (10^6) (median)	51.0	5.3–284	50.8	6.0–290	0.22
Cycle length (days)	28.1	23–33	28.1	23–33	0.84
Current smoking woman, no (*n*, %)	2272	(75%)	2820	(80%)	0.03
Current smoking woman, yes (*n*, %)	757	(25%)	209	(20%)	—
Current smoking man, no (*n*, %)	2005	(66%)	328	(68%)	0.29
Current smoking man, yes (*n*, %)	1024	(34%)	2701	(32%)	—

[a]Difference in baseline characteristics between women with and without data on BMI, tested with ANOVA.
[b]TMC, Total motile sperm count.

Table II. Results of the univariable and multivariable Cox' regression analysis.

	Univariable analysis		Multivariable analysis	
	HR	95% CI	HR	95% CI
BMI (kg/m^2)				
per unit<21	0.97	(0.87–1.07)	0.95	(0.86–1.05)
21–29[a]	1	—	1	—
per unit≥29	0.95	(0.91–0.99)	0.96	(0.91–0.99)
Potential confounders				
Female age (year)				
<31 per year	0.99	(0.95–1.02)	0.98	(0.94–1.01)
≥31 per year	0.94	(0.91–0.98)	0.94	(0.90–0.97)
Duration of subfertility per year	0.91	(0.84–0.99)	0.94	(0.86–1.03)
Subfertility, primary (%)	1	–	1	–
Subfertility, secondary (%)	1.5	(1.3–1.8)	1.6	(1.3–1.9)
Referral status (second care)	1	–	1	–
Referral status (third care)	0.65	(0.46–0.92)	0.67	(0.48–0.95)
Semen motility (per %)	1.009	(1.004–1.013)	1.008	(1.004–1.013)
Current smoking woman, no (*n*, %)	1	–	1	–
Current smoking woman, yes (*n*, %)	1.1	(0.96–1.4)	1.2	(0.98–1.4)
Current smoking man, no (*n*, %)	1	–	1	–
Current smoking man, yes (*n*, %)	0.97	(0.82–1.1)	0.94	(0.78–1.1)

[a]Women with a BMI 21–29 kg/m^2 were used as reference group.

0.87–1.07)] (Table II). The proportional hazards assumption, necessary to perform the Cox analysis in a correct way, was fulfilled.

The multivariable analysis, adjusted for female age, duration of subfertility, previous pregnancy, referral status (second or third care), semen motility and current smoking of the female and male partner, did not change the results [HR 0.96 per kg/m^2 (95% CI 0.91–0.99)]. In case of a woman with a BMI of 35 kg/m^2, the probability of spontaneous pregnancy was 26% lower, and in case of a woman with a BMI of 40 kg/m^2, it was 43% lower compared with women with a BMI between 21 and 29 kg/m^2.

Discussion

This cohort study showed that obesity is an important risk factor for pregnancy chances in subfertile, ovulatory women. For every BMI unit above 29 kg/m^2, the probability was reduced by ~5%, being a reduction comparable to the increment of one year in female age. Given the increased prevalence of obesity, this is a worrying finding.

Up till now, the relationship between BMI and pregnancy chances had not been established in ovulatory subfertile women. This is the first prospective cohort study to demonstrate this. It differs from previous studies on obesity and pregnancy chances in two ways. First, all other studies dealt with proven fertile populations, whereas our study included subfertile women. Second, many studies dealt with obesity as a categorical variable. In contrast, in this study, BMI was analysed as a continuous variable that allowed a subtle decline in pregnancy rate starting at 29 kg/m^2 to be demonstrated. In proven fertile women, BMI was reported to be a risk factor for the chance of conception in the category of women with a BMI over 25 kg/m^2 [HR 0.77 (95% CI 0.70–0.84) Jensen *et al*., 1999]. In the category of women with a BMI over 30 kg/m^2, BMI was reported to be a risk factor of having a delayed conception with an odds ratio of 12 (95% CI 3.7–36) (Bolúmar *et al*., 2000).

A limitation of this study is that frequency of intercourse was not taken into account. Recently, a review found support that obesity is associated with decreased intercourse frequency, reduced sexual desire and erectile dysfunction (Larsen *et al*., 2007). However, in view of the paucity of data, confounding factors like medication and adverse lifestyles could not be ruled out.

Another limitation of our study is the fact that the BMI of the male partner was not taken into account. Male obesity has been reported to increase the chance of becoming subfertile (Ramlau-Hansen *et al*., 2007), although the effect was weak. Nevertheless, because these data were missing in our study, we were not able to confirm or reject their findings. Finally, in the present study, BMI was lacking in 17% of the women. As our purpose was to examine the relation between BMI and the probability of pregnancy, this could have led to biased estimates of associations. To examine the impact of this partial verification, we explored whether there were any systematic differences between women in whom BMI was known and women in whom data on BMI was lacking. This was indeed the case with respect to female age, being secondary subfertile, referral status and smoking habits of the women, although differences were small. However, we may have selected a group here that was more fertile than the overall group.

We can only speculate about the pathophysiological explanations for the lower pregnancy chances in obese women. It has been suggested that leptin may be of importance (Rosenbaum and Leibel, 1999; Mantzoros, 2000; Chan and Mantzoros, 2005). Genetically mediated states of leptin deficiency result in obesity and subfertility (Rosenbaum and Leibel, 1999). Decreasing leptin levels due to starvation result in decreased estradiol levels and amenorrhoea (Mantzoros, 2000). There is evidence that leptin may influence ovarian steroidogenesis directly. Further research of the role of intra-ovarian leptin action in relation to subfertility remains of interest.

It could be hypothesized that lifestyle interventions that focus on weight reduction are an effective intervention (Knowler *et al*., 2002). This study focused on the BMI at start of the fertility work-up, rather than on weight changes. In subfertile anovulatory women, several studies have reported such a beneficial effect (Hollmann *et al*., 1996; Pasquali *et al*., 1997; Crosignani *et al*., 2003). A next step could be to randomly allocate obese and subfertile, ovulatory women to a controlled low-calories diet, or to their normal diet and compare HR.

In conclusion, the results of this study indicate that ovulatory subfertile women with a BMI over 29 kg/m^2 have lower pregnancy rates compared with those with normal weight. Now, we know that not only obese women with anovulation have lower chances of conception, but also obese women with a regular cycle. Owing to the fact that more women of child-bearing age are becoming overweight and obese, this is a worrying finding.

Author contributions

Ben W.J. Mol, Fulco van der Veen and Peter G.A. Hompes designed the study. Jan Willem van der Steeg and Pieternel Steures promoted it, co-ordinated this cohort study, collected the data and sought ethical approval. Jan M. Burggraaff and Jur G.J.E. Oosterhuis included couples and collected data. Jan Willem van der Steeg did the analysis, under the supervision of Ben W.J. Mol and Marinus J.C. Eijkemans. J. Dik F. Habbema and Patrick M.M. Bossuyt provided statistical advice. All authors helped to prepare the final report. Other contributors in this multicentre study included couples and are mentioned as a part of the CECERM study group.

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Appendix

CECERM study group (Collaborative Effort for Clinical Evaluation in Reproductive Medicine).

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17. C.J.C.M. Hamilton; 's Hertogenbosch, Jeroen Bosch Ziekenhuis
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23. P. Bourdrez; Venlo/Venray, Vie Curi Medisch Centrum
24. W.W.J. Riedijk; Zaandam, Zaans Medisch Centrum

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