Obesity and time to pregnancy

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BACKGROUND: Obesity may reduce fecundity. We examined the obesity–fecundity association in relation to menstrual cycle regularity, parity, smoking habits and age to gain insight into mechanisms and susceptible subgroups.

METHODS: Data were provided by 7327 pregnant women enrolled in the Collaborative Perinatal Project at 12 study centres in the United States from 1959 to 1965. Prepregnancy body mass index (BMI) was analysed continuously and categorically [underweight (<18.5 kg/m²), optimal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²) and obese (≥30.0 kg/m²)]. Adjusted fecundability odds ratios (FORs) were estimated using Cox proportional hazards modelling for discrete time data. RESULTS: Fecundity was reduced for overweight [OR = 0.92, 95% confidence interval (95% CI): 0.84, 1.01] and obese (OR = 0.82, 95% CI: 0.72, 0.95) women compared with optimal weight women and was more evident for obese primiparous women (OR = 0.66, 95% CI: 0.49, 0.89). Fecundity remained reduced for overweight and obese women with normal menstrual cycles. Neither smoking habits nor age modified the association. CONCLUSIONS: Obesity was associated with reduced fecundity for all subgroups of women and persisted for women with regular cycles. Our results suggest that weight loss could increase fecundity for overweight and obese women, regardless of menstrual cycle regularity, parity, smoking habits and age.

Key words: fecundity/fertility/obesity/reproduction

Introduction

Since 1971, the total fertility rate in the United States has been below the threshold required to maintain a steady population size (i.e. less than 2.1 births per woman over her reproductive lifetime) (Hamilton, 2004). This deficit can be explained partly by social changes in desired family size, increased availability and effectiveness of contraception and increased availability and use of induced abortion (Sallmen et al., 2005). However, between 1996 and 2002, the number of assisted reproductive technology (ART) procedures increased by 78%, and the number of conceptions due to ART increased by 120% (Wright et al., 2005), suggesting that among other factors, the decreased fertility rate may be explained in part by a decrease in human fecundity.

Obesity has been associated with reduced fecundity (Green et al., 1988; Zaadstra et al., 1993; Rich-Edwards et al., 1994, 2002; Lake et al., 1997; Jensen et al., 1999; Bolumar et al., 2000; Hassan and Killick, 2004) as well as impaired pregnancy success for women using ARTs (Bellver et al., 2003; 2006; Pasquali et al., 2003; Mitchell et al., 2005; Franks, 2006; Pasquali and Gambineri, 2006). One hypothesized mechanism is that obesity affects the hypothalamic–pituitary–ovary axis resulting in irregular cycles (Pralong et al., 2002; Pasquali et al., 2003; Haslam and James, 2005). However, some evidence indicates that the effect of obesity on fecundity persists for women with regular menstrual cycles (Jensen et al., 1999; Bolumar et al., 2000). Additionally, other evidence suggests fecundity may only be reduced for obese women who smoke (Bolumar et al., 2000). Given the increasing prevalence of obesity for women in their prime reproductive years (20–39 years old) (Flegal et al., 2002; Ogden et al., 2004), a closer look at risk factors that modify the obesity–fecundity association is in order as it may provide insights into mechanisms and highlight susceptible subgroups.

Our objective was to examine the obesity–fecundity association in relation to parity, menstrual cycle regularity, smoking habits and age. We hypothesized that (i) increasing body mass index (BMI) would be associated with reduced fecundity; (ii) the association would be stronger for previously nulliparous women because, as a group, they have a broader range of fertility represented; (iii) the association would persist for women with normal menstrual cycle characteristics (Jensen et al., 1999; Bolumar et al., 2000), suggesting a mechanism other than irregular menstrual cycling; (iv) smoking status would modify the association such that the effect would be stronger for smokers (Bolumar et al., 2000), especially given the...
independent association between smoking and reduced fecundity (The Practice Committee of the American Society for Reproductive Medicine, 2004) and (v) age would modify the association such that the effect would be stronger with increasing age given the independent association of age and reduced fecundity (ESHRE Capri Workshop Group, 2005).

**Materials and methods**

From 1959 to 1965, when smoking prevalence was high, over 55,000 pregnant women were enrolled in the Collaborative Perinatal Project at 12 study centres across the United States (Broman, 1984). The Collaborative Perinatal Project was a large prospective study designed to investigate the developmental consequences of complications arising during pregnancy or the perinatal period. Information was collected on prepregnancy weight, height and time to pregnancy; demographic and smoking-related data and reproductive, medical and gynaecological history.

Information on time to pregnancy was assessed at the initial study visit (median 16 weeks’ gestation). Among other questions, women were asked, ‘Have you been trying to become pregnant?’ Those who responded, ‘Yes’ were asked, ‘How long did it take you to become pregnant?’ The response was recorded in months starting at 1 month. We used this self-reported estimate as the time-to-pregnancy measure for our primary analysis. However, we also compared the results substituting the original time to pregnancy estimates with a time-to-pregnancy estimate corrected for miscarriage (recalculated starting from the date of recent miscarriage, if miscarriage date was included in the time-to-pregnancy interval), post-partum subfertility (crediting a 2-month period of subfertility) and lactational amenorrhoea (crediting a 4-month period of subfertility) (Gesink Law *et al.*, 2005).

Continuous prepregnancy BMI was calculated using self-reported height and prepregnancy weight, then categorized into underweight (<18.5 kg/m²), optimal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²) and obese (≥30.0 kg/m²). Subjects were asked about current smoking status, total years smoked and number of cigarettes smoked per day. Women were classified as having irregular cycles if they reported irregular menstrual cycles, skipped one or more menstrual periods regularly or if the usual length of their menstrual cycles varied by more than 7 days (Cooper *et al.*, 2005). Demographic data included age, race/ethnicity, education and occupation. Detailed information about each previous pregnancy and its outcome was also available. Information on alcohol and drug use ascertained severe abuse only, which was reported rarely; so, we did not use these data. Data on waist size, waist-to-hip ratio, diet, caffeine consumption, knowledge of the fertile window and frequency and timing of intercourse were not collected.

Of the 59,391 enrolled pregnancies, we excluded 47,399 unplanned pregnancies because they lacked time-to-pregnancy estimates and 2969 planned pregnancies that were missing time-to-pregnancy estimates. Of the remaining 9023 planned pregnancies with time-to-pregnancy estimates, 671 were missing height, 151 were missing prepregnancy weight and 225 were missing both height and prepregnancy weight estimates. Of the remaining 7976 planned pregnancies, we retained all entries for women with only one enrolled pregnancy (n = 7002), the first planned pregnancy for women with more than one enrolled pregnancy (n = 403) and one pregnancy record for women with plural births because each twin or triplet had their own entry (n = 71). Thus, there were 7476 eligible pregnancies for analysis. However, our results reflect the fecundability of 7327 women because 149 of the original 7476 women were missing data on covariates in the final model (Figure 1).

**Data analysis**

For descriptive purposes, we compared more fertile women (those who became pregnant in 3 months or less) with less fertile women (those who became pregnant in more than 3 months) according to risk factors known to increase time to pregnancy. We also compared women who planned their pregnancy with women who had not planned their pregnancy on BMI, age, smoking habits, parity and other demographic, gynaecological and reproductive characteristics.

Fecundability odds ratios (FORs) (Weinberg and Wilcox, 1998) describing the association between time to pregnancy and BMI were estimated using a Cox proportional hazards model (Cox, 1972) modified for discrete time data (SAS 9.0, The SAS Institute, Cary, NC, USA; STATA/SE 9, Statacorp, College Station, TX, USA). FORs <1 signified decreased fecundity or increased time to pregnancy. Time to pregnancy was censored at 13 months in the event that women with longer times to pregnancy received treatment for infertility (Baard *et al.*, 1986). One thousand one hundred and ninety-three (16%) pregnancies were censored at 13 months. BMI was categorically examined by using underweight, optimal weight, overweight and obese categorizations and by continuously using a quadratic spline to allow more flexible estimation of the non-linear relationship between BMI and fecundability.

*A priori*, we decided that our base model needed to adjust for age and investigated confounding in the age-adjusted model. Covariates that changed any of the β-coefficients describing the association between categorical BMI and time to pregnancy by 10% or more were considered confounders (Rothman and Greenland, 1998). We evaluated the following covariates for confounding: current smoking status (yes; referent no), race (non-white; referent white), maternal education (number of years), maternal current or most recent occupation (referent never worked; blue collar; white collar) and study centre (for methodological reasons including interviewer and population differences among centres).

We evaluated effect modification by smoking habits and age, as well as by race and study centre. We evaluated effect modification in
age- and covariate-adjusted models using a likelihood ratio test. If an interaction term was significant at the $\alpha = 0.10$ level, we examined stratum-specific estimates to determine if effect modification was substantively important enough to report separate estimates. Smoking variables included smoking status (yes; referent no), number of cigarettes smoked per day, number of years smoked and pack years (referent 0, 0–10, 10–20 and >20).

Nulliparous women represent a broader spectrum of fertility than parous women (Axmon et al., 2006). Consequently, the effect of obesity on fecundity may be more apparent for primiparous women than multiparous women. Therefore, we stratified our analysis by parity. We also restricted our analyses to women with regular menstrual cycle characteristics (Cooper et al., 2005), and again to women with normal cycle lengths (27–29 days), to test the hypothesis that reduced fecundity is the result of irregular cycles in overweight and obese women.

We conducted several secondary analyses to verify the robustness of our results. We restricted our analysis to women with singleton births, without indication of metabolic or endocrine dysfunction (including diabetes) and without indication of prior gynaecological condition (vaginitis, infertility, incompetent cervix, surgery for incompetent cervix, gynaecological surgery, leiomyoma, other gynaecological tumour and other gynaecological problem).

**Results**

Compared with women in the Collaborative Perinatal Project who had not planned their pregnancies, a greater proportion of women in our analysis were white, married, more highly educated, employed in a white-collar job and had not been pregnant before. However, these two groups of women did not differ on BMI, age, smoking habits, gynaecological characteristics or frequency of spontaneous abortion (Table I). Furthermore, among primiparas, BMI did not differ between planners and non-planners (data not shown).

Most of the women in our analysis were young, white and working (Table II). Ninety-four percent were married or in common law marriages. 64% of the women had been pregnant before, 21% had a history of miscarriage and 45% were currently smokers. On average, smokers smoked 13 cigarettes per day for 7 years (mean pack-years = 5). The mean and median BMIs were within the optimal range; 13% were overweight, and 5% were obese. As expected, fecundity was reduced (longer time to pregnancy) for older women, smokers, non-whites and women with irregular cycles. Fecundity was also lower for women with less education. Women in white-collar occupations had increased fecundity (shorter time to pregnancy), possibly because they were in better health (Artazcoz et al., 2004) or because they were more highly educated and knowledgeable about their fertile window. The relation of education to fecundity, however, varies across studies (Axmon et al., 2006).

Planners had a median (first quartile and third quartile) time to pregnancy of 3 months (1 month and 9 months). By BMI, median time to pregnancy was 3 months (1 month and 8 months) for underweight women, 3 months (1 month and 9 months) for optimal weight women, 4 months (2 months and 12 months) for overweight women and 5 months (2 months and 18 months) for obese women. Multiparous women had higher fecundity or shorter time to pregnancy [FOR: 1.17, 95% confidence interval (95% CI): 1.09, 1.24], compared with primiparous women, after adjusting for BMI, age, smoking, race, occupation, education and study centre.

After adjusting for age, fecundability was reduced for underweight (FOR = 0.94; 95% CI: 0.86, 1.03), overweight (FOR = 0.84; 95% CI: 0.77, 0.92) and obese (FOR = 0.72; 95% CI: 0.63, 0.83) women, compared with women with an optimal BMI.

Adjustment for smoking, race, occupation, education and study centre changed the $\beta$-coefficients for each category of BMI by more than 10% when compared with the age-adjusted model. Time to pregnancy increased for overweight and obese women compared with women with an optimal BMI, after adjusting for age, smoking, race, education, occupation and study centre (Table III). The probability of conception had an inverse-U shape with increasing BMI, indicating that fecundability was highest for women in the lower end of the optimal range and decreased for underweight, overweight and obese women (Figure 2). The upward turn for women with very high BMIs is because of the small number of women in that range.

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### Table 1. Characteristics of women in the Collaborative Perinatal Project who planned their pregnancies (planners) compared with those who did not (non-planners)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Planners (n = 8514) % or median (Q1, Q3)</th>
<th>Non-planners (n = 39,683) % or median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>17 (21.3, 23.8)</td>
<td>15 (21.5, 24.5)</td>
</tr>
<tr>
<td>Optimal weight (18.5–24.9 kg/m²)</td>
<td>11 (63)</td>
<td>13 (60)</td>
</tr>
<tr>
<td>Overweight (25.0–29.9 kg/m²)</td>
<td>8 (11)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Obese (≥30 kg/m²)</td>
<td>8 (Age)</td>
<td>8 (Age)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>23 (20, 27)</td>
<td>23 (19, 28)</td>
</tr>
<tr>
<td>20–23</td>
<td>25 (20–23)</td>
<td>25 (23)</td>
</tr>
<tr>
<td>23–27</td>
<td>32 (23–27)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>≥28</td>
<td>23 (26)</td>
<td>23 (26)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>46 (44)</td>
<td>46 (44)</td>
</tr>
<tr>
<td>Prior pregnancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (40)</td>
<td>32 (32)</td>
</tr>
<tr>
<td>1</td>
<td>27 (27)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>2+</td>
<td>33 (33)</td>
<td>47 (47)</td>
</tr>
<tr>
<td>Prior miscarriages among women with prior pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>67 (67)</td>
<td>74 (74)</td>
</tr>
<tr>
<td>1</td>
<td>24 (24)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>2+</td>
<td>9 (9)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Irregular cycles</td>
<td>8 (11)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never worked</td>
<td>13 (13)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>White collar</td>
<td>44 (44)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Blue collar</td>
<td>44 (44)</td>
<td>56 (56)</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>17 (17)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Less than high school</td>
<td>32 (32)</td>
<td>41 (41)</td>
</tr>
<tr>
<td>High school</td>
<td>33 (33)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>More than high school</td>
<td>18.5 (18.5)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64 (64)</td>
<td>42 (42)</td>
</tr>
<tr>
<td>Non-white</td>
<td>36 (36)</td>
<td>58 (58)</td>
</tr>
</tbody>
</table>

Q. quartile. Women in the Collaborative Perinatal Project were enrolled at 12 study centres in the United States from 1959 to 1965.
Age, race and study centre did not modify the association between obesity and fecundity. However, evidence of effect modification by smoking habits was mixed. The association was not modified by number of cigarettes smoked per day \((P = 0.21)\) nor by number of years smoked \((P = 0.15)\). Effect modification by smoking status was of borderline statistical significance.
and overweight, the ORs showed no suggestion of dose–smoking categories had similar ORs, and for the underweight, statistical evidence for modification by pack-years smoked was different smoking categories were similar (Table III). Statistically, significance ($P = 0.04$), but again, obese subjects in different smoking categories had similar ORs, and for the underweight and overweight, the ORs showed no suggestion of dose–response relations. Overall, evidence of effect modification by smoking was not compelling.

The association between BMI and time to pregnancy was essentially unchanged when we restricted our analyses to women with regular menstrual cycles or menstrual cycles 27–29 days long. When we stratified our analysis on parity, the association was stronger for primiparous women, especially obese primiparous women (Table III).

The association between BMI and time to pregnancy was unchanged when we restricted our analyses to singleton pregnancies, normal metabolic and endocrine function or women without gynaecological conditions. Similarly, correcting 344 time-to-pregnancy estimates for unaccounted miscarriage, post-partum subfertility and lactational amenorrhoea (see Materials and methods; results not shown) did not alter the observed associations either.

Discussion

Fecundability, or the probability of conceiving a pregnancy for a given cycle (Baird et al., 1986), was reduced for overweight and obese women compared to women with an optimal BMI enrolled in the Collaborative Perinatal Project. Overall, the probability of conceiving in a given cycle was reduced 8% for overweight women and 18% for obese women. This translated to a median 1 month longer for overweight women to become pregnant and 2 months longer for obese women to become pregnant compared with optimal weight women. Cumulatively, this meant it took about 3 months longer before 75% of overweight women became pregnant and 9 months longer before 75% of obese women became pregnant compared with optimal weight women. Focusing on the results for previously nulliparous women (primiparous in our analysis), the probability of conceiving per cycle was reduced even further: by about 16% for overweight and 34% for obese nulliparous women.

Our investigation confirms those of Jensen et al. (1999), Bolumar et al. (2000) and Hassan and Killick (2004). Similar to Jensen et al. (1999) and Bolumar et al. (2000), the associations we observed were maintained when we restricted our analyses to women with regular menstrual cycles. However, contrary to Bolumar et al. (2000), we only found subtle differences between smokers and non-smokers. Bolumar and colleagues reported that reduced fecundability among underweight, overweight and obese women occurred only among smokers, but compared with our analysis, they had a much smaller sample, a lower percentage of smokers and a lower proportion of overweight and obese women. We conclude that there was no effect modification by smoking nor was there any by age. The greater reduction in fecundity for overweight and obese primiparous women further supports our central hypothesis.

We restricted our analysis to women who planned their pregnancy. This could be a problem if women who did not plan their pregnancy had different BMIs or differed from women who planned their pregnancies in other important characteristics. When we compared planners with non-planners, we did not find a difference in BMI, age, smoking habits, cycle length, cycle regularity or previous gynaecological condition. However, more planners were primiparous. This difference could explain some of the association we observed if planners had lower fecundity than non-planners.

The association between obesity and fecundity may be weaker than we observed. Obesity and infertility are common characteristics of polycystic ovary syndrome (PCOS), which occurs in ~4% of women (Guzick, 2004). Given that the prevalence of obesity was lower in the 1960s (5%) than it is today (over 25%), it is possible that a higher proportion of obese women in our study had PCOS. The fertility problems women with PCOS experience, such as anovulation, may not be a consequence of their obesity (Pralong et al., 2002; Pasquali et al., 2003). PCOS was not recognized at the time of this study, but during the physical examination, physicians noted whether hirsutism and obesity were ‘normal’ or ‘abnormal’ for a subset of women in our analysis ($n = 4115$). Less than 10 women were identified as potentially having PCOS regardless of whether we defined PCOS as women with hirsutism and menstrual cycle length greater than 36 days ($n = 7$); hirsutism and obesity ($n = 8$); or hirsutism, obesity and menstrual cycle length greater than 36 days ($n = 3$) (Hartz et al., 1979). However, PCOS can exist without hirsutism, and although PCOS is likely to explain some of the associations we observed, we believe the prevalence is low in our participants and unlikely to explain all our results.

The association between obesity and reduced fecundity may also be stronger than we observed because our sample did not include women who did not become pregnant. Consequently, we may be missing a group of women whose ability to
conceive a detectable pregnancy is particularly sensitive to the mechanism(s) by which obesity reduces fecundity. This is further supported by the stronger association between fecundity and increased weight or obesity that we observed when we stratified our analysis on parity.

The biological mechanism responsible for the association between BMI and fecundity is unclear. One hypothesis is that obesity affects the hypothalamic–pituitary–ovary axis (Pralong et al., 2002; Pasquali et al., 2003; Haslam and James, 2005). Excess free estrogen, resulting in part from increased peripheral conversion of androgens to estrogens in adipose tissue, combined with decreased availability of GnRH, could interfere with hypothalamic–pituitary regulation of ovarian function, causing irregular or anovulatory cycles (Hartz et al., 1979; Pralong et al., 2002; Haslam and James, 2005). However, like Jensen et al. (1999), we found that fecundity remained reduced for overweight and obese women with regular menstrual cycles, which suggests that anovulation despite regular menses or the release of ova with reduced fertilization potential or even endometrial abnormalities, may be the more likely mechanism.

Another possibility is that obese women have reduced fecundity because of a complex interplay of psychosocial, sociobiological and physiological factors. Obese people do not have sexual intercourse as frequently as slimmer people, even if they have a cohabiting sexual partner (Brody, 2004). This could be explained, in part, by decreased sex drive resulting from decreased dopamine activity and increased serotonin levels in the brain due to overeating (Brody, 2004) and increased sexual dysfunction (Trischitta, 2003). Additionally, chronic fat or sugar consumption could have psychopharmacological effects, relabelling sexual desire as a cue to eat (Brody, 2004). For obese women then, especially primiparous obese women, knowledge of the fertile window and timing of intercourse is even more important, because the probability of capturing the fertile window by chance is lowered with decreased frequency of sexual intercourse.

Our conclusions are based on an analysis of 7327 women who were trying to get pregnant and conceived in the late 1950s/early 1960s, when the prevalence of maternal smoking was high (46%), but the prevalence of obesity (5%) and oral contraception could have psychopharmacological effects, relabelling sexual desire as a cue to eat (Brody, 2004). For obese women then, especially primiparous obese women, knowledge of the fertile window and timing of intercourse is even more important, because the probability of capturing the fertile window by chance is lowered with decreased frequency of sexual intercourse.

References


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