Human Reproduction Vol.19, No.7 pp.1644–1646, 2004
Advance Access publication May 13, 2004

DOI: 10.1093/humrep/deh277

Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case–control study

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BACKGROUND: Obesity has become a major health problem worldwide and is also associated with adverse pregnancy outcome. The aim of this study was to assess the impact of obesity on the risk of miscarriage in the general public. METHODS: This was a nested case–control study. The study population was identified from a maternity database. Obese [body mass index (BMI) >30 kg/m^2] women were compared with an age-matched control group with normal BMI (19–24.9 kg/m^2). Only primiparous women were included in the study to avoid including the subject more than once, and to be able to correctly identify recurrent miscarriages. The prevalence of a previous history of early (6–12 weeks gestation), late (12–24 weeks gestation) and recurrent early miscarriages (REM) (more than three successive miscarriages <12 weeks) was compared between the two groups. RESULTS: A total of 1644 obese and 3288 age-matched normal weight controls with a mean age of 26.6 years [95% confidence interval (CI) 26.5–26.7] were included in the study. The risks of early miscarriage and REM were significantly higher among the obese patients (odds ratios 1.2 and 3.5, 95% CI 1.01–1.46 and 1.03–12.01, respectively; *P* = 0.04, for both]. CONCLUSIONS: Obesity is associated with increased risk of first trimester and recurrent miscarriage.

Key words: obesity/miscarriage/recurrent miscarriage

Introduction

Obesity has become a major health problem across the world. In the UK, obesity affects one-fifth of the female population (Anonymous, 2001). Maternal obesity has been reported as a risk factor for adulthood obesity in offspring (Parsons *et al*., 2001). Obesity may also lead to a poor pregnancy outcome, such as sudden and unexplained intrauterine death (Froen *et al*., 2001), and in women with polycystic ovary syndrome (PCOS) receiving infertility treatment is associated with an increased risk of miscarriage (Hamilton-Fairley *et al*., 1992; Wang *et al*., 2000). However, in the general population there is less evidence for a link between obesity and spontaneous miscarriage (Risch *et al*., 1990). The aim of this study was to determine whether there is any association between obesity and the risk of spontaneous miscarriage in a general population.

Materials and methods

The database of Solihull Maternity Unit from 1985 to 1999 was reviewed. This is a comprehensive, prospectively collected database that records maternal gynaecological and obstetric history, as well as current pregnancy details and outcome. All data are entered at the time of birth; therefore, all the participants in this study gave birth to their first child during that period. The outcome of previous pregnancies of all women who delivered during the study period was retrieved. Only miscarriages occurring after 6 weeks gestation were recorded to avoid confusion with early pregnancy loss. The body mass index (BMI) of all mothers at booking (10–14 weeks gestation) was calculated using the Quintelet formula (weight in kg/height in meters squared).

Obese women (BMI >30 kg/m^2) and an age-matched control group with normal BMI (19–24.9 kg/m^2) were included in the study, based on the WHO criteria. For every obese woman, two age-matched normal weight (BMI 19–24.9) controls were selected at random from the next database entry.

The two groups were compared with regard to their previous history of early (6–12 weeks gestation), late (12–24 weeks gestation) and recurrent early (more than three) miscarriages using binary logistic regression analysis.

The prevalence of pre-pregnancy diabetes mellitus and gestational diabetes based on impaired oral glucose tolerance test (post prandial glucose of >7.5 mmol/l) were also compared between the two groups. Statistical analysis was carried out using Minitab for Windows, release 13.32 (Minitab Inc., PA, USA). The data are presented as mean or odds ratios (ORs) with the relevant 95% confidence intervals (CIs). A *P*-value <0.05 was considered significant.

Results

A total of 1644 obese women and 3288 normal weight controls (NWC) were included in the study. The percentages (95% CI) of early, late and recurrent early miscarriage (REM) in the obese group were 12.5% (10.9–14), 2% (1.5–2.5) and 0.4% (0.1–0.7), respectively. The same measures in the NWC group

were 10.5% (9.5–11.5), 2% (1.5–2.5) and 0.1% (0.02–0.2), respectively. The relative risks were 1.25, 1 and 4 for early, late and recurrent miscarriages, respectively. The obese women had a significantly higher incidence of early and recurrent early miscarriages compared with the NWC ($P = 0.04$). The ORs (95% CI) are 1.2 (1.01–1.46) and 3.51 (1.03–12.01) for early miscarriage and REM, respectively.

The prevalence of diabetes mellitus in the two groups was very low, as only four patients in the obese group (0.2%) and none in the NWC group had pre-pregnancy diabetes. The prevalence of gestational diabetes was significantly higher among the obese patients (4.5%; 95% CI 3.5–5.5) compared with the NWC group (0.4%; 95% CI 0.2–0.6). This difference was statistically significant (OR 13.05; 95% CI 7.07–24.07). $P < 0.001$.

Discussion

Spontaneous miscarriage affects 12–15% of all pregnancies (Zinman *et al*., 1996). Eighty percent of miscarriages occur before 12 weeks of gestation, and the majority are due to chromosomal abnormalities (Harlap *et al*., 1980). Our figures from this study population are consistent with previously published data.

The risk of miscarriage after the detection of a fetal heart on ultrasound scan is reduced to 5%, except in patients who have had recurrent miscarriages (van Leeuwen *et al*., 1993).

Many factors have been described to increase the risk of spontaneous miscarriage; however, obesity was not found to be a risk factor by Risch *et al*. (1990). Recent evidence indicated that obese women undergoing infertility treatment were at increased risk of spontaneous miscarriage (Hamilton-Fairley *et al*., 1992; Wang *et al*., 2000). However, this point has also been controversial (Lashen *et al*., 1999; Roth *et al*., 2003).

In this study, we compared the incidence of early, late and recurrent miscarriage between a group of obese women and a randomly selected group of age-matched NWC. This is the first study of its kind, nested case–control, to assess such relationship in the general population according to the timing of miscarriage, i.e. early or late. Furthermore, this is also the first study to examine the prevalence of recurrent miscarriage among obese women in comparison with NWC. The exact reason for the obesity-related increased risk of miscarriage is not known. The possibility of oocyte abnormality was refuted by a recent study of obese women receiving oocyte donation who experienced a higher rate of spontaneous miscarriage compared with normal weight peers (Bellver *et al*., 2003). The prevalence of overweight and obesity among PCOS patients is ~50% (Pasquali and Casimirri, 1993). Therefore, it is unlikely that the increased risk of miscarriage among obese patients in this study population can solely be attributed to PCOS, owing to the low prevalence of PCOS in this general population with mostly spontaneous miscarriage. Furthermore, evidence has been reported that obesity is an independent risk factor for miscarriage (Fedorcsak *et al*., 2000). Furthermore, Wang *et al*. (2001) suggested that spontaneous abortion reported in women with PCOS may be due to their high prevalence of obesity.

A four-fold increase in the risk of spontaneous miscarriage was reported in diabetic pregnant women with poor glycaemic control in early pregnancy (Temple *et al*., 2002). However, in our study population the prevalence of pre-pregnancy diabetes was very low, precluding further assessment of this point. Notably, a higher incidence of gestational diabetes was observed in the obese group, which reflects an unphysiological insulin resistance that may play a role in the reported increased miscarriage risk. One could argue that type II and gestational diabetes are one condition differing in the time of detection, and that the worse the insulin resistance at the time of conception and in early pregnancy the higher the risk of miscarriage. This hypothesis can not be addressed in the context of this study, and perhaps a prospective cohort study is better suited to address this issue.

Endometrial receptivity is yet another plausible explanation for early miscarriage; however, evidence is lacking to rule out the oocyte as a potential cause. An unfavourable intrauterine milieu associated with obesity is an alternative explanation for the increased prevalence of miscarriage. However, the fact that all these patients had a successful pregnancy suggests a non-recurring cause for the miscarriage, pointing again to the oocyte quality issue. The retrospective nature of this study and the lack of some information regarding the patients who miscarried but who were not included in the database preclude identification of the cause for the increased risk of miscarriage in the obese population. Furthermore, some may argue that obesity can confer a protective effect in some obese patients, hence their successful pregnancy on this occasion. The weight of evidence so far does not support this hypothesis, and a specially designed cohort study is better suited to address it. This nonetheless, does not reduce the value of this study in identifying a link between obesity and early and recurrent miscarriages. A more precise cause is a prime subject for future research, which is justifiable in view of our and other researchers' findings.

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Submitted on October 8, 2003; accepted on March 29, 2004