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Review

Systematic review and meta-analysis on the association of prepregnancy underweight and miscarriage

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ABSTRACT

Background: Maternal underweight, overweight and obesity have been associated with a higher risk of miscarriage. Most individual reports and all meta-analyses have addressed high body mass index.
Objectives: To review the literature and summarize the risk of miscarriage in underweight women vs those with normal weight.
Methods: A Medline Search (1st January 1990–20th November 2015, human, in English, French, Italian, Spanish or Portuguese) was conducted. Both spontaneous pregnancies and pregnancies after assisted reproduction techniques were considered. Cohort and case control studies were included if they reported data on the outcome of interest (clinical miscarriage), in underweight and normal weight women. Information on clinical miscarriage in other body mass index categories was collected when available. Two investigators reviewed the abstracts, full text papers and extracted data. Review Manager 5.1 software was used to summarize the results.
Results: 32 studies (30 cohort, 2 case control) and a total of 265,760 women were included. In cohort studies, the relative risk (RR) of clinical miscarriage in underweight women was 1.08, 95% CI 1.05–1.11; $p < 0.0001$). The corresponding figures were RR 1.09, 95% CI 1.04–1.13; $p < 0.0001$ for overweight women and RR 1.21, 95% CI 1.15–1.27; $p < 0.00001$ for obese women. In case control studies, the odds ratio (OR) of clinical miscarriage in underweight women was 1.02, 95% CI 0.46–2.30; $p = 0.95$). The corresponding figures were OR 1.01, 95% CI 0.88–1.16; $p = 0.89$ for overweight women and OR 1.26, 95% CI 1.01–1.57; $p = 0.04$ for obese women. The limitations of this study are that it is restricted to studies with information on underweight women and that I^2 ranges from 0 to 91% in different subgroups.
Conclusion: We conclude that maternal underweight is associated with a slightly increased risk of clinical miscarriage, similar to that of overweight women and lower than the risk observed in obesity. The heterogeneity displayed in some subgroups limits the strength of the conclusion.

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Introduction

In the last two decades, numerous studies have considered the association between maternal weight and miscarriage. Maternal underweight, overweight and obesity have been associated with a higher risk of miscarriage [1] but most individual reports and all meta-analyses have addressed high body mass index (BMI). Maheshwari et al. [2], Metwally et al. [3], Boots and Stephenson [4] and Rittenberg et al. [5] have reported an increased risk of miscarriage in women with high BMI in meta-analyses that have addressed different BMI categories and different types of pregnancy (spontaneous and/or after assisted reproduction techniques (ART)) (Table 1).

Most studies addressing the association of miscarriage with maternal underweight include a small number of subjects in this category [6,7] with non-concordant results [6–9]. No meta-analysis has been performed on this subject.

We aimed to perform a systematic review and meta-analysis on the risk of clinical miscarriage in underweight women vs those with normal weight with no restriction regarding the type of pregnancy. Secondary aim: to indirectly compare the risk of clinical miscarriage in underweight women with that in overweight and obese women.

Material and methods

The study was conducted according to PRISMA [10] guidelines.

The protocol of the study was not registered but it is available for researchers.

Eligibility criteria

PICO criteria

- Population: Pregnant women with prepregnancy BMI in the underweight category according to the World Health Organization (<18.5 kg/m^2, a deviation of ±1.5 kg/m^2 was accepted).
- Intervention: No specific criterion for intervention was considered; both pregnancies after spontaneous conception or any type of assisted reproduction technique were considered.
- Comparator: Pregnant women with prepregnancy BMI in the normal category according to the World Health Organization (18.5–24.9 kg/m^2, a deviation of ±1.5 kg/m^2 was accepted).
- Outcome: Clinical miscarriage was defined as a fetal loss after a documented clinical pregnancy, length of follow-up as defined by the authors.

Both cohort and case control studies were considered. When studies of the same center displayed substantial overlap (arbitrarily defined as >20% of the subjects included) we excluded the study with the lower number of subjects. We did not consider exclusion after specific risk factors for miscarriage (i.e. recurrent miscarriages).

BMI categories

They were defined after World Health Organization as follows:

- Underweight: <18.5 kg/m^2
- Normal weight: 18.5–24.9 kg/m^2
- Overweight: 25.0–29.9 kg/m^2
- Obesity: ≥30.0 kg/m^2
- Obesity I: 30.0–34.9 kg/m^2
- Obesity II: ≥35.0 kg/m^2

A deviation of ±1.5 kg/m^2 was accepted.

Information source and search strategy

We performed a Medline Search from 1st January 1990 to 20th November 2015. The search strategy combined (with AND) two sets of keywords, one searching for studies on miscarriage (spontaneous abortion OR abortion OR miscarriage OR pregnancy loss OR female infertility OR infertility therapy) and the other for maternal weight category (body mass index OR underweight OR malnutrition OR body weight OR thinness OR obesity OR BMI). Studies were limited to those in human subjects and published in English; French; Italian; Spanish or Portuguese.

We did not contact authors to identify additional studies.

Study selection and data extraction

Two investigators (MB and A G-P) reviewed the abstracts, full text papers and extracted data. Discrepancies were solved by consensus with a third one (RC). Full text papers were reviewed if eligibility criteria were clearly fulfilled in title and/or abstract and whenever there was a doubt. All eligible studies were included in

Table 1
Published meta-analyses on the association of body mass index category and clinical miscarriage.

Author	Year	Type of pregnancy	Reference BMI category	Study BMI category	Summary measure (CI 95)
Maheshwari et al. [2]	2007	ART	<25	≥25	OR 1.33 (1.06, 1.68)
Metwally et al. [3]	2008	Spontaneous/ART	19–24.9	≥25	OR 1.67 (1.25, 2.25)
Boots and Stephenson [4]	2011	Spontaneous	Normal weight	Overweight	OR 1.11 (1.00, 1.24)
				Obesity	OR 1.31 (1.18, 1.46)
Rittenberg et al. [5]	2011	ART	<25	≥25–29.9	RR 1.23 (1.12, 1.34)
				≥30	RR 1.43 (1.22, 1.67)

ART = assisted reproduction technology, BMI = body mass index, CI = confidence interval, OR = odds ratio, RR = relative risk.