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Obesity and recurrent miscarriage: A systematic review and meta-analysis

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Abstract

The aim of this study is to perform a systematic review and meta-analysis on the relationship between excess weight and risk of recurrent pregnancy loss (RPL) and to highlight the common immunological mechanisms of these two conditions. The PubMed and MEDLINE databases were searched for publications in English available as of November 2017. The search terms used were 'recurrent pregnancy loss', 'body mass index' (BMI), 'overweight' and 'obesity'. For calculation of the odds ratio (OR) and 95% confidence intervals (CI) for miscarriage in different BMI groups, RevMan software was used (Review Manager, Version 5.3.5 for Windows; The Cochrane Collaboration). In total, 100 publications including the search terms were identified. Six studies were included for qualitative analysis, and two studies were included for quantitative analysis (meta-analysis). The association between excess weight and RPL was significant (OR, 1.34; 95% CI, 1.05–1.70; $P = 0.02$). The isolated analyses of the groups of obese and overweight women revealed an association only between obesity and RPL (OR, 1.75; 95% CI, 1.24–2.47; $P = 0.001$). The data available in the current literature revealed that obese women with a history of RPL have a high risk of future pregnancy losses, a risk which was not found among overweight women.

Key words: body mass index, obesity, overweight, recurrent miscarriage.

Introduction

Historically, recurrent pregnancy loss (RPL) has been defined as the loss of three or more consecutive pregnancies at less than 20 weeks of gestation. RPL can be classified as primary RPL (with no previous pregnancy lasting longer than 20 weeks of gestation) or secondary (with a previous pregnancy lasting longer than 20 weeks of gestation).[1] In the recent decades, different conceptions of this obstetric pathology have been offered. Some have considered different numbers of prior miscarriages, irrespective of whether the miscarriages were consecutive. Recently, several medical societies and non-medical entities have come to a consensus on the concept of RPL, defining it as the loss of two or more prior pregnancies.[2]

The incidence of RPL described in the literature varies substantially from 0.5 to 2.3%, a range that may be due to different definitions and different methodologies used in the statistical calculation. However, an increase in the incidence of recurrent miscarriage has been observed. Roepke *et al*. evaluated Swedish women who were pregnant between 2003 and 2012 and found a 58% increase in the number of new cases of RPL (three or more prior miscarriages) during this period. The authors suggested that this significant increase in the incidence is because of couples' decisions to conceive later in life and obesity.[3]

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RPL is a pregnancy complication with a multifactorial etiology; there are well-established causes in the literature, although others still require more evidence. Genetic abnormalities in the couple, hormone disorders, anatomical abnormalities of the uterus (whether congenital or not) and antiphospholipid syndrome are the most common causes of RPL. Factors associated with recurrent miscarriage are mostly attributed to the woman. In more than half of the cases, at least one factor associated with RPL is found, although in a considerable number of couples, still no defined cause has been found. Some conditions are associated with idiopathic cases of RPL, including immune system abnormalities, behavioral conditions and environmental conditions, as well as obesity.[4]

The number of obese people around the world has tripled since 1975. In 2016, more than 1.9 billion adults (≥18 years) were overweight worldwide. This alarming increase in the number of overweight and obesity cases in the recent decades has become a major public health challenge worldwide, particularly because of the high risk of their association with many other diseases and mortality.[5]

Recent statistics have shown that two-thirds of women aged >20 years in the United States have a body mass index (BMI) of ≥25 kg/m^2, indicating that they are overweight or obese, and 36% of people in the United States are classified as obese (BMI ≥ 30 kg/m^2). Thus, excess weight and obesity are also a cause for concern among specialists in reproductive medicine because of the higher risk of these conditions inducing complications in the perigestational period. Such complications include miscarriage, fetal death, congenital malformations, fetal macrosomia, gestational diabetes, pre-eclampsia, complications during vaginal delivery, higher cesarean section rates, thromboembolic events, post-partum infection and difficulty in breastfeeding.[5]

The mechanisms responsible for pregnancy losses among overweight and obese women with a history of RPL are poorly understood. Given the high number of women of childbearing age who are overweight and in light of the fact that the cause of many RPL cases is undetermined, it is imperative that any associations between obesity and RPL be established, the pathophysiology of pregnancy loss in these cases be clarified and therapeutic measures to improve these patients' outcomes be defined.

Therefore, the objective of this systematic review was to evaluate the data in the literature to determine the association between excess weight and RPL, identify any possible immunological mechanisms involved in the pathophysiology and highlight therapeutic proposals.

Methods

This systematic review was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PubMed and MEDLINE databases were searched for publications available up to and including November 2017. The search terms used were 'recurrent pregnancy loss', 'body mass index', 'overweight' and 'obesity'.[6]

The articles identified in the initial search were independently evaluated by the author according to the following inclusion criteria: types of study, population (women with a history of recurrent miscarriage), risk factor assessment (overweight or obesity) and primary outcome (miscarriage). The articles were limited to studies on human subjects and those published in English. Studies investigating physiopathological mechanisms were also evaluated and discussed.

The data available were imported into Review Manager, version 5.3.5 (The Cochrane Collaboration) for quantitative analysis. The reviewer sent emails to the authors of the studies selected in order to obtain unpublished data that could nevertheless be included in the meta-analysis, but no responses were received.

Results

In total, 100 publications including the search terms were identified, among which six articles were included for qualitative analysis and two for quantitative analysis (meta-analysis) (Fig. 1). The details of the studies included in the statistical analysis and discussion are described in Table 1. No prospective studies or interventions were identified; therefore, six observational studies were selected. The studies were performed in the United Kingdom (four studies), the United States (one study) and South Africa (one study); they were published between 2004 and 2017 and evaluated pregnant women's outcomes from 1985 to 2016.

Most of the studies defined cases of RPL as a history of three or more miscarriages after pregnancies lasting less than 20 weeks of gestation.[7–11] Only one study considered RPL as two or more pregnancy

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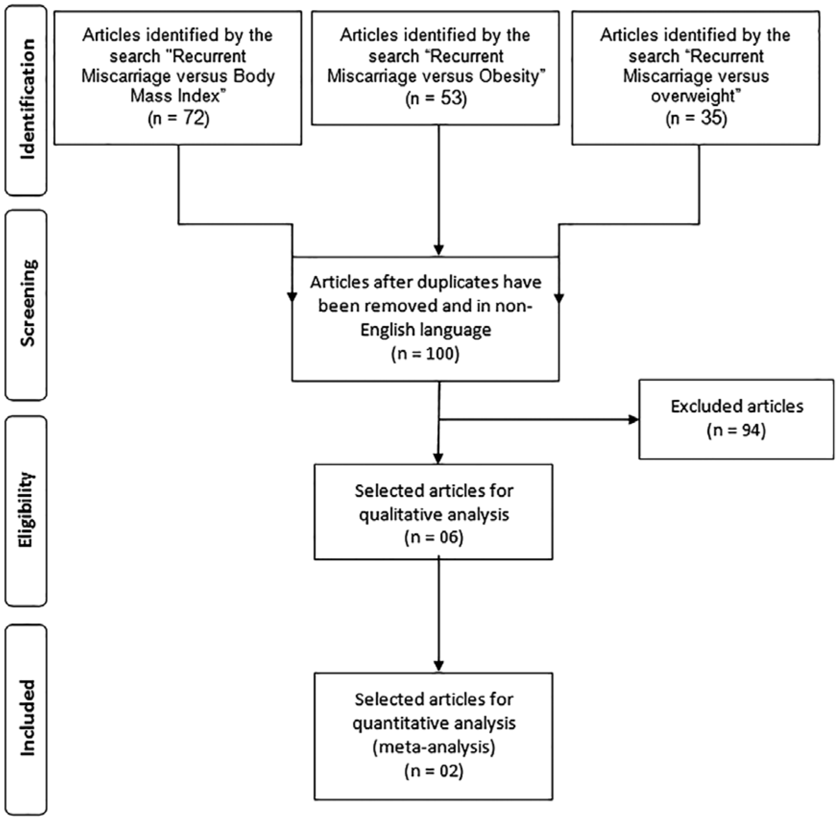

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the search.

losses after less than 20 weeks of gestation.[12] The average age between the groups of patients evaluated in the selected studies ranged from 27.4 ± 2.0 years in Metwally *et al.*[8] to 36.5 ± 4.6 years in Bhandari *et al.*[10]

Most of the studies used the World Health Organization (WHO) classification of BMI to define which women would be in the low-weight group (BMI, <18.5 kg/m^2), normal weight group (BMI, 18.5–24.9 kg/m^2), overweight group (BMI, 25.0–29.9 kg/m^2) and obesity group (BMI, >30.0 kg/m^2).[13] The exception was the study by Metwally *et al.*,[8] who defined normal weight as a BMI of 19.0–24.9 kg/m^2. The percentages of women in the normal weight, overweight and obesity groups among the total number of patients studied (*n* = 2193) were 47.1% (*n* = 1033), 29.0% (*n* = 636) and 22.5% (*n* = 493), respectively (Fig. 2).

The first study to establish the relationship between obesity and RPL was published by Lashen *et al.*,[7] in which the number of pregnancy losses among 1644 obese women (BMI >30 kg/m^2) was compared to that among 3288 pregnant women of normal weight. The percentages of early miscarriage (pregnancy lasting between 6 and 12 weeks of gestation), late miscarriage (pregnancies lasting between 12 and 24 weeks of gestation) and recurrent miscarriage (more than three miscarriages of pregnancies lasting less than 12 weeks of gestation) in the obese group were 12.5, 2 and 0.4%, respectively. Pregnant women of normal weight had a lower frequency of pregnancy losses: 10.5, 2 and 0.1% in the cases of early miscarriage, late miscarriage and recurrent miscarriage, respectively. The occurrence of early and recurrent miscarriages was significantly higher among obese women, with an odds ratio (OR) of 1.2 (95% confidence interval [CI], 1.01–1.46) in the case of early miscarriage and 3.51 (95% CI, 1.03–12.01) in the case of recurrent miscarriage.[7]

Metwally *et al.*[8] evaluated predictors of future miscarriage based on data of 844 pregnancies among 491 women with a history of RPL. They concluded that age, obesity (OR, 1.71; 95% CI, 1.05–2.8) and low weight (OR, 3.98; 95% CI, 1.06–14.92) were factors associated with the occurrence of another pregnancy loss. No higher risk of miscarriage was observed in the overweight group compared with the normal weight group. The study was the first to demonstrate the U-shaped relationship between the rate of

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Table 1 Studies on the risk of miscarriage among obese women with a history of recurrent pregnancy loss (RPL)†

Author, year	Study type	Study population	Evaluated groups	Primary outcome	Conclusions
Lashen *et al.*, 2004	Case–control	1644 obese patients; 3288 patients of normal weight	Normal: BMI, 19–24.9 kg/m^2; obesity: BMI, ≥30 kg/m^2	Subsequent miscarriage	Early and recurrent miscarriage was significantly more common among obese women (OR, 1.2; 95% CI, 1.01–1.46 and OR, 3.51; 95% CI, 1.03–12.01, respectively)
Metwally *et al.*, 2010	Prospective cohort	491 patients with RPL (844 pregnancies)	Low weight: BMI, <19 kg/m^2; normal: BMI, 19–24.9 kg/m^2; overweight: BMI, 25–29.9 kg/m^2; Obesity: BMI, ≥30 kg/m^2	Subsequent miscarriage	Age, obesity (OR, 1.71; 95% CI, 1.05–2.8) and low weight (OR, 3.98; 95% CI, 1.06–14.92) were factors associated with the occurrence of another pregnancy loss
Lo *et al.*, 2012	Prospective cohort	1259 patients with a history of RPL, 696 of whom had no defined cause	Low weight: BMI, <18.5 kg/m^2; normal: BMI, 18.5–24.9 kg/m^2; overweight: BMI, 25–29.9 kg/m^2; obesity: BMI, ≥30 kg/m^2	Subsequent miscarriage	Maternal obesity increased the risk of miscarriage in women with RPL with no defined cause
Boots *et al.*, 2014	Prospective cohort	117 products of conception evaluated	Not obese: BMI, <30 kg/m^2; Obese: BMI, ≥30 kg/m^2	Subsequent miscarriage	Higher frequency of miscarriages without embryonic genetic abnormalities among obese patients (58% vs 37%; RR, 1.48; 95% CI, 1.16–1.89; P = 0.001)
Bhandari *et al.*, 2016	Observational retrospective	414 women with RPL (201 of normal weight, 131 overweight and 82 obese)	Low weight: BMI, <18.5 kg/m^2; normal: BMI, 18.5–24.9 kg/m^2; overweight: BMI, 25–29.9 kg/m^2; obesity: BMI, ≥30 kg/m^2	Subsequent miscarriage and an interval before another pregnancy	Obese women had better fertility rates and a higher cumulative pregnancy rate in 3–6 months (65.2% and 80%, respectively) compared with those for women of a normal weight (49.2% and 65.8%, respectively)
Matjila *et al.*, 2017	Retrospective cohort	592 patients with RPL	Low weight: BMI, <18.5 kg/m^2; normal: BMI, 18.5–24.9 kg/m^2; overweight: BMI, 25–29.9 kg/m^2; obesity: BMI, ≥30 kg/m^2	Risk factors for recurrent miscarriage	Overweight/obesity present in 73% of patients; 42% had obesity of class I, II or III

†Associated factors and treatment performed in each patient group: 1. Lashen *et al.*, 2004: not available; no treatment. 2. Metwally *et al.*, 2010: RPL patients treated for hormonal, anatomical and hematological factors (RPL of known cause) or untreated (RPL of unexplained cause). 3. Lo *et al.*, 2012: included 696 unexplained pregnancy loss and evaluated only untreated couples with recurrent miscarriages of unknown cause. 4. Boots *et al.*, 2014: anatomical factors were less frequent in obese women (12% vs 22%; P = 0.04); cytogenetic anomalies were also less frequent in obese women (0% vs 7%; P = 0.01), other factors were similar between obese women and non-obese patients as the following: endocrine factor (69% vs 63%), autoimmune factors (40% vs 38%) and endometritis (18% vs 14%); no treatment. 5. Bhandari *et al.*, 2016: not available; no treatment. 6. Matjila *et al.*, 2017: 50% of patients with no identified associated disorders, 38% of patients had endocrine disorder, 10% had uterine factor, antiphospholipid syndrome and thrombophilias constituted 3% and 2% of patients, respectively; RPL patients treated for hormonal, anatomical and hematological factors (RPL of known cause) or untreated (RPL of unexplained cause). and BMI, body mass index; CI, confidence interval; OR, odds ratio.

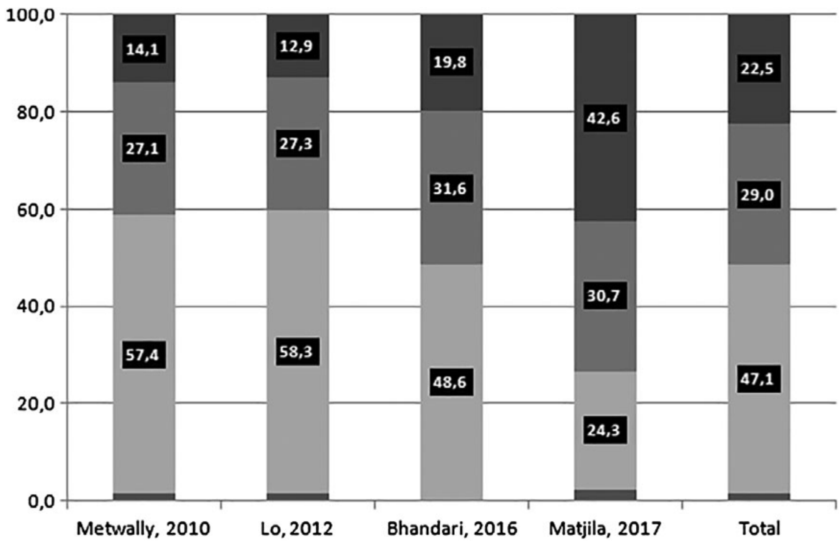

Figure 2 Body mass index (BMI) distribution across the articles evaluated. (■) Obesity; (■) overweight; (■) normal BMI; (■) underweight.

miscarriage and BMI of pregnant women with a history of RPL.

Lo *et al.*[9] evaluated 696 women with a history of RPL, and their results were similar to those previously described in the literature. Univariate analysis showed that BMI, maternal age, number of prior miscarriages and ethnicity were factors associated with pregnancy outcome. Multivariate analysis revealed that obese women had a significantly higher risk of another miscarriage (53/90, 59%) when compared with women with a normal BMI (177/406, 44%; $P = 0.028$; OR, 1.73; 95% CI, 1.06–2.83). There was no statistical difference in the rate of miscarriage when overweight women were compared with underweight women. Maternal age and the number of prior miscarriages have also been positively correlated with future pregnancy loss.

Boots *et al.*[12] observed a higher frequency of miscarriages with no embryonic genetic abnormalities among obese women relative to women of a normal weight (58%, 18/31 vs 37%, 32/86; relative risk [RR], 1.48; 95% CI, 1.16–1.89; $P = 0.001$). In 2016, Bhandari *et al.*[10] studied the relationship between pregnancy loss and fertility among 414 women with a history of RPL. They concluded that obese women had better fertility, with a higher cumulative rate of pregnancy after 3 and 6 months of follow-up (65.2% and 80%, respectively) when compared with women of a normal weight (49.2% and 65.8%, respectively).

Recently, Matjila *et al.*[11] performed a retrospective analysis of 592 patients with a history of RPL and found that the mean BMI of all patients was 29.58 ± 6.96 kg/m^2. Based on the WHO classification for the calculation of BMI, 2.36% of the patients (14/592) were underweight, 24.4% (144/592) were at a normal weight, 30.6% (181/592) were overweight, 23.1% (137/592) had class I obesity (BMI, 30–34.9 kg/m^2), 11.3% (67/592) had class II obesity (BMI, 35–39.9 kg/m^2) and 8.1% (48/592) had class III obesity (BMI, >40 kg/m^2). Therefore, 73% of the patients had excess weight (were overweight or obese) and 42% had obesity of class I, II or III. The most common diagnosis among women with RPL was polycystic ovarian syndrome (PCOS). Among patients with PCOS, the mean BMI was 30.86 ± 7.79 kg/m^2, 74.5% were overweight or obese and 47% had class I, II or III obesity.

Among the six studies selected for qualitative evaluation, only Metwally *et al.*[8] and Lo *et al.*[9] clearly presented the data necessary for a statistical analysis. Initially, a relationship between overweight and RPL was observed (OR, 1.34; 95% CI, 1.05–1.70; $P = 0.02$) (Fig. 3). However, the isolated analyses of the obesity groups (Fig. 4) and the overweight groups (Fig. 5) revealed that a correlation exists only between obesity (BMI, >30.0 kg/m^2) and RPL (OR, 1.75; 95% CI, 1.24–2.47; $P = 0.001$).

Discussion

For women in the perigestational period, the relationship between excess weight and drop in reproductive capacity seems to be well defined in the literature. Studies have demonstrated an association between overweight, obesity and sporadic miscarriages of

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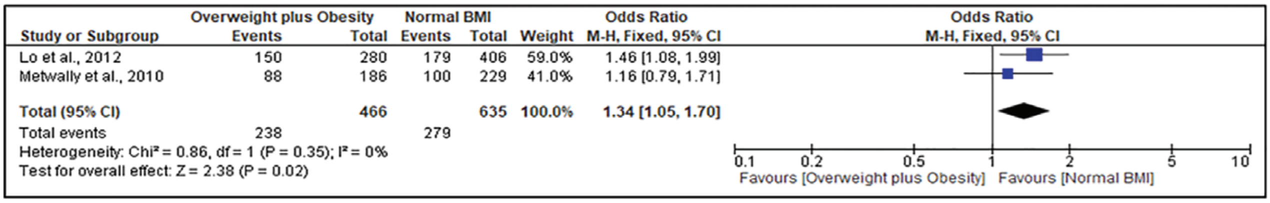

Figure 3 Forest plot of overweight and obesity versus normal body mass index (BMI): Recurrent miscarriage.

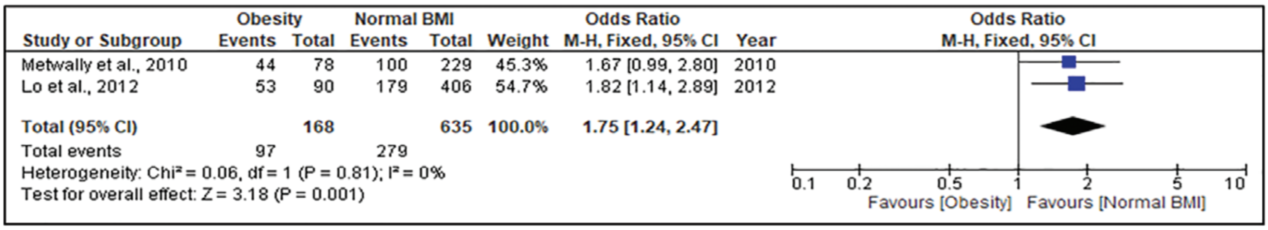

Figure 4 Forest plot of obesity versus normal body mass index (BMI): Recurrent miscarriage.

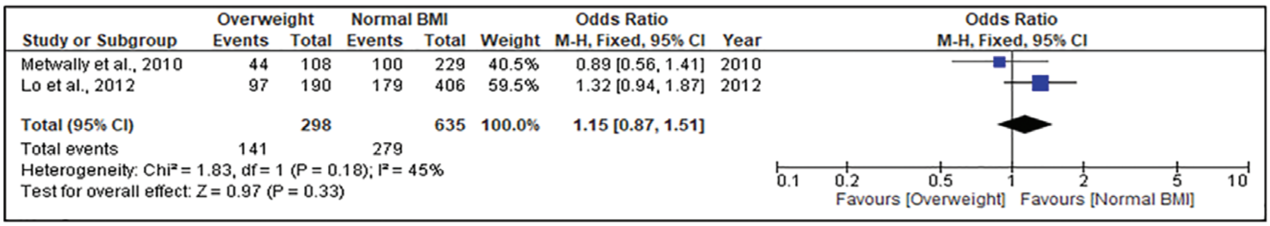

Figure 5 Forest plot of overweight versus normal body mass index (BMI): Recurrent miscarriage.

naturally occurring pregnancies (those that did not require the need for assisted reproductive techniques).[14] According to the WHO, estimate of overweight and obese women in the United Kingdom and in others world regions are higher than observed in the included studies.[5] Obesity has a great impact on female fertility, being related not only to gestational loss, but also to conjugal infertility. Therefore, this fact could explain the difference between the prevalence of observed obesity in women with recurrent miscarriage and in general populations.

Little is known about the associations between overweight, obesity and RPL. The two studies included in this statistical analysis used similar inclusion criteria (three or more consecutive miscarriages) and the same classification system to define overweight and obesity. It was possible to establish a positive correlation between obesity and RPL but not between overweight and RPL. This negative impact of obesity on female fertility has also been observed in pregnancies resulting from autologous cycles in cases of assisted reproduction (those with fresh embryo transfers). A large study that evaluated the influence of BMI on all autologous fresh *in vitro* fertilization (IVF) cycles in the United States from 2008 to 2013 (n = 494 097 cycles, n = 402 742 transfers, n = 180 855 pregnancies) found that obese women had a statistically lower likelihood of intrauterine pregnancy (RR, 0.94; 95% CI, 0.94–0.95) and live birth (RR, 0.87; 95% CI, 0.86–0.88). Obesity has been associated with a significantly higher risk of miscarriages (RR, 1.23; 95% CI, 1.20–1.26).[15] These results are similar to those of other studies and meta-analyses.[16,17]

Abnormalities in the hypothalamic–pituitary–gonadal hormonal axis, direct effects on oocyte quality, effects on embryo development and effects on endometrial receptivity are the possible physiopathological mechanisms responsible for pregnancy failure among pregnant women with excess weight.[18] A significantly lower number of mature oocytes, as well as oocytes that were reduced in diameter, were observed in ovarian aspirations in IVF cycles among obese

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women compared with women of a normal weight.[19] Embryos formed from ova of overweight and obese women also exhibited a lower potential for development after IVF, as well as a lower rate of blastocyst formation.[20]

In order to compare the endometrial receptivity of overweight women to that of normal weight women, studies have evaluated the results of assisted reproduction cycles in which embryos generated from normal weight egg donors were transferred. Bellver *et al*.[21] studied the results of 9587 ovulation cycles of normal weight donors and observed a lower rate of implantation, lower rate of pregnancy and fewer live births among obese recipients, although rates of miscarriage were similar. In a recent meta-analysis, Jungheim *et al*.[22] concluded that obesity did not affect IVF results among women who used oocytes from normal weight donors, suggesting that oocyte quality rather than endometrial receptivity could be the main factor influencing IVF results in obese women who used autologous oocytes. Another possibility is that the mechanisms involved in miscarriages among obese women are triggered in a post-implantation phase, a process which involves its own mechanisms.

Several immunological disorders have been discussed as possible causes of idiopathic RPL; these disorders manifested most commonly in the first weeks of pregnancy.[23] Among the main immunological mechanisms studied, the following are of particular importance: hyperactivity of natural killer cells[24,25]; imbalance of T-helper 1 (Th1) and Th2 response, with a predominance of Th1 response[26–28] and low concentration of regulatory T cells, CD4+ CD25+ FoxP3+.[29]

Obesity is a condition of chronic inflammation, as evidenced by numerous markers, such as high levels of C-reactive protein (CRP) and interleukin-6 (IL-6).[30–32] Similarities in the immunological profiles of obese women and women with a history of idiopathic RPL may be the starting point for explaining the high risk of obstetric complications in these groups of women, from the difficulty of embryo implantation to complications in childbirth and in the post-partum period.[23,33]

In light of the direct correlation between excess weight and different obstetric complications, weight control has become a necessity in preconception counseling for couples because it is a complex risk factor. Recently, a meta-analysis evaluated the efficacy of weight loss interventions on pregnancy outcomes. The meta-analysis of three randomized studies did not observe a decrease in the rate of miscarriages (RR, 0.96; 95% CI, 0.89–1.04) in the intervention group (n = 331, diet and physical activity) relative to the control group (n = 337, no intervention).[34]

Different treatment protocols for patients with idiopathic RPL propose the use of immunological therapies in the perigestational period to induce a favorable immune response to embryonic implantation. However, there is still considerable debate in the literature over the safety and efficacy of these immunotherapies.[35–37] Therefore, in light of the similarities in the immunological mechanisms involved in cases of RPL and obesity, the importance of diet on immunomodulation during the female reproductive process should be investigated as a therapeutic measure meant to improve pregnancy outcomes.

The failure of weight management measures to reduce rates of miscarriage needs to be better evaluated. There is evidence to suggest that diet plays a major and central role in regulating chronic inflammation.[38,39] Certain special dietary components may influence inflammation, thereby reducing or increasing the potential risk of obstetric complications.[40–42] Diets with large amounts of red meat, high-fat dairy products and simple carbohydrates are associated with high levels of CRP and IL-6, which are immunological markers also observed in obesity and RPL. On the other hand, the Mediterranean diet, which largely consists of grains, fish, fruits, leafy greens, legumes, moderate amounts of alcohol and olive oil and limited amounts of red meat, is associated with low levels of inflammation.[43–46]

Shin *et al*.[47] found that a high BMI prior to pregnancy is associated with a pro-inflammatory diet and high levels of CRP during pregnancy.[47] In order to evaluate the inflammatory potential of diet in terms of the risk of recurrent miscarriage, Vahid *et al*.[48] examined the relationship between dietary inflammatory index scores and risk of miscarriage among women with a history of RPL. They concluded that women who consumed a more pro-inflammatory diet had a higher risk of miscarriage compared with women who consumed a more anti-inflammatory diet.[48]

The main limitation of article was the diversity in the methodology of the included studies, some of them were only observational (untreated patients) and others ones with interventions (treatment of patients with known causes) in the group of RPL patients. Lashen *et al*.[7] and Bhandari *et al*.[10] studied gestational outcomes in untreated patients. Metwally *et al*.[8] and Matjila *et al*.[11] evaluated the risk of

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miscarriage in groups of RPL patients treated for hormonal, anatomical and hematological factors (RPL of known cause) or untreated (RPL of unexplained cause). Lo *et al*.[9] evaluated only untreated couples with recurrent miscarriages of unknown cause. Boots *et al*.[12] observed the risk of RPL in women through the genetic study of the conception material.

Another limitation of this study was the heterogeneity of the evaluated population that may limit the conclusions regarding to the relation between obesity and pregnancy losses in women diagnosed with PCOS or with unknown cause. The relationship between PCOS and gestational losses is discussed in the literature. Among the selected studies, few of them evaluated the associations between PCOS, insulin resistance and pregnancy loss. Metwally *et al*.[14] described that the presence of PCOS did not increase the risk of miscarriage neither in the obese nor in the normal BMI group.

Based on the data available in the current literature, a positive correlation between obesity and RPL can be established. Little is known about the mechanisms responsible for pregnancy losses in overweight patients, but the immunopathological pathways in common seem to be responsible.

There is still insufficient evidence to prove that weight control interventions alone (such as low-calorie diets and physical activity) are sufficient to reduce rates of miscarriages. Future studies are needed to establish the role of neurotherapy in immunomodulation in the perigestational period and whether it can reduce chronic inflammation and, as a consequence, the risk of miscarriage.

Disclosure

None declared.

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