

Excess weight and dyslipidemia and their complications during pregnancy: a systematic review

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Abstract

Objectives: to identify bibliographically disorders related to excess weight, dyslipidemia and their complication during pregnancy and in the fetus and newborn.

Methods: a systematic review including observational and interventional studies and reviews, based on MEDLINE, LILACS, Embase and the Cochrane Library between 2000 and 2015. The key-words "lipids, pregnancy, obesity and newborn" were used to establish a selective stage for inclusion/exclusion of titles, repeated studies, key-words, abstracts, methodological incompatibility and correlation with objectives.

Results: 58 studies were selected, of which 36 (62%) addressed prevention and the risk in pregnancy of excess weight and lipid disorders and 19 (32.7%) suggestions and/or consequences for the fetus and newborn.

Conclusions: excess weight and lipidemic disorders in pregnancy are causes for concern in scientific studies, posing risks both for the mother and the newborn. Higher prevalence of caesarian and pre-eclampsia were the two most noteworthy complications for gestational outcomes. In short, the impact on care of maternal habits and excess weight during pregnancy is highly significant, owing to the different degrees of complication in obstetric outcomes and their influence on the clinical characteristics of the newborn.

Key words *Lipids, Pregnancy, Obesity, Infant, newborn*

Introduction

Dyslipidemia is characterized by abnormal levels of cholesterol and triglycerides. Generally speaking, the disorders caused by dyslipidemia gradually increase indices of overweight and is the principle cause of the nutritional disequilibrium that affects contemporary human beings and future generations, who will tend to face serious health problems in the long term.¹ According to the World Health Organization (WHO), there are expected to be 700 million obese individuals in 2016, compared to an estimated 400 million in 2005.¹

Under the conditions inherent to pregnancy, excess weight is a worrying disorder, especially when the woman has been obese or overweight since the first trimester, increasing the possibility of an adverse outcome.² Hence, the high prevalence and lack of control of overweight and obesity prior to pregnancy require that more efficient procedures for managing weight gain be adopted in Brazil.³ Studies reveal that these problems are addressed in between 25% and 30% of pregnant women in the country.^{3,4}

The risks of obesity are various and include heightened cholesterolemia or triglyceridemia in isolation and mixed hyperlipidemic disorders.⁵ Studies have shown^{2,6,7} that excessive weight gain in pregnancy poses greater risks both for the mother and the newborn. Gestational diabetes mellitus, preeclampsia and a higher frequency of caesarians may occur in the pregnant women, while the newborns are at risk of macrosomia and a greater likelihood of hospitalization in special care units.²

It is clear that obesity in pregnancy has become a common problem in pregnant women around the world. Since the early 1990s there has been growing concern among researchers and health professionals regarding excess weight during pregnancy.^{2,3,5} It is thus now of fundamental importance that researchers turn their attention to the specificities and peculiarities of gestational disorders, conditions which are not so normal in clinical terms and much less normal from a physiological point of view.⁸

Thus, apart from issues of overweight and obesity, it is worth also noting the relations between risks and results observed, as in the study by Dempsey *et al.*,⁹ which included suggestions regarding the identification of factors associated with growth in the uterus. This may help prevent possible risks subsequent to alterations to lipid metabolism during pregnancy, which may be related to the occurrence of preeclampsia.

Although various factors may play a part in dyslipidemia and gestational weight gain, few studies have quantified and clarified these alte-

rations. The present study thus aims to evaluate, based on scientific publications between 2000 and 2015, obesity and maternal dyslipidemia and complications during pregnancy in the fetus and the newborn.

Methods

The study focuses on pregnant women and obstetric outcomes between 2000 and 2015. A systematic search of the published bibliography was carried out in the MEDLINE, LILACS, Embase and Cochrane Library databases.

The selected key-words were “lipidic, pregnancy, obesity and newborn”, combined with the Boolean operators “AND” and “OR” in such a way as to obtain articles relevant to the theme. 2909 articles were found.

The inclusion criteria for the articles evaluated in this study were applied as follows:

Scope of the study: a systematic review of clinical trials, cross-sectional; cohort; and case-control studies.

The population: pregnant women aged 18 years or over presenting excess weight and a profile of dyslipidemia.

Complications investigated: the relation between physiological disorders and lipid metabolism, obesity and the lipid profile during pregnancy; dyslipidemia and gestational outcomes; lipid metabolism and transfer through the placenta and the effects of maternal dyslipidemia on the baby.

Exclusion criteria: scientific articles that address dyslipidemia in conditions other than pregnancy and articles published in languages other than Portuguese, English or Spanish.

The theoretical framework of the selection process for systematic reviews: the initial selection of publications, using the chosen databases and proposed criteria, resulted in 2909 articles. The selection process framework for systematic reviews was then applied (Figure 1) in the following stages: identification of repeated studies; reading of key-words; reading of titles; reading of abstracts and methodological analysis and exclusion of low-impact publications. A table was drawn up of articles that best fitted the study (Table 1).

Analysis of co-citation of key-words: after applying the process of selecting articles for systematic reviews, the key-words were then analyzed in such a way as to assess the frequency and interaction of key-words in the selected articles. Analysis of key-words thus enabled retrospective evaluation of the quality of the selection process for articles used in this systematic review.

Results and Discussion

Relation between physiological disorders and lipid metabolism

Although most of the studies addressed concerns during pregnancy, covering various factors resulting from dietary imbalance and calorie consumption, it

is worth pointing out the relation between physiological disorders and lipid metabolism during pregnancy.^{2,3,5}

Herrera *et al.*⁵ have shown that, during pregnancy, adipose tissue and its lipolytic activity bring about an increase in serum levels of glycerol, which is converted into glucose (in the liver) and made available for the fetus.

Figure 1

Flow-chart of activities in bibliographical selection process.

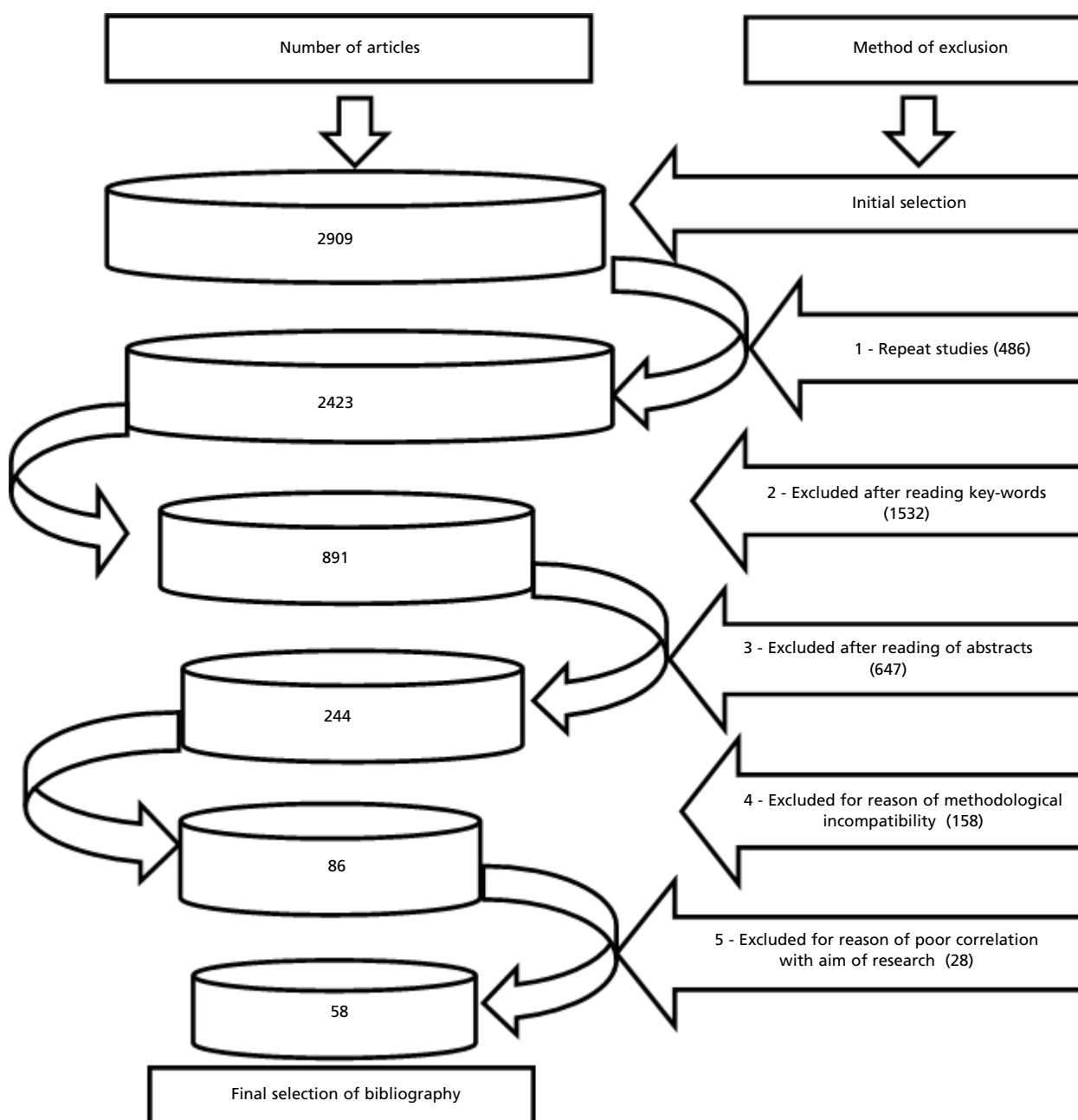


Table 1

The main studies of pregnant women covered by this systematic review (2000-2015).

Authors	Type of study	Year of publication
Adamo <i>et al.</i> ⁷	Randomized clinical trial	2013
Oliveira <i>et al.</i> ⁸	Cross-sectional study	2012
Dempsey <i>et al.</i> ⁹	Prospective cohort study	2004
Ywaskewycz Benitez <i>et al.</i> ¹⁰	Case-control study	2010
Ueland <i>et al.</i> ²⁰	Cross-sectional study	2008
Dann <i>et al.</i> ²⁸	Prospective cohort study	2006
Aliyu <i>et al.</i> ²⁹	Cross-sectional study	2010
Salihu <i>et al.</i> ³⁰	Retrospective cohort study	2009
Coussons-Read <i>et al.</i> ³³	Case-control study	2012
Kramer <i>et al.</i> ³⁴	Prospective cohort study	2009
Alleman <i>et al.</i> ³⁵	Retrospective cohort study	2013
Crume <i>et al.</i> ⁴²	Prospective cohort study	2015
Watkins <i>et al.</i> ⁴³	Case-control study	2003
Silva <i>et al.</i> ⁴⁹	Cross-sectional study	2014
Aviram <i>et al.</i> ⁵¹	Systematic review	2011
Fitzsimons <i>et al.</i> ⁵²	Systematic review	2010
Kristensen <i>et al.</i> ⁵³	Prospective cohort study	2005
Sebire <i>et al.</i> ⁵⁴	Cross-sectional study	2011

During pregnancy, the authors identified an increase in levels of high-density lipoprotein cholesterol (HDLc) and very low density lipoprotein cholesterol (VLDL). The concentrations obtained by measuring lipids and lipoproteins, through a comparative study with non-pregnant women, provided guidance regarding when a physiological indicator may be associated with diseases or disorders of pregnancy.¹⁰

It is indispensable that researchers identify the various lipid conditions that are adverse in the trimesters of gestation, thereby corroborating the work of authors whose studies have confirmed the physiological factors caused by obesity in animals. Other studies have noted disorders of the central nervous system and peripheral tissue and concomitant production of ketone bodies leading to lipid oxidation.^{11,12}

Given the evidence, it is worth noting that Herrera *et al.*⁵ stressed that gestational diabetes mellitus (GDM) and maternal fasting alter serum levels of lipids, as a result of lipolysis of adipose tissue and the production of non-esterified fatty acids (NEFAs), enabling the production of ketone bodies that are made available for the fetal plasma.⁴ Studies were soon developed to control adipose tissue, such as that of Ohnuki *et al.*,¹² which highlighted the use of streptozotocin regulator Acetoacetyl-CoA Synthase (AACS) in the brains of obese rats, causing a reduction in the synthesis of

cholesterol.

The increase in lipids in pregnancy is a condition characterized physiologically as normal, principally because of changes in hormones during the trimesters of gestation. However, Basaran¹³ has suggested that the level of total cholesterol (TC) should not exceed 337 mg/dL nor that of triglycerides (TG) 332 mg/dL, in the third trimester of pregnancy. It is worth noting the particularities of the dyslipidemic alterations in pregnancy, owing to the likelihood of the development of hyperlipidemia in the mother, given that the aforementioned studies found that pregnancy-induced hyperlipidemia contributes to an increase in certain morbidities such as GDM and pre-eclampsia.

A more recent study has compared pregnant and non-pregnant women, both of normal weight, and noted a significantly higher result for means of TG, TC, VLDL, LDLc in normal-weight pregnant women and concomitant reduction in HDLc.¹⁴ Other studies have identified a gradual increase in lipid patterns of TG, CT, VLDL and HDLc, after the 12th week of pregnancy, especially in the second and third trimesters, in response to estrogen stimulation and resistance to insulin and pointed to the increased TG during gestation, which suggests a correlation with the risk of pre-eclampsia and preterm birth.^{15,16} It can be deduced that, for pregnant women of adequate weight, the increase or decrease in HDLc parameters will diverge in some scientific studies.

However, the change in lipid patterns may suggest indicators of pathology.

Previous scientific studies including overweight and obese pregnant women have produced hypotheses and suggestions regarding a consecutive increase in dyslipidemic disorders. Studies by Mangucci *et al.*,¹⁷ in an attempt to identify cardiometabolic risks by comparing normal weight with overweight pregnant women, found an increase in levels of TG, CT, VLDL, LDLc for both categories, although levels of HDLc remained unaltered in normal weight pregnant women, while they were significantly low in those who were overweight.

Dyslipidemia in pregnancy and the parameters for lipid transfer from the mother to the fetus are still not fully understood. However, studies have shown that gestational dyslipidemia is influenced by the placental hormones that affect both the metabolism of glucose and that of lipids, to ensure that the fetus is supplied with nutrients essential for its development. There is, however, less flexibility in terms of metabolic adaptation in obese pregnant women compared to those of normal weight.^{5,18} In obese pregnant women, therefore, both the regulation and the extent of transport of materno-fetal lipids are prone to undergo substantial physiological variations in the course of pregnancy.

It is worth noting that, even though it is clear that there are alterations in pregnancy and it is incontestable that there is a clinical and physiological disequilibrium during the gestational period, it is indispensable that the pregnant woman be accompanied and her weight controlled for the good of the health of mother and fetus alike.^{2,19} Research with obese pregnant women has indicated that retinol-binding protein-4 (RBP4) increases throughout pregnancy and is associated with a decline in sensitivity to insulin, thereby enabling a correlation between fasting levels of TG, LDLc, HDLc, levels of total cholesterol and resistance to insulin.²⁰

With all the metabolic alterations and the mother's difficulty adapting, i.e. a condition that involves necessary changes, accuracy in examinations is of fundamental importance for stable gestation, owing to the various factors that hinder weight control and performance of medically advised procedures during pregnancy.³ Pregnancy should thus be addressed as a special clinical condition, characterized by changes in the physical, psychological and social behavior of the woman.⁸

Meanwhile, these correlations enable the reader to identify in each variable analyzed the consequences on maternal excess weight and the parameters used by the researchers for definition of obesity

during pregnancy. Some studies have used body weight in relation to ideal weight, while others have employed the gestational body mass index (BMI).²¹⁻²³ Authors have also shown that there is a relation between dyslipidemia and preeclampsia, especially heightened hypertriglyceridemia which has been correlated with pre-pregnancy and the body mass index of the pregnant woman.²⁴ A scientific study by different authors reported that the increased lipolytic activity in maternal adipose tissue contributes to the development of hyperlipidemia.⁵ Another study noted the rates of (maternal, fetal and neonatal) complications caused by maternal obesity, such as hyperglycemia, insulin resistance and hyperlipidemia, and concluded that obesity may pose a risk to a term pregnancy.²⁵

Even though various changes are to be expected during pregnancy, alterations during gestation may make it difficult to adapt to hyperlipidemic tensions and these changes may predispose the woman to other diseases, such as diabetes mellitus, chronic kidney failure and pre-eclampsia.^{7,26}

Studies with animals may also aid scientific progress on the alterations caused by obesity.^{13,14} Mertens *et al.*²⁷ studied obese insulin-resistant animals with severe dyslipidemia and found a deficiency of leptin and LDL receptors in the metabolism of the animal and an increase in oxidative stress.

Although most studies address the high incidence of excessive gestational weight gain, the association between dyslipidemia, overweight and maternal outcomes are equally worrying and merit the attention of local health services, in view of their implications for the health of mother and fetus alike.

Dyslipidemia and gestational outcomes

The past decade has seen more research focused on the effects of maternal dyslipidemia.^{5,9,10,24} One complication noted concerns intra-hepatic cholestase, which shows that dyslipidemia may contribute to the pathogenesis of the disease and that heightened LDL and reduced HDL cholesterol may provide prior evidence of gestational intra-hepatic cholestase.²⁸ As a consequence, a larger number of caesarians, the incidence of preeclampsia and the development of gestational diabetes mellitus are complications related to heightened pre-gestational BMI and excessive weight gain during pregnancy.^{7,29} Previous studies have already identified other complications, such as preeclampsia, chronic hypertension and diabetes.³⁰

Another study identified the relation existing

between levels of lipids and the risks of preterm birth. Mudd *et al.*³¹ found low levels of lipids (TC, LDLc and HDLc) to be associated with moderately increased risks for medically indicated preterm births, and of high concentrations of TC, LDLc and TG for spontaneous preterm births.

Studies have related preterm birth to tumor necrosis factor alpha (TNF- α) and likewise with lipid levels during gestation.³¹⁻³⁴ Research has established a link between TNF- α and the release of lipids by adipocytes, meaning that TNF- α can be induced by lipolysis.^{35,36} Studies have thus shown that, in mid-pregnancy, an increase in TNF- α and the lipid profile of pregnant women may enable the development of gestational hyperlipidemia, leading to the hypothesis of an interrelation between hyperlipidemia, TNF- α and preterm birth.^{32,37}

Lipid metabolism and transfer through the placenta

Thanks to various studies that have shown the consequences of gestational obesity, it can be stated that overweight and poorly controlled diabetes trigger physiological alterations in both the pregnant woman and the fetus.^{24,38,39}

It is important to mention the function of the placenta, which plays a fundamental role in transferring lipid radicals to the fetal compartment, which may subsequently be affected by maternal diseases associated with compromised lipid homeostasis, which has an impact on fetal growth.⁴⁰ However, other variables may alter the body composition of the fetus, although these are not fully understood, especially those that relate to growing levels of resistance to maternal insulin.

Research on maternal insulin and the role it plays in the placenta has shown that insulin does not traverse the placenta, but serves to regulate nutrient sensors, which subsequently have the function of stimulating proliferation of fetal cells and growth.⁴¹ A similar process occurs with polyunsaturated fatty acids (LC-PUFA), which, in the presence of lipoprotein receptors in the placenta facilitate their acceptance, metabolizing fatty acids and spreading them to the fetus.⁵

Crume *et al.*⁴² have identified certain proteins that indirectly influence neonatal adiposity, including leptin and adiponectin, which may be stimulated when there is resistance to maternal insulin, altering the placenta transport mechanisms. At the end of pregnancy, lipid catabolism is increased and this may lead to the development of maternal hyperlipidemia and an increase in the

concentration of triacylglycerols in the mother's plasma.⁵ It is worth noting that the metabolism of the pregnant mother is related to the production of ketone bodies, which are subsequently used by the fetus for synthesis of fatty acids, with the transfer to ketone bodies to the fetal plasma occurring by way of simple diffusion.⁵ For Watkins *et al.*,⁴³ however, the effect of fatty acids may be favored or restricted, causing serious problems for organs and fetal tissue. Physiopathological problems may thus be related to materno-fetal transport mechanisms, in the same way as the influence of the mother's lipid catabolism, which, directly or indirectly, may favor or hinder the transfer of lipids to the fetus.

The effects of maternal dyslipidemia on the baby

Gestational weight gain and obesity, in so far as they alter the intrauterine environment, are considered relevant factors and may be associated with cardiopathy and multiple anomalies in the newborns of obese women.⁴² However, the association between gestational obesity and neonatal characteristics has only relatively recently been studied scientifically.⁴⁴

Research in the 2000s have corroborated the importance of rigorous control of adequate exams and care in pregnancy relating to prevention and the occurrence of large for gestational age newborns in pregnant women with GMD.⁴⁵⁻⁴⁷ In another scientific study, well-controlled anthropometric measurements of children of mothers with GDM were found not to differ from those of the babies of non-diabetic mothers.⁴⁸ It is worth pointing out that pregnant women starting treatment late, having fewer consults and a higher two-hour glycemia level in the oral glucose tolerance test (OGTT 75g.) are factors frequently related to neonatal macrosomias.⁴⁹

Studies of the relation between excessive weight gain and macrosomia in newborns have concluded that there is a prevalence of 10.4% for the children of women with excessive gestational weight gain and of 2.5% for those of women with normal gestational weight gain and that this results in a larger number of caesarians and a lower Apgar score.^{28,50,51}

Macrosomia, congenital diseases, neonatal death, hypoglycemia and low Apgar score in the first or fifth minute were the most frequent outcomes in this review and are also correlated with excessive weight gain during pregnancy.^{27,52-55} Macrosomic babies born to obese and diabetic mothers are prone to develop glucose intolerance and childhood and

adult obesity.^{7,56} Studies also suggest that obese mothers may develop early insulin resistance in the maternal uterus, which may alter fetal metabolism.^{7,29}

Frantz *et al.*⁵⁷ found in hyperlipidemia a build-up of collagen in fetal tissue creating a susceptibility to atherosclerosis in the adult life of the newborn, which may be a factor in the development of early-onset atherosclerosis.

A study in primates has revealed that dyslipidemia may be present even in non-obese patients, when chronic consumption of a diet rich in fat may result in greater transfer of lipids to the fetus, regardless of maternal obesity and/or diabetes. Research therefore suggests that the developing fetus is highly vulnerable to excess lipids, which increase the risk of other diseases.⁵⁸

Final considerations

Research has shown that authors are concerned

about excess weight and lipidemic alterations in pregnancy, showing the risks for mother and newborn alike. In terms of the negative association “obesity-pregnancy”, a larger number of caesarians and cases of preeclampsia were the two most noteworthy complications for gestational outcomes.

It is clear there is a physiological demand for lipids during pregnancy. However, pathological dyslipidemia may give rise to adverse implications and complications during gestation, for the fetus and the newborn. There is no treatment for these disorders during pregnancy.

In short, the impact of care regarding maternal habits and excess weight during pregnancy is significant, given the various degrees of complications in obstetric outcomes and the influence of clinical characteristics on the newborn.

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