Dyslipidemia and maternal obesity: Prematurity and neonatal prognosis

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Summary

Objective: To identify the changes caused by dyslipidemia and obesity in pregnancy suggesting causes for premature birth, and the prognosis for the newborn.
Method: Systematic review based on the Medline, Lilacs, Embase and Cochrane library databases between 1996 and 2016. The search for studies included the following keywords: "dyslipidemia, pregnancy, obesity, preterm birth." A protocol was programmed and a protocol for inclusion/exclusion of studies was implemented.
Results: Of the 5,789 articles initially selected between March 1996 and July 2016, only 32 were in accordance with the established criteria. Of these, 28.12% discussed risk factors of prematurity; 37.50%, metabolic alterations and gestational dyslipidemia; 21.87%, dyslipidemic complications in preterm birth; and 12,50%, lipid metabolism, glycemic and placental transfer.
Conclusion: There is a reduced adaptation of obese pregnant women to the metabolic changes of gestation. This favors dyslipidemic intercurrences in the mother, which, directly or indirectly, suggests the occurrence of premature births and high lipid transfer to the fetus. Therefore, preterm newborns, whose mothers were dyslipidemic during pregnancy, have greater risk of epicardial fat, both in early (first year of life) and in later (adult) phases of life.

Keywords: Dyslipidemias. Pregnancy. Obesity. Premature Birth.

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Introduction

Prematurity results from multifactorial and unpredictable circumstances in all social classes and locations, and implies better understanding of perinatal causes and outcomes. Among other comorbidities, the relationships between a preterm birth and the newborn's low weight and a prognosis of growth deficit are evident.[1] A study carried out in the last decade emphasizes that prematurity increases the likelihood of developing cardiovascular diseases and other chronic diseases.[2] Still, despite a rather recent interest in it, a reduced number of papers on the subject and its specific etiological factors, a higher survival rate of premature infants favored by the advancement in health technologies is suggested.[3]

Dyslipidemia is characterized by abnormal levels of cholesterol and triglycerides, which generally increases the overweight rates and, when associated with pregnancy, is a worrisome change that can increase adverse pregnancy outcomes.[3] Among the various gestational outcomes, a study revealed that, in the year 2000, premature births accounted for 28% of neonatal deaths in 193 countries.[4] Risk factors for prematurity are relevant elements pending further research.[5,6]

Accordingly, it is of the utmost importance that we understand the relationships between dyslipidemia and obesity with prematurity and the specificities and peculiarities regarding changes during the gestational period, such as the isolated increase in serum cholesterol and

triglycerides, and mixed hyperlipidemic changes.[6,7] However, during pregnancy, physical, psychological and social behavior are altered due to the special conditions of the pregnant state, which is neither physiologically normal neither clinically abnormal.[8,9] Hence, based on scientific publications from 1996 to 2016, our study was aimed at identifying the changes brought about by dyslipidemia and obesity that may suggest the causes of premature birth and the prognosis for the newborn.

Method

Identification of studies

We undertook a selective review of the literature between March 1996 and July 2016 on which are the changes caused by dyslipidemia and obesity that suggest causes of premature birth and their coadjuvancy regarding the prognosis for the newborn. At first, we developed a protocol establishing the sources to be searched, languages, keywords and dates of publication over the past 20 years. Among methodological criteria, we prioritized sample size and the most recent years of publication. Papers published between 1996 and 2016 were extracted from the Medline, Lilacs, Embase and Cochrane databases. We selected the keywords "dyslipidemias," "pregnancy," "obesity" and "premature birth," which we checked against the DeCS – Descritores em Ciências da Saúde (Descriptors in Health Sciences), associated with the Boolean operators "AND" and "OR," published in Portuguese, English or Spanish.

Inclusion criteria

The papers to be evaluated and/or selected for our study should present research results on obesity and dyslipidemia in pregnancy and the predisposing factors therefore suggestive of the causes of prematurity and its relationship with the prognosis for the newborn (NB). Our selection included clinical trials; cross-sectional studies; cohort studies; case-control studies; epidemiological studies; and bibliographic reviews. In clinical trials, cohort studies; and case-control studies, in addition to the abovementioned criteria, we prioritized studies having a longer follow-up period. Literature reviews and epidemiological studies needed to be related to the subject and goal of our research. All members of our group participated in selecting the articles. Whenever there were any divergences regarding two or more articles, the scholars then analyzed the study in its entirety, discussing and debating it at previously scheduled meetings.

Population

Overweight pregnant women with a dyslipidemic profile, aged 18 years or older, and preterm NBs.

Exclusion criteria

Non-relevant scientific articles dealing with dyslipidemias in non-gestational conditions or articles published in languages other than Portuguese, English or Spanish.

Selection process of theoretical references for systematic reviews

From the initial selection of publications, together with the chosen databases and the proposed criteria, we obtained a total of 5,789 articles compatible with the proposed subject. Subsequently, we proceeded to select the references for systematic reviews (Figure 1) by following the exclusion steps: identification of repeated studies; reading of titles; reading of abstracts and methodological analysis; and identification of studies having no correlation with our study's goal. After double-checking the criteria and acquiring the articles to be used, we reorganized the number of selected studies into four topics: prematurity outcomes; metabolic changes and gestational dyslipidemia; dyslipidemic complications during preterm birth; lipid and glycemic metabolism and placental transfer.

Results and Discussion

In the systematic review, after applying the selection criteria mentioned above, we obtained 32 scientific studies, of which 28.12% (n=9) were on prematurity outcomes; 37.50% (n=12) on metabolic changes and gestational dyslipidemia; 21.87% (n=7) on dyslipidemic complications during preterm birth; and 12.50% (n=4) on lipid and glycemic metabolism and placental transfers. The scientific studies that met the selection criteria and were used in our study are shown in Table 1. Consecutively, we developed a schematic model for lipid alteration from tumor necrosis factor alpha (TNF-α), according to Figure 2. Figure 3 depicts the representation of an artery with dyslipidemia.

Prematurity outcomes

As from the last decades, prematurity has been considered the main cause of infant mortality and some important pulmonary, neurocognitive and ophthalmologic morbidities. Due to these factors, it was recognized as a serious public health problem.[10,11] Studies on prematurity indicated high neonatal morbidity and mortality rates and the occurrence of sequelae of varied natures.[4,10]

Some authors showed the associations between prematurity and the development of some complications related to glucose intolerance and dyslipidemias, both in children and in preterm-born adults who presented with increased blood pressure and insulin resistance at 30 years of age.[11]

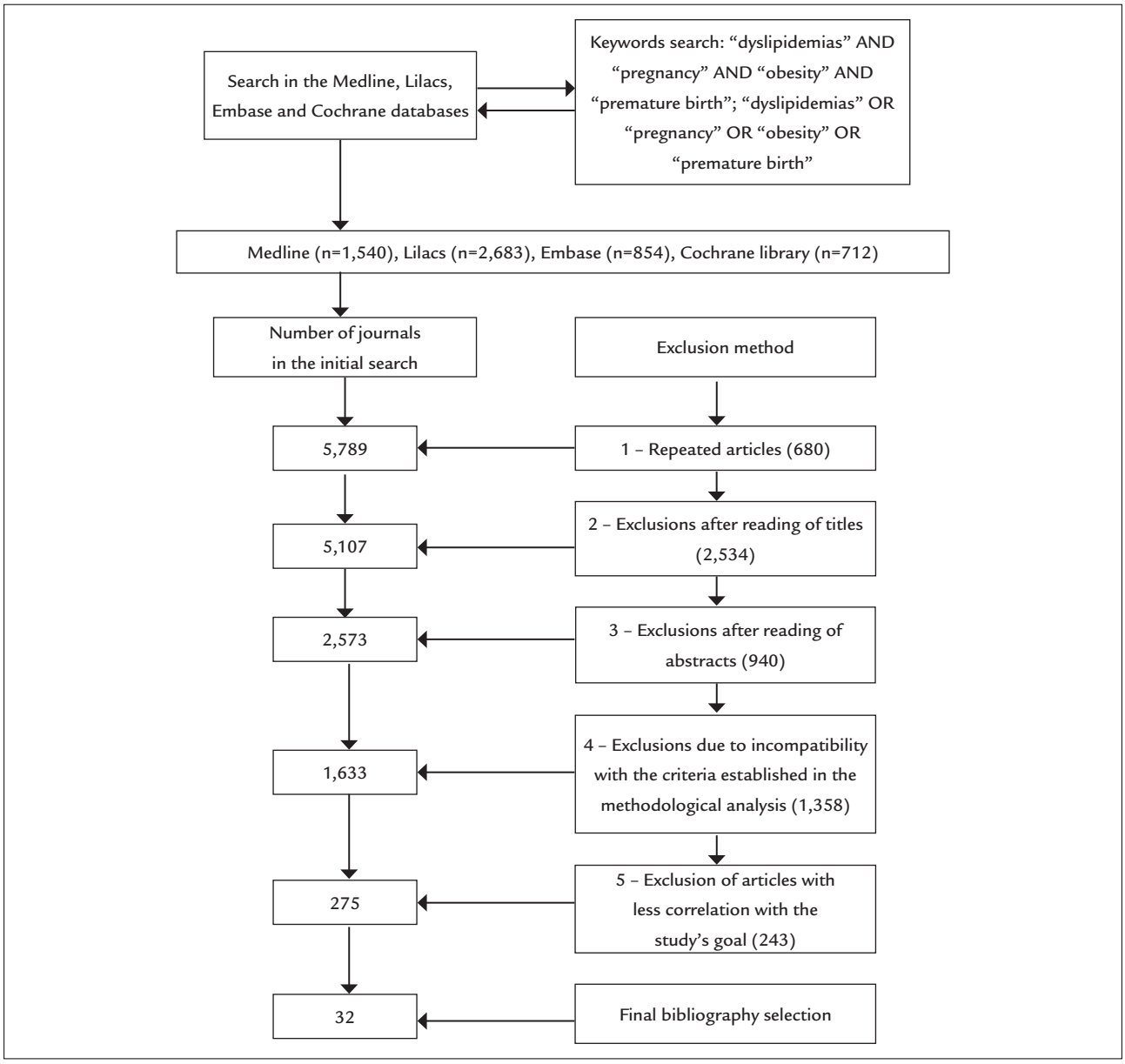

FIGURE 1 Flowchart of the activities of the selection process in the years 1996-2016.

TABLE 1 Studies that met the selection criteria (1996–2016).

Authors	Type of study	Year of publication	Population
Pessoa et al.[1]	Retrospective cohort	2015	Newborns
Bassareo et al.[2]	Prospective cohort	2016	Newborns
Castaño et al.[3]	Retrospective cohort	2013	Pregnant women
Lawn et al.[4]	Review study	2010	Newborns
Herrera et al.[5]	Review study	2006	Pregnant women
Nucci et al.[6]	Retrospective cohort	2001	Pregnant women
Stulbach et al.[7]	Retrospective cohort	2007	Pregnant women
Oliveira et al.[8]	Cross-sectional study	2012	Pregnant women
Cheung et al.[9]	Prospective cohort	2004	Newborns

(*Continues*)

TABLE 1 (Cont.) Studies that met the selection criteria (1996–2016).

Authors	Type of study	Year of publication	Population
Lorena et al.[10]	Cross-sectional study	2009	Newborns
Dalziel et al.[11]	Prospective cohort	2007	Newborns
Tomashek et al.[12]	Retrospective cohort	2006	Newborns
Shapiro-Mendoza et al.[13]	Retrospective cohort	2008	Newborns
Machado et al.[14]	Retrospective cohort	2016	Pregnant women
Hentges et al.[15]	Prospective cohort	2010	Newborns
Luz et al.[16]	Cross-sectional study	2008	Pregnant women
Oliveiros Donohue et al.[17]	Retrospective cohort	2003	Newborns
Ywaskewycz Benitez et al.[18]	Case-control	2010	Pregnant women
Ghio et al.[19]	Review study	2011	Pregnant women
Mangucci et al.[20]	Prospective cohort	2014	Pregnant women
Oliveira et al.[21]	Case-control	2016	Pregnant women
Mudd et al.[22]	Prospective cohort	2012	Pregnant women
Adamo et al.[23]	Clinical trial	2013	Pregnant women
Jelliffe-Pawlowski el al.[24]	Retrospective cohort	2014	Pregnant women
Joy et al.[25]	Case-control	2009	Pregnant women
Berkowitz et al.[26]	Retrospective cohort	1998	Newborns
Merzouk et al.[27]	Prospective cohort	2000	Newborns
Sebire et al.[28]	Cross-sectional study	2001	Pregnant women
Higa et al.[29]	Review study	2013	Pregnant women
Crume et al.[30]	Prospective cohort	2015	Pregnant women
Watkins et al.[31]	Case-control	2003	Pregnant women
Hull et al.[32]	Review study	2008	Pregnant women

Tomashek et al.[12] highlighted the group of borderline preterm newborns, i.e. the group of late preterm newborns (L-PTNB) defined as premature with a gestational age (GA) between 34 complete weeks and 36 weeks and 6 days. The researchers identified a percentage of deaths among preterm infants born at 36 weeks twice as high as compared to that among infants born at 34 weeks. Another study revealed a seven-fold higher risk of morbidity among L-PTNB when compared to term newborns (TNB).[13]

Nevertheless, it is noteworthy that the L-PTNB group has begun to be studied more systematically as from the 2000s, with a significant increase in morbidity and mortality and associated risks related to respiratory pathologies, thermal instability, a greater number of neurological alterations and lower Apgar scores.[13,14] Even though there are studies identifying a diversity of risks related to neonatal morbidity and mortality and high-incidence rates of prematurity-related sequelae of varied natures, both L-PTNB and their diversity of high risk when compared to TNB deserved our special consideration in this systematic review.[11,13,15] It is a well-known fact that the main cause of maternal death is complications caused by high blood pressure during pregnancy or at the time of delivery, as well as hemorrhages and other morbidities.[16,17]

However, studies on birth weight and changes in arterial blood pressure throughout the child's life were more unanimous in investigating possible risks, especially when compared with studies on GA and current infant weight.

Metabolic changes and gestational dyslipidemia

Despite the fact that most studies focused on gestational concerns, which correspond to several factors arising from dietary imbalance and caloric expenditure, the relationship between physiological changes and lipid and glycemic metabolism during pregnancy deserved special attention in the studies.[3,6,7] It was thus found that, over the course of gestation, adipose tissue and its lipolytic activity cause an increase in serum levels of glycerol being converted into glucose in the liver, which in turn is gradually made available to the fetus.[6]

During pregnancy, investigators found an increase in the levels of high-density lipoprotein cholesterol (HDL-c) and very-low-density lipoprotein cholesterol (VLDL), as well as in the concentrations obtained from lipid and lipoprotein

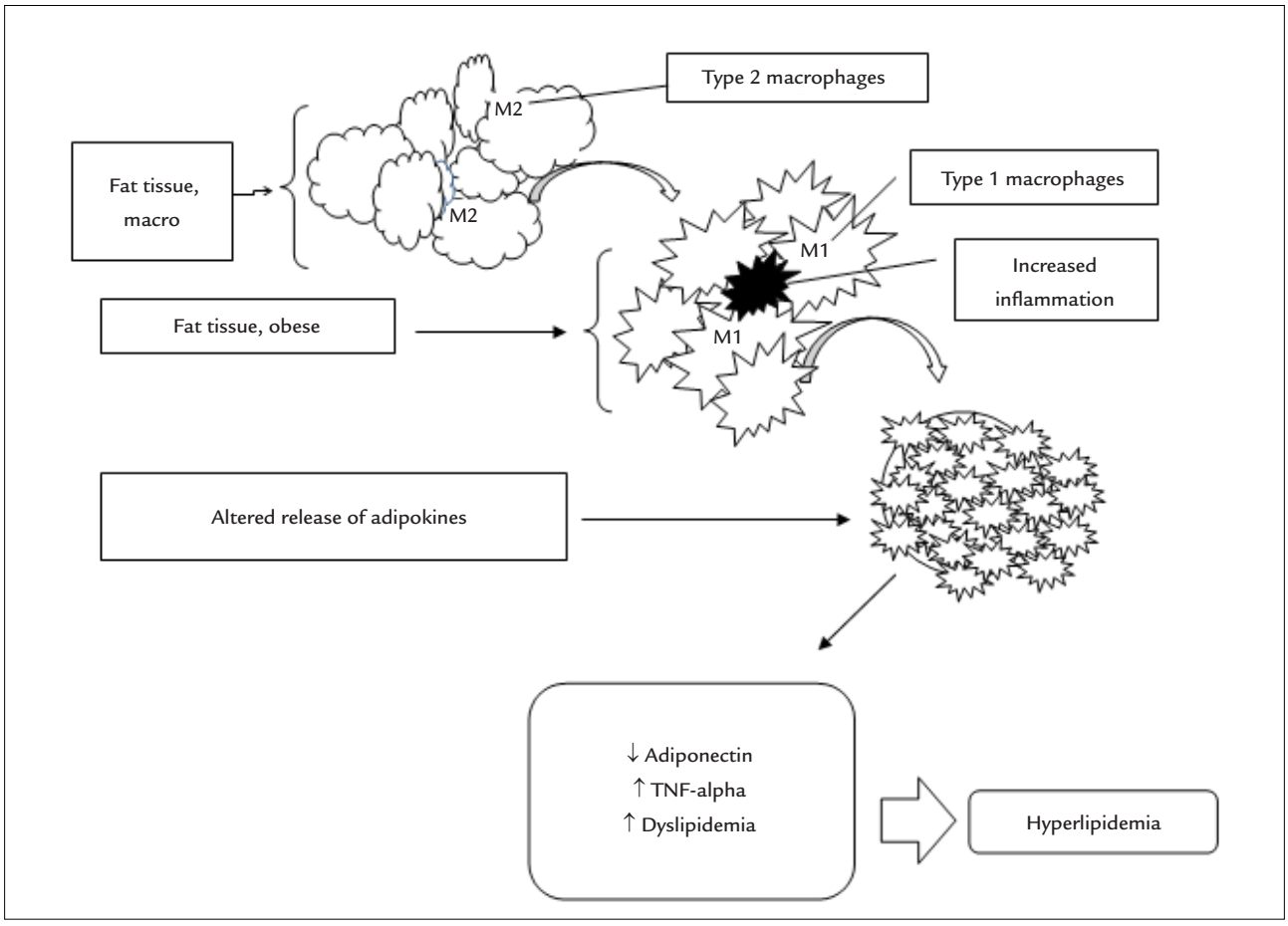

FIGURE 2 Schematic model of tumor necrosis factor alpha (TNF-α) altering the lipid profile.

measurements by a comparative study with non-pregnant women. That study provided guidelines as to when a physiological indicator may be associated with pregnancy diseases and/or disorders.[18] Ghio et al.[19] observed a gradual increase in the triglycerides, total cholesterol (TC), VLDL and HDL-c lipid patterns from the 12th week of pregnancy, especially in the second and third trimesters in response to estrogen stimulation and insulin resistance, as well as an increase in the risk of pre-eclampsia and premature birth.

In previous scientific studies including overweight and obese women, the hypotheses and suggestions pertaining to a consecutive increase in dyslipidemic changes and gestational complications are notorious. The studies conducted by Callegari et al.[20] in an attempt to identify cardiometabolic risks comparing normal-weight pregnant women with overweight pregnant women found an increase in the levels of triglycerides, TC, VLDL and low-density lipoprotein cholesterol (LDL-c) in both groups. Yet, the HDL-c levels remained unchanged in normal-weight pregnant women, in contrast with the significantly low levels found in overweight pregnant women.

In carrying out this study, we conclude that, among pregnant women with an adequate weight, ancestry or descent on HDL-c parameters showed diversities in some scientific studies. The alternating patterns allow for suggestions for pathological indicators, including prematurity and future cardiac events for the newborn.[21]

Hence, with respect to each variable analyzed, these correlations make it possible for the reader to identify the events caused by maternal overweight and to deem dyslipidemic alternations as indicators of complications, such as predisposition to high systemic arterial blood pressure, cardiometabolic events and the outcomes of a premature delivery.[18,22,23]

Dyslipidemic complications in preterm birth

Even though changes in pregnancy are evident, the likelihood of a clinical and physiological imbalance during the gestational period is indisputable. It is therefore essential that pregnant women be followed up and have their weight controlled to ensure both maternal and fetal health.[1,3] Mudd et al.[22] demonstrated an existing relationship between

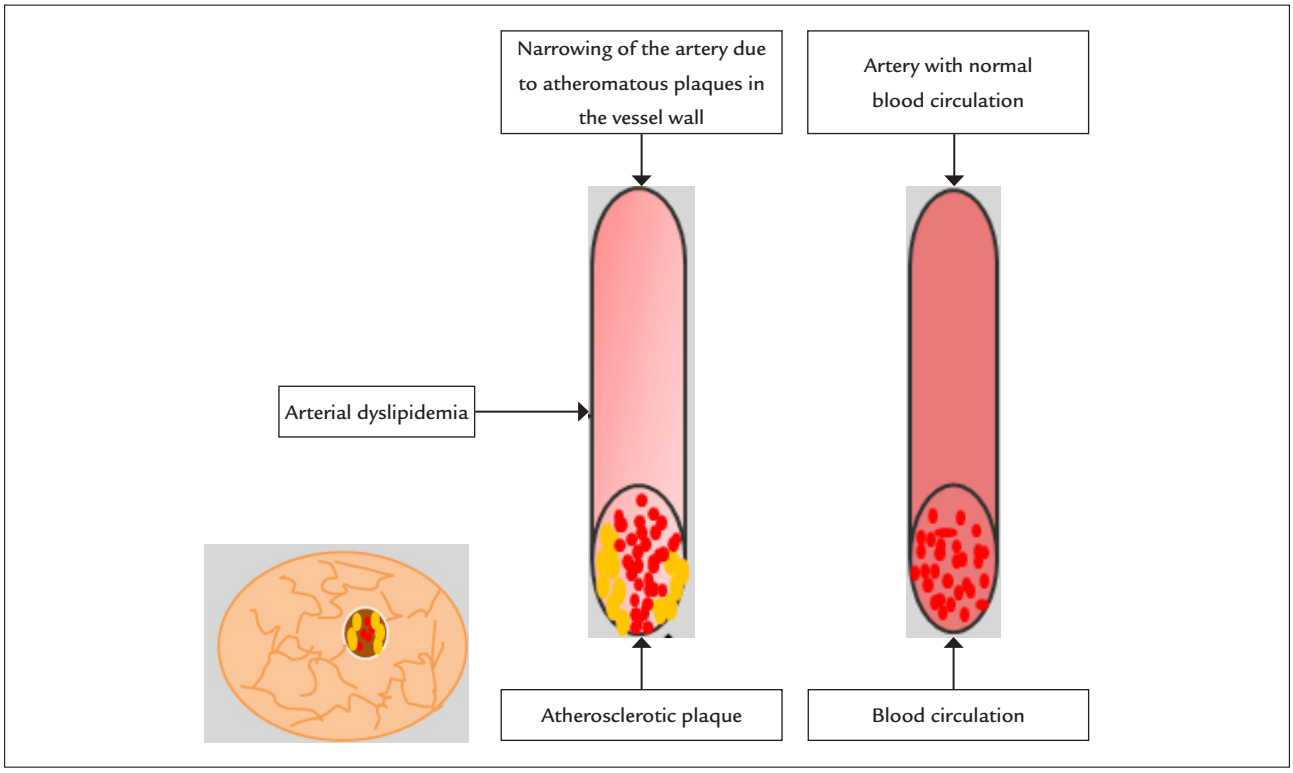

FIGURE 3 Schematic model of an artery with dyslipidemia.

lipid levels and the risk of premature birth complications. According to the authors, low TC, LDL-c and HDL-c values are associated with a moderately increased risk of medically indicated preterm deliveries, whereas high TC, LDL-c and triglycerides are associated with spontaneous preterm deliveries.

There is an established link between TNF-α and the release of lipids by adipocytes, i.e. TNF-α being induced by lipolysis. A study revealed that, midway through gestation, an increase in TNF-α and lipid levels can lead to the development of gestational hyperlipidemia. It also suggested an interrelationship involving TNF-α, hyperlipidemia and a preterm delivery.[24] Another study emphasized the rates of complications attributed to maternal obesity, such as hyperglycemia and hyperlipidemia, with complications in materno-fetal and neonatal outcomes. This leads us to deduce that obesity and dyslipidemic alterations may place a full-term pregnancy in jeopardy.[25] On the other hand, so researchers found an inconsistency in the association between obesity and preterm delivery, due to the fact that some pregnant women presented with obesity-related diseases.[26]

The relationship between dyslipidemia and risks of materno-fetal complications is significantly independent of maternal obesity. In the studies by Merzouk et al.,[27] the increase in fetal lipid levels showed an association with the metabolic levels of poorly-controlled diabetic mothers and consecutively their macrosomic newborns had increased values of all serum lipids and in their apolipoprotein and lipoprotein lipid levels.

Regarding the possibility of prematurity being caused by dyslipidemic and hyperglycemic changes and overweight during pregnancy, we must bear in mind that the association between maternal obesity and preterm birth is controversial, with particularities yet to be uncovered. In other words, while some studies reported high risks or a diminished relationship, other studies found no correlation at all.[22,25,26,28] Nevertheless, some researchers state that prematurity is independent of maternal hyperglycemia,[5] suggesting thus that it is more closely associated with maternal dyslipidemia.

Lipid and glycemic metabolism and placental transfers

The placenta plays a key role in transferring lipid radicals to the fetal compartment, which can be consecutively affected by maternal diseases associated with the impairment of lipid homeostasis.[29] Therefore, the role of long chain polyunsaturated fatty acids (LC-PUFA) becomes emphasized: the presence of lipoprotein receptors in the placenta promotes their uptake, which causes fatty acids to be metabolized and diffused to the fetus.[6]

A study deserving special mention is an observational epidemiological study on pregnant women indicating certain proteins that indirectly influence neonatal adiposity, such as leptin and adiponectin, two proteins that can be stimulated when there is maternal insulin resistance, thereby altering the mechanisms of placental transport.[30] According to the scientific literature, metabolism during pregnancy is related to the production of ketone bodies being consecutively used by the fetus for fatty acid synthesis. This emphasizes the fact that the contribution of maternal fatty acids to the fetus and the possible bioenergetic conversions can be either intensified or restricted, which can cause serious problems to fetal organs and tissues in either case.[6,31]

With regard to glycemic and lipid metabolism and placental transfer, a study showed that pathophysiological problems can be related to materno-fetal transport mechanisms. Similarly, the influence from the mother's lipid catabolism can also be involved, which can directly or indirectly favor or limit the transfer of lipids to the fetus.[32]

In this context, dyslipidemia during pregnancy and the parameters of lipid transfer from mother to fetus have been scientifically shown to be influenced by placental hormones affecting both glucose and lipid metabolism to ensure that the fetus has a sufficient supply of essential nutrients for its development.[5] However, as far as scientific results and/or parameters we surveyed are concerned, metabolic adaptations are notoriously less flexible among obese pregnant women than they are in normal-weight pregnant women, which may impair the materno-fetal transport mechanism.

Our systematic review has some limitations, such as difficulties in finding factors relating dyslipidemia to prematurity in the studies with the population defined according to the initial protocol, given that we aimed at investigating scientific studies of populations with human beings. Another limiting factor was the small number of epidemiological studies on the particularities involving causes and risks of prematurity and consecutively the abbreviated follow-up on the possible dyslipidemic outcomes among newborns. Conversely, one strength of our study was the number of studies with dyslipidemic obese pregnant women, which greatly allowed for comparative analyses and/or suggestions as to prognoses according to the statistical results.

Conclusion

There is a reduced adaptation of obese pregnant women to the metabolic changes of gestation. This favors dyslipidemic intercurrences in the mother, which, directly or indirectly, suggests the occurrence of premature births and high lipid transfer to the fetus. Therefore, preterm newborns, whose mothers were dyslipidemic during pregnancy, have greater risk of epicardial fat, both in early (first year of life) and in later (adult) phases of life.

Resumo

Dislipidemia e obesidade materna: prematuridade e prognóstico neonatal

Objetivo: Identificar as alterações provocadas pela dislipidemia e pela obesidade na gestação que sugerem causas de partos prematuros e o prognóstico para o recém-nascido.
Método: Revisão sistemática nas bases de dados Medline, Lilacs, Embase e da biblioteca Cochrane entre os anos de 1996 e 2016. O processo de seleção ocorreu a partir dos descritores dislipidemia, gravidez, obesidade, nascimento prematuro. Um protocolo foi programado, havendo uma etapa seletiva de inclusão/exclusão das pesquisas.
Resultados: Dentre os 5.789 artigos inicialmente selecionados entre março e julho de 2016, somente 32 estavam de acordo com os critérios estabelecidos. Desses, 28,12% focavam nos fatores de risco da prematuridade; 37,50%, em alterações metabólicas e dislipidemia gestacional; 21,87%, em intercorrências dislipidêmicas no parto prematuro; 12,50%, em metabolismo lipídico, glicêmico e transferências pela placenta.
Conclusão: Existe uma menor adaptação da gestante obesa às mudanças metabólicas da gestação, favorecendo intercorrências dislipidêmicas na mãe, o que, direta ou indiretamente, sugere a ocorrência de partos prematuros e uma elevada transferência de lipídios para o feto. Portanto, recém-nascidos prematuros de mães dislipidêmicas durante a gravidez apresentam maior risco de desenvolver gordura epicárdica tanto na fase precoce (primeiro ano de vida) quanto na tardia (vida adulta).

Palavras-chave: Dislipidemias. Gravidez. Obesidade. Nascimento Prematuro.

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