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Original Research Article

Assessment of the Association of Maternal Early Pregnancy Lipid Levels with Patterns of Foetal Growth and the Risk of SGA and LGA: An Analytical Study

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Abstract

Aim: The aim of this study was to examine the association of maternal early pregnancy lipid levels with foetal growth, patterns of foetal growth and the risk of SGA and LGA independent of maternal BMI and glucose levels.

Methods: The present study was undertaken in the Department of Obstetrics & Gynecology, Madhubani Medical College & Hospital, Madhubani, Bihar, India. For the present study, we included 500 women with a live born singleton and available information on lipid measurements in early pregnancy.

Results: We included 500 women. These women were on average 29.5 (± 5.1) years of age, and most women had a pre-pregnancy BMI < 25.0 kg/m2 (72%). Foetal growth parameters were available in 480 (96%) and 480 (96%) children in mid- and late pregnancy, respectively. Of all children, 300 were born AGA, 100 SGA and 100 LGA. Women with a child born LGA had higher levels of triglycerides and remnant cholesterol in early pregnancy than women with a child born AGA. No differences were observed in lipid distribution between women with a child born SGA and AGA.

Conclusion: Our study suggests a novel association of early pregnancy triglyceride and remnant cholesterol levels with foetal growth, patterns of foetal growth and the risk of LGA. Future studies are warranted to explore clinical implication possibilities.

Keywords: Pregnancy, Lipoproteins, Foetal weight, Infant; Small-for-gestational age, Foetal programming

Introduction

According to Developmental Origins of Health and Disease (DOHAD) theory, maternal metabolism and intrauterine environment could affect fetal development and further impact their health status in adulthood. [1,2] Among the prenatal metabolic factors, maternal lipids play an important role in excess fetal growth. During pregnancy, maternal lipid profiles, including total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-c), and high-density

lipoprotein cholesterol (HDL-c), are taken up by placenta and primarily provide energy for maternal metabolism and fetal development. [3,4] To adapt to maternal-fetal physiology, maternal lipid levels rise progressively throughout gestation, suggesting the importance of these metabolic changes in fetal development. [5]

Adverse pregnancy outcomes have serious consequences (e.g. increased perinatal morbidity and mortality of mother and child) in the short term [5] and also increase the manifestation of disease later in life. For instance, preterm delivery and being born small for gestational age (SGA) or large for gestational age (LGA) are associated with increased risk for type 2 diabetes, cardiovascular diseases, and hypertension at adult age. [6-9] Although obstetric care has improved, pregnancy complications and perinatal morbidity are still present in Western societies. [10]

One of the causal factors for perinatal morbidity and mortality could be the maternal atherogenic lipid profile early in pregnancy. During normal pregnancy, women show an increase in lipid levels, including levels of triglycerides (TG) and total cholesterol (TC) as gestational age progresses. [11,12] Both TG and TC are taken up by the placenta and metabolized and transported to the fetus in various forms; this shows that both lipids are essential for the development of the fetus. [13]

Adverse birth outcomes, including small-for-gestational age (SGA) and LGA, may affect short-term (e.g. increased morbidity and mortality) and long-term (increased risk of hypertension, diabetes and metabolic syndrome) health of the child. [14,15] Lipid levels in early pregnancy are associated with maternal pregnancy complications, such as pre-eclampsia, independent of pre-pregnancy body mass index (BMI). [16] Our hypothesis is that according to the Developmental Origins of Health and Disease (DOHaD) theory, maternal lipid levels may also lead to adverse birth outcomes such as LGA due to adverse growth patterns. [7]

Therefore, the aim of this study was to examine the association of maternal early pregnancy lipid levels with foetal growth, patterns of foetal growth and the risk of SGA and LGA independent of maternal BMI and glucose levels.

Methods

The present study was undertaken in the Department of Obstetrics & Gynecology, Madhubani Medical College & Hospital, Madhubani, Bihar, India. For the present study, we included 500 women with a live born singleton and available information on lipid measurements in early pregnancy.

We excluded women with a twin pregnancy, diabetes mellitus and gestational diabetes and those on lipid or glucose regulating treatment during study enrolment.

Gestational diabetes was diagnosed according to Dutch guidelines using the following criteria: either a random glucose level > 11.0 mmol/L, a fasting glucose level ≥ 7.0 mmol/L or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test (glucose level > 7.8 mmol/L after glucose intake).

Exposure: maternal lipid levels in early pregnancy

Non-fasting plasma samples were obtained in early pregnancy (median 13.4 weeks of gestation, 90% range [10.5 to 17.2]). Total cholesterol (mmol/L), triglyceride (mmol/L) and high-density lipoprotein cholesterol (HDL-c) (mmol/L) concentrations were analysed. LDL-c (mmol/L), remnant cholesterol ([total cholesterol − LDL-c] − HDL-c) and non-HDL-c (total cholesterol − HDL-c) were calculated.

Outcome measures: foetal growth parameters and adverse birth outcomes

The primary outcome of this study was adverse birth outcomes. Secondary outcomes were foetal growth and foetal growth patterns. Ultrasound measurements were performed in mid-pregnancy (median 20.4 weeks of gestation, 90% range [19.1 to 22.5]) and late pregnancy (median 30.2 weeks of gestation, 90% range [29.1 to 31.9]) using protocols describing standardized planes Foetal growth parameters included the head circumference, femur length and abdominal circumference. We calculated the estimated foetal weight (EFW) using the Hadlock 3 formula.[17] Longitudinal growth curves and gestational-age-adjusted standard deviation scores (SDS) were constructed for all foetal growth parameters. These gestational-age-adjusted SDS were based on reference growth curves from the whole-study population and represent the equivalent of z-scores.[18]

Statistical Analysis

In all analyses, a P value < .05 was considered statistically significant. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 24.0 for Windows (SPSS Incl., Chicago, IL, USA) and the Statistical Analysis System version 9.4 (SAS, Institute Inc., Cary, NC, USA).

Results

Table 1: Baseline characteristics

Outcomes	
Maternal characteristics	
Maternal age at enrolment (years)	29.5
Educational level	**N%**
Primary or no education	60 (12)
Secondary	230 (46)
Higher	210 (42)
Pre-pregnancy BMI (kg/m2)	
Normal or underweight (< 25.0)	360 (72)
Overweight (25.0–30.0)	100 (20)
Obesity (≥ 30.0)	40 (8)
Nulliparous	300 (60%)
No folic acid supplementation	140 (28%)
Gestational age at blood sampling (weeks)	13.4 (10.5 to 17.2)
Glucose levels (mmol/L)	4.4 (0.8)
Foetal characteristics	
Mid-pregnancy measurements	480 (96)
Gestational age (weeks)	20.5 (19.1 to 22.6)
Head circumference (mm)	179 (13)
Femur length (mm)	33 (3)
Abdominal circumference (mm)	156 (14)
Estimated foetal weight (g)	372 (77)
Late pregnancy measurements	480 (96)
Gestational age (weeks)	30.4 (29.0 to 32.2)
Head circumference (mm)	285 (12)
Femur length (mm)	57 (3)
Abdominal circumference (mm)	263 (16)
Estimated foetal weight (g)	1604 (177)
Birth characteristics	

Gestational age at birth (weeks)	40.1 (36.9 to 42.1)
Boy	250 (50)
Birth measurements	490 (98)
Head circumference (mm)	338 (17)
Length (mm)	502 (24)
Birth weight (g)	3401 (560)
Gestational hypertension	218 (3.8)
Pre-eclampsia, n (%)	139 (2.4)
Early onset (< 34 weeks of gestation)	20
Late onset (> 34 weeks of gestation)	100
NICU admission	50 (10)

We included 500 women. These women were on average 29.5 (± 5.1) years of age, and most women had a pre-pregnancy BMI < 25.0 kg/m2 (72%). Foetal growth parameters were available in 480 (96%) and 480 (96%) children in mid- and late pregnancy, respectively.

Table 2: Maternal lipid profile in early pregnancy and foetal growth

	SGA (n = 100)	**AGA (n = 300)**	**LGA (n = 100)**
Gestational age at blood sampling, weeks	13.4 (10.5 to 17.2)	13.4 (10.5 to 17.2)	13.2 (10.9 to 17.1)
Total cholesterol, mmol/L	4.77 (0.90)	4.82 (0.87)	4.83 (0.88)
Triglycerides, mmol/L	1.23 (0.68 to 2.33)	1.26 (0.72 to 2.34)	1.33 (0.73 to 2.51)
LDL-c, mmol/L	2.40 (0.74)	2.43 (0.72)	2.43 (0.73)
HDL-c, mmol/L	1.77 (0.35)	1.78 (0.35)	1.74 (0.35)
Remnant cholesterol, mmol/L	0.56 (0.31 to 1.06)	0.57 (0.33 to 1.06)	0.60 (0.33 to 1.12)
Non-HDL-c, mmol/L	3.00 (0.85)	3.05 (0.83)	3.08 (0.85)

Of all children, 300 were born AGA, 100 SGA and 100 LGA. Women with a child born LGA had higher levels of triglycerides and remnant cholesterol in early pregnancy than women with a child born AGA. No differences were observed in lipid distribution between women with a child born SGA and AGA.

Table 3: Associations of maternal lipid profile in early pregnancy with birth outcomes

	AGA n = 300	**SGA OR (95% CI) n = 100**	**P value**	**LGA OR (95% CI) n = 100**	**P value**
Total cholesterol, SDS					
Basic model	Reference	0.94 (0.85 to 1.03)	0.16	1.00 (0.92 to 1.10)	0.94
BMI model	Reference	0.96 (0.87 to 1.05)	0.33	0.97 (0.88 to 1.06)	0.51
Glucose model	Reference	0.95 (0.87 to 1.05)	0.32	0.97 (0.87 to 1.07)	0.57
Triglycerides, SDS					
Basic model	Reference	0.91 (0.83 to 1.00)	0.04	1.18 (1.07 to 1.29)	0.001
BMI model	Reference	0.94 (0.85 to 1.03)	0.17	1.11 (1.01 to 1.22)	0.04
Glucose model	Reference	0.94 (0.85 to 1.03)	0.19	1.09 (0.99 to 1.20)	0.08
LDL-c, SDS					
Basic model	Reference	0.95 (0.87 to 1.04)	0.28	1.01 (0.92 to 1.10)	0.91
BMI model	Reference	0.98 (0.89 to 1.07)	0.59	0.96 (0.88 to 1.06)	0.43
Glucose model	Reference	0.98 (0.89 to 1.07)	0.59	0.97 (0.88 to 1.06)	0.47
HDL-c, SDS					
Basic model	Reference	1.01 (0.92 to 1.10)	0.91	0.88 (0.81 to 0.97)	0.01

BMI model	Reference	0.98 (0.90 to 1.07)	0.67	0.92 (0.84 to 1.01)	0.09
Glucose model	Reference	0.98 (0.89 to 1.07)	0.62	0.93 (0.85 to 1.03)	0.16
Remnant cholesterol, SDS					
Basic model	Reference	0.91 (0.83 to 1.00)	0.05	1.18 (1.08 to 1.30)	< 0.001
BMI model	Reference	0.94 (0.86 to 1.03)	0.20	1.11 (1.01 to 1.23)	0.03
Glucose model	Reference	0.94 (0.86 to 1.04)	0.23	1.10 (1.00 to 1.21)	0.06
Non-HDL-c, SDS					
Basic model	Reference	0.93 (0.85 to 1.02)	0.13	1.05 (0.96 to 1.15)	0.27
BMI model	Reference	0.96 (0.88 to 1.06)	0.40	1.00 (0.91 to 1.09)	0.95
Glucose model	Reference	0.96 (0.88 to 1.06)	0.41	1.00 (0.91 to 1.09)	0.92

Table 3 shows the association of maternal lipid concentrations in early pregnancy with adverse birth outcomes. Triglyceride and remnant cholesterol levels in early pregnancy were positively associated with the risk of LGA. The association of triglycerides and remnant cholesterol with LGA was attenuated when adjusting for pre-pregnancy BMI. However, after adjustment for glucose, the associations were not significant anymore. The negative association between HDL-c and LGA attenuated to non-significant levels after adjustment for pre-pregnancy BMI and early pregnancy maternal glucose levels. Total cholesterol, LDL-c and non-HDL-c were not associated with LGA. We observed no association between maternal lipid levels in early pregnancy and the risk of SGA.

Discussion

The worldwide incidence of overweight and obese women of reproductive age is increasing.[19-22] High maternal weight and hyperglycaemia are established risk factors for increased foetal growth and a child born large-for gestational age (LGA). Maternal hyperglycaemia is associated with a higher flux of glucose over the placenta leading to foetal upregulation of insulin, increased foetal growth and ultimately a child born LGA. [23]

Lipid levels were divided into quintiles, and women in the highest quintile had a mean triglyceride level of 2.15 (± 0.52) mmol/L. In our study, women had lower levels of triglycerides with a mean of 1.72 (± 0.54) mmol/L in the highest quintile. The study of Vrijkotte et al. found that the highest triglyceride quintile was associated with a higher birth weight and a higher prevalence of a child born LGA. [24] However, a limitation of this study is that they did not take the influence of glucose into account, even though this is a well-known confounder for triglyceride levels. [25,26] In our study, we corrected for both maternal BMI and early pregnancy glucose levels and showed that the positive association between triglycerides and LGA remained significant if maternal BMI was considered. However, after adjustment for glucose levels, the association attenuated to non-significant levels.

Triglycerides and remnant cholesterol levels reflect an impaired metabolism of triglyceride-rich lipoproteins and their remnants, which are controlled by placental lipoprotein lipases such as placental lipoprotein lipase (pLPL) and placental endothelial lipase (pEPL) activity. [27,28] The only study which assessed maternal remnant cholesterol levels, representative of the remnant lipoproteins, was performed in mice and showed that remnant cholesterol is associated with accelerated foetal growth in mice. [29] In our study, maternal remnant cholesterol levels in early pregnancy are positively associated with foetal growth, increased foetal growth pattern of head circumference and abdominal circumference and the risk of LGA, independent of maternal BMI. After correction for glucose, the association of

remnant cholesterol and LGA attenuated to just non-significance. This may be explained by the close relation between remnant cholesterol levels and insulin resistance, the association of insulin resistance with glucose levels and the association of insulin resistance with an atherogenic plasma lipid profile. [30-32]

To fully comprehend the association of maternal lipid levels and foetal growth, it is important to understand the maternal-placental-foetal transport pathways but also the development of the foetal lipid metabolism. Unfortunately, to date, this is still largely unknown. However, we assume that the contribution of the foetal metabolism will be ignorable or very little in early pregnancy, and therefore, we expect that this will have a limited effect on our results. Our results are in line with a meta-analysis of Wang et al. describing a positive association of triglycerides with LGA and birth weight and a negative association of HDL-c with birth weight. [33] The associations were even stronger in overweight or obese women prior to pregnancy. Our study adds to these findings that the associations are even independent of pre-pregnancy BMI.

We hypothesized that HDL-c was in contrast to the other lipid levels negatively associated with foetal growth. However, the negative associations of HDL-c with birth weight and LGA attenuated to non-significance after adjustment for pre-pregnancy BMI and glucose. This may be explained by the inverse association between BMI and HDL-c. [34] In this study, we found no association of lipid levels in early pregnancy with adverse birth outcomes in a subset of relatively healthy women (nulliparous, non-smoking, lean women). If the association of lipid levels with adverse birth outcomes would be fully explained by genetics, we would have expected to also find an association of early pregnancy lipid levels with adverse birth outcomes in this relatively healthy population. Since no association was found, we hypothesize that in addition to genetics, lifestyle factors also play an important role in the association of lipid levels with adverse birth outcomes. Currently, non-high-density lipoprotein cholesterol (non-HDL-c) is often used to describe the total of proatherogenic particles (low-density lipoprotein cholesterol [LDL-c], lipoprotein-a, intermediate-density lipoprotein [IDL] and VLDL). High maternal levels of non-HDL-c may therefore be more specific to depict the future cardiovascular risk of the foetus than maternal hypercholesterolemia. [35]

Our results suggest a novel association of early pregnancy maternal lipid levels and the risk of a child born LGA. However, it should be noted that foetal growth alone may be a weak surrogate for perinatal harm since there was no difference in NICU admission for women with a child born AGA compared to women with a child born LGA in our study. Before implementation of lifestyle interventions to decrease maternal lipid levels in early pregnancy, future studies are warranted to examine whether maternal lipid levels are not only associated with foetal growth, but also with subsequent perinatal harm such as shoulder dystocia, neonatal asphyxia and neonatal death. [36]

Conclusion

This study suggests a novel association of triglycerides and remnant cholesterol in early pregnancy with foetal growth rates and the risk of a child born LGA. The elevated maternal TG levels in the first trimester of pregnancy are a significant, but modest, contributor in the expression of PIH, preeclampsia, induced preterm birth, and children to be born LGA. With this observation, inclusion of a lipid profile may be considered early in pregnancy or perhaps even in the preconception screening. Additional studies are needed to evaluate whether lowering TG levels by means of lifestyle programs (e.g. diet and

physical activity) is beneficial in reducing adverse pregnancy outcome. However, future studies are warranted to explore clinical implication possibilities.

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