Maternal serum cholesterol as predictive factor for large-for-gestational age newborn in pre-pregnant underweight women

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Abstract

Objective: To determine the relationship between lipid profile and risks of adverse pregnancy outcomes in pre-pregnant underweight women. Design: This study was part of an ongoing cohort study which Chinese gravidas delivered from January 2015 to December 2016. Setting: Pre-pregnant body mass index (pre-BMI) was classified into underweight (<18.5 kg/m2), normal weight (18.5-22.9 kg/m2) and overweight/obesity ([?]23 kg/m2). Population: There're 1203 underweight- women, 3281 normal-weight women and 1209 overweight women met the criteria. Methods: Data of 6233 women and medical information including lipid concentrations, pregnancy complications, pregnancy and perinatal outcomes were analyzed. Results: The proportion of underweight women 19.2% and overweight/obese women19.4% was similar in South China. Serum TC level of underweight women was significantly higher than overweight/obese women ($p < 0.001$). After adjusting for maternal age, underweight women with high TC level had significantly higher occurrence of LGA [OR=2.24, 95%CI (1.08, 4.63)], and lower occurrence of SGA [OR=0.71, 95%CI (0.59, 0.85)], while there were no significant associations between TC and LGA or SGA in other groups. Conclusion: Underweight women with high TC had higher occurrence of LGA, while there was no association between TC levels and LGA in normal and overweight/obese women. Thus, we should recommend underweight women to manage the lipid. Funding: This work was supported by the National Natural Science Foundation of China (Grant No: 81771606), Shenzhen Science and Technology Innovation Commission (Grant No: JCYJ20170817172241688, JCYJ20180228163459314), and Clinical Medical Project 5010 of Sun Yat-sen University, China (Grant No: 2012004). Key words: underweight; cholesterol; LGA; overweight;

Title Page

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Maternal serum cholesterol as predictive factor for large-for-gestational age newborn in pre-pregnant underweight women: A cohort study

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Running Title: Cholesterol and newborn size in underweight women

Abstract

Objective : To determine the relationship between lipid profile and risks of adverse pregnancy outcomes in pre-pregnant underweight women.

Design : This study was part of an ongoing cohort study which Chinese gravidas delivered from January 2015 to December 2016.

Setting : Pre-pregnant body mass index (pre-BMI) was classified into underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2) and overweight/obesity ([?]23 kg/m^2).

Population : There're 1203 underweight- women, 3281 normal-weight women and 1209 overweight women met the criteria.

Methods: Data of 6233 women and medical information including lipid concentrations, pregnancy complications, pregnancy and perinatal outcomes were analyzed.

Results : The proportion of underweight women 19.2% and overweight/obese women19.4% was similar in South China. Serum TC level of underweight women was significantly higher than overweight/obese women ($p < 0.001$). After adjusting for maternal age, underweight women with high TC level had significantly higher occurrence of LGA [OR=2.24, 95%CI (1.08, 4.63)], and lower occurrence of SGA [OR=0.71, 95%CI (0.59, 0.85)], while there were no significant associations between TC and LGA or SGA in other groups.

Conclusion : Underweight women with high TC had higher occurrence of LGA, while there was no association between TC levels and LGA in normal and overweight/obese women. Thus, we should recommend underweight women to manage the lipid.

Funding: This work was supported by the National Natural Science Foundation of China (Grant No: 81771606), Shenzhen Science and Technology Innovation Commission (Grant No: JCYJ20170817172241688, JCYJ20180228163459314), and Clinical Medical Project 5010 of Sun Yat-sen University, China (Grant No: 2012004).

Key words: underweight; cholesterol; LGA; overweight;

Tweetable abstract

Our results showed that under the proper pre-pregnant BMI criteria in South China, the proportion of underweight women was nearly equal to that of overweight/obese women. Underweight women had significant higher TC level than those of normal-weight women and overweight/obese women. Moreover, underweight women with high TC level had significantly higher occurrence of LGA, and lower occurrence of SGA, while there were no significant associations between serum TC and LGA or SGA in normal-weight women and overweight/obese women. Therefore, we recommend pre-pregnant underweight women to control their serum lipid level properly for preventing the occurrence of LGA and other adverse maternal and fetal outcomes.

Introduction

Maternal overweight and obesity has drawn worldwide attention increasingly in recent years. The data from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of obesity in women aged 20-39 years was 31.8% in the United States[1]. Furthermore, based on the data of single term nulliparous, 48% and 24% of the pre-pregnant women were overweight or obesity in the US and Germany, respectively. In UK, about one quarter of pregnant women or women aged over 20 years were obesity according to the European Peristat Database and WHO data. However, in Asia, the proportion of obesity among women in childbearing age is not as high as those in the western countries. Such as in South Korea, less than 10% of women in reproductive age were classified as obesity with body mass index (BMI) more than 30 kg/m^2. The similar condition is found in China, especially in south China. Even though the WHO's lower definitions for Asia-specific (overweight: BMI[?]23 kg/m^2; obesity: BMI[?]25 kg/m^2) were used, only 15.8% of Hong Kong Chinese pregnant women were classified as obesity at the first visit. Although some studies reported that 10%–24% of pregnant women were overweight or obesity in China[2] the phenomena of underweight is also common with almost 11%–13% of women in China were underweight. This proportion is nearly equal to the overweight and obesity.

Increasing risks of gestational diabetes mellitus (GDM), gestational hypertension (GH), pre-eclampsia (PE) and caesarean section et al. were associated with increasing BMI in the Chinese pregnant population, which were similar to the Caucasian studies. Considering the prevalence of obesity in China is lower than those in the western countries, the risks of GDM and other complications should be decreased in Chinese pregnant women. However, the facts are on the contrary. The occurrence rate of GDM is relatively higher than those in many western countries in spite of the larger proportion of underweight and normal weight pregnant women in China. Whether the factors related to GDM and other complications in the underweight group are different from those in the overweight/obese women group need to be addressed.

Increasing evidences have been found to pronounce the positive association between dyslipidemia and adverse pregnancy outcomes such as GDM and large for gestational age (LGA). Markedly elevated triglyceride (TG) levels were found throughout the course of pregnancy in GDM, while high-density lipoprotein cholesterol (HDL-C) levels were reduced in the late course of pregnancy. In a large community-based cohort study, serum TG levels in the first trimester of pregnancy were demonstrated to positively associated with adverse maternal (gestational hypertension, GH and preeclampsia, PE) and fetal (LGA) outcomes[3]. In addition, a larger retrospective study in China showed that early pregnancy total cholesterol (TC) level was an independent risk factor for GDM, TG level was independently associated with the prevalence of GDM and PE, and low-density lipoprotein cholesterol (LDL-C) level was significantly associated with the risk of GDM and preterm birth. However, rare studies concerned about whether the associations of the maternal and fetal morbidity with lipid profiles are different in different pre-gestational BMI categories. Among pregnant women with obesity, differences in metabolic profile, including exaggerated dyslipidaemia, were evident at least 10 weeks prior to a diagnosis of GDM in the late second trimester [4]. Nevertheless, whether the relationship is specific to the underweight pregnant women has not been well investigated to date.

Therefore, a prospective cohort study was performed to evaluate the correlations between maternal lipid profiles and adverse pregnancy outcomes after grouping pregnant women by pre-pregnant BMI as underweight,

normal weight and overweight/obese women. We specifically assess the predictive value of lipid profiles on the risks of GDM, LGA and other adverse pregnancy outcomes in the underweight pregnant group.

Method

Study population

This study was part of an ongoing cohort study in which Chinese pregnant women, delivered from January 2015 to December 2016 in the First Affiliated Hospital of Sun Yat-sen University, were recruited at the time of antepartum screening for GDM. Inclusion criteria were: 1) singleton pregnancy without known chronic non-communicable diseases (except obesity); 2) attending regular prenatal care in our hospital; and 3) had integrated medical records. Women were excluded if they had any of the following conditions: multiple pregnancy, preexisting hypertension, preexisting diabetes, diseases of immune system or other diseases that may influence the lipid profile, taking drugs which affected lipid levels, i.e. glucocorticoids, before or during pregnancy and missing data on crucial items like height, pre-pregnant and pre-partum weight, lipids profile in second trimester, 75g oral glucose tolerance test (OGTT) results and pregnancy outcomes. Overall, a total of 6, 233women met the criteria and were included in the final study.

Data collection

A file including demographic and medical records was collected. Demographic data included maternal age, gravidity, parity, height, pre-pregnant weight and gestational weight gain (GWG). Besides, medical information including lipid concentrations (TC, TG, HDL-c and LDL-c) at second trimester, results of 75g OGTT, concentrations of liver enzymes (aspartate transaminase [AST], alkaline phosphatase [ALP], lactate dehydrogenase [LDH]), pregnancy complications (GDM, GH, PE), pregnancy outcomes (mode of delivery and the occurrence of postpartum hemorrhage [PPH]) and perinatal outcomes (the occurrence of LGA, SGA, and preterm birth [PTB]).

Definition

Pre-pregnant body mass index (pre-BMI) was calculated as dividing the pre-pregnant body weight (kilograms) by the square of height (meters), and classified into underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2) and overweight/obesity ([?]23 kg/m^2) based on the Asia-Pacific classification of BMI[5].

According to the diagnostic criteria, which was founded by the Chinese Medical Association in 2014, GDM was diagnosed when any serum glucose value equaled or exceeded the thresholds during OGTT:fasting blood glucose (FBG), 5.1 mmol/l; 1 hour, 10.0mmol/l; and 2 hour, 8.5mmol/l. However, FBG[?]7.0mmol/l or 2 hour result[?] 11.1mmo/l was considered as pre-gestational diabetes mellitus (PGDM), and then excluded from our study[6].

Gestational hypertension was defined as new-onset hypertension (systolic blood pressure[?]140 mmHg and/or diastolic blood pressure[?]90 mmHg) after 20 weeks of gestation in the absence of proteinuria, which returned to normal within 12 weeks after delivery[7]. PE was the progression of GH, which was defined as new-onset hypertension with albuminuria ([?] 0.3g protein of urine in 24 hours or positive detection of random urine protein) or other biochemical or haematological abnormalities.

Postpartum hemorrhage was defined by the International Federation of Gynecology and Obstetrics [8] criteria (24 hours postpartum bleeding [?] 500 ml in vaginal delivery; [?] 1000 ml in caesarean delivery).

Small for gestational age (SGA) was defined as neonatal birth weight less than the 10$^{\text{th}}$percentile for gestational age, while LGA was above the 90$^{\text{th}}$ percentile; both of them were based on the Chinese Neonatal Birth Weight Curve for Different Gestational Age[9]. PTB was defined as gestational age at delivery smaller than 37 weeks[10].

Statistical analysis

Data analyses were performed by the SPSS 20.0 (Inc., Chicago, IL, USA). Normally distributed continuous variables were expressed as means +- standard deviation (SD), non-normal distributed variables were pre-

sented as median with interquartile (IQR), and categorical variables were presented as number and percentage. Differences between groups were assessed by Mann-Whitney U test, Kruskal Wallis test or Chi-square test as appropriate. Logistic regression analysis was used to explore the risk of pregnancy complications or outcomes in underweight women adjusting the effects of gestational age. As our previous study suggested that TG/HDL-c ratio could be a good marker to predict the risks of GDM and LGA[11], we also analyzed the association between TG/HDL-c ratio and perinatal outcomes. A ROC analysis was conducted to evaluate the ability of the special factor in the model from logistic analysis for correctly discriminating the adverse perinatal outcomes. Plots of the sensitivity (true positive) versus 1-specificity (false positive) for the two models were made and the overall diagnostic accuracy between the two models was quantified using AUC. P <0.05 was considered statistically significant.

Results

A total of 6, 233 women were recruited in this study. The overall rate of underweight, normal-weight and overweight/obese women was 19.2% (1, 203/6, 233), 61.3% (3,821/6,233) and 19.4% (1,209/6,233), respectively. Among the overweight/obese women, pre-BMI range of 23 to 25 kg/m^2 was 10.6% (661/6, 233), pre-BMI range of 25 to 30 kg/m^2 was 7.3% (455/6, 233), and pre-BMI range [?] 30 kg/m^2 was 1.5% (93/6, 233). As presented in Table 1, mean age of the women grouped by the pre-BMI were 29.5+-3.94 years, 31.4+-4.3 years, and 32.6+-4.17 years, respectively ($p < 0.001$). Table 1 showed maternal lipid profiles at GDM diagnosis stratified by pre-BMI. Serum TC level of underweight women was significantly higher than overweight/obese women ($p < 0.001$). The concentration of TG in underweight women was significantly lower than those in normal-weight women and overweight/obese women ($p < 0.001$), and the concentration of HDL-c was on the contrary ($p < 0.001$). In addition, TG/HDL-c ratio of underweight women was significantly lower than normal-weight and overweight/obese women ($p < 0.001$).

Among the 6, 233 women, 1, 363 (21.9%) cases were diagnosed with GDM, and 256 (4.1%) cases were diagnosed with GH/PE as shown in Table 2. In addition, there were 507 (8.1%) cases with PTB, 305 (5.0%) cases with LGA, 642 (10.3%) cases with SGA and 432 (6.9%) cases with PPH. The occurrences of GDM and GH/PE in overweight/obese women were significantly higher than those in underweight and normal-weight women ($p < 0.001$). The occurrence of LGA in underweight women was significantly lower than those in normal-weight women and overweight/obese women ($p < 0.001$), and the odds of SGA was on the contrary ($p < 0.001$). Besides, underweight women had lower risk of PPH, compared with normal-weight women and overweight/obese women. However, there was significant difference only between the underweight group and normal-weight group ($p = 0.008$).

Odd ratios between maternal lipid profiles at GDM diagnosis and adverse pregnancy outcomes in underweight women were displayed in Table 3. After adjusting for maternal age, underweight women with high TC level had significantly higher occurrence of LGA [OR=2.24, 95%CI (1.08, 4.63)], and lower occurrence of SGA [OR=0.71, 95%CI (0.59, 0.85)], while there were no significant associations between serum TC and LGA or SGA in normal-weight women and overweight/obese women (Table 3 or Table 4). Underweight women with high TG levels had significantly higher incidence of GDM [OR=1.21, 95%CI (1.01, 1.44)] and GH/PE [OR=1.73, 95%CI (1.10, 2.74)], which were similar in normal-weight women and overweight/obese women (Table 4), but a significantly lower incidence of SGA [OR=0.79, 95%CI (0.66, 0.94)]. In addition, the increase of LDL-c [OR=0.70, 95%CI (0.59, 0.84)] and TG/HDL-c ratio [OR=0.79, 95%CI (0.66, 0.94)] had a decreased risk for SGA in underweight women, but no significant relationship was found in overweight/obese women (Table 4).

Discussion

In the present study, among the South Chinese pregnant cohort, 19.2% were pre-pregnant underweight women according to the WHO criteria for Asian populations, while 19.4% were overweight/obese women. We found that the proportion of underweight women was almost equivalent to the proportion of overweight/obese women. This finding showed that the phenomenon of underweight was actually common in South China. As was expected, a lower BMI cut-off at 25 kg/m^2 for defining obesity would be better than BMI cut-off

at 28kg/m2 for defining obesity for pregnant women in South China, which had been demonstrated in our previous study[12].

We found underweight women had significant higher TC level than normal-weight women and overweight/obese women (Table 3 or Table 4). In line with Kulkarni et al[13] , a research in Pune showed that TC concentrations went higher in rural underweight women at 18 and 28 gestational weeks. Kulkarni,et al[13] demonstrated in rural, undernourished, normoglycemic Indian pregnant women a significant association between maternal circulating lipids and fetal growth, which was at least as strong as that of glucose. During gestation, maternal lipid alters form anabolic to a catabolic state during, which causes maternal physiological hyperlipidemia(MPH) [14]. This phenomenon could be ascribed to an adaptive response to satisfy the increasing fetal demand[15, 16]. Cholesterol is essential for fetal growth, steroid synthesis and neurodevelopment, at least 1g cholesterol is essential for placenta to synthesis placenta[17]. Fetus is unable to synthesize cholesterol in the early pregnancy, since their liver and adrenal gland is immature, most of them utilize endogenously cholesterol at term. Facing such greatly demanded, increasing maternal serum TC seems like significant to satisfy fetus rapid growth. Moreover, fetus need to uptake maternal cholesterol to synthesis cell membrane [18] to maintain neurodevelopment. Abnormal cholesterol metabolism appears to related to impair neurological development[19] and low birthweight[17] or IUGR [20]. Insufficiency of LDL-C and TG may associate with FGR[21]. Besides, a thin-fat phenotype was reported in South Asia[22], which was caused by undernourished state, thin-fat women has low body mass with a high concentration of TC. This phenomenon probably indicate that cholesterol is more necessary for underweight pregnant women.

According to the study by Butte NF[15], Cholesterol is used by the placenta for steroid synthesis to meet maternal requirement. Estrogen production is 3-8 times higher at term than non-pregnancy, cholesterol as an essential material of steroid is in greatly demanded. Estrogen also strongly stimulates LDL receptor expression and improve uptaking of cholesterol, which results in maternal hypercholesterolemia[23, 24]. Thus, we presume that lipocatabolic enhance in underweight women than normal weight women and overweight/obese women to meet maternal and fetal demand.

Our results showed that underweight women with high TC level had significantly higher occurrence of LGA, and lower occurrence of SGA, while there was no significant association between serum TC and LGA or SGA in normal-weight women and overweight/obese women. Meanwhile, the increase of LDL-c and TG/HDL-c ratio decreased risk for SGA in underweight women, but no significant relationship was found in overweight/obese women. In line with Adu-Afarwuah[25], TC level, and a lipid-based nutritional supplement intake could result in increase of birth weight. A research in Pune showed that TC concentrations went higher in rural underweight women at 18 and 28 gestational weeks and positively related to the newborn birth size. Serum cholesterol concentration was directly associated with all newborn measurements except head circumference. A 1-SD-higher maternal TC concentration was associated with a 54-g-higher birth weight. According to the study by Krstevska B[26], LGA also attributed to maternal serum LDL-c. High concentrations of HDL-c seemed like a protector for LGA[27, 28]. However, this conclusion is still controversial. In the contrary, Eslamian L[29] and Wang J[28] did not find significant association of maternal LDL-C levels and LGA newborn. Our results revealed an association between high TC level and LGA in underweight women, but the potential mechanisms were unknown. We presume that cholesterol plays a more significant and complex role for underweight women in gestation, because it is essential material to maintain maternal pregnancy and fetal development. Moreover, we should pay more attention on this 'thin-fat' phenotype, since the proportion of underweight women and overweight/obese women is equivalent. Unfortunately, we had paid much more attention on the diet and weight control of overweight/obese women, while ignored the management of underweight women on their serum lipid profile. Furthermore, underweight women may tend to take more food during gestation, especially in China, and this may aggravate the hypercholesteremia of underweight women, which may lead to adverse outcomes.

In addition, our results are in line with other researchers who reported associations between serum TG levels and adverse maternal and fetal outcomes. Maternal TG was an independent predictor for GDM[30] and birth weight[31-33]. Meanwhile, the prevalence of GDM, PIH, PTL and macrosomia were higher in pregnant women

with high TG level[34]. Thus, the results above remind us the necessity to control serum lipid level.

The main strengthen of our study was that we used a more proper criteria to stratify the underweight women in South of China, and investigate the lipid level and corresponding maternal and fetus outcome. This makes our results more reliable. Additionally, we focus the relationship of underweight women and cholesterol level, which has not been well investigated before. Few researchers explored and interpreted the relationship among underweight women, high level cholesterol and newborn size. At last our study has a huge sample size about 6,000 which seemed like to have compelling results. Thus, this study can contribute new insights into controlling of underweight women serum lipid counseling.

There were some limitations in our study. The height and weight of gravidas were recalled and self-reported by patients, and so it was likely there were more error variation and potential bias than measured. The second limitation was that diet before the blood drawing may affect the serum lipid profile. The amount and composition of dietary fat seem to be associated with serum concentrations of lipids[35, 36]. In consideration of this, we had given them proper diet guidance before their blood tests.

Conclusion

Our results showed that under the proper pre-pregnant BMI criteria in South China, the proportion of underweight women was nearly equal to that of overweight/obese women. Underweight women had significant higher TC level than those of normal-weight women and overweight/obese women. Moreover, underweight women with high TC level had significantly higher occurrence of LGA, and lower occurrence of SGA, while there were no significant associations between serum TC and LGA or SGA in normal-weight women and overweight/obese women. The higher TC level in underweight women could be an adaptive response to satisfy the maternal and increasing fetal demand, and we presume cholesterol may be a more significant material for maintaining pregnancy and fetal development. Moreover, considering the association between serum lipid levels of underweight women and neonate birth weight, we recommend pre-pregnant underweight women to control their serum lipid level properly for preventing the occurrence of LGA and other adverse maternal and fetal outcomes.

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