Research Article

Dyslipidemia in Pregnancy and the Proper Reference Values: A Retrospective Study in South China

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Abstract

Background: Dyslipidemia during pregnancy is associatied with the risk of adverse pregnancy outcomes. However, there is no uniform diagnostic criteria. "Williams Obstetrics 24th Edition" (WO24) and Wang et al gave different lipid references based on ethnic groups. To address the proper reference values of pregnant lipid, we conducted this retrospective study in pregnant women in South China.

Methods: 642 pregnant women were calculated the normal lipid range by 95th percentile and analyzed the association between lipid levels and adverse pregnancy outcomes by logistic regression models. Prevalence of adverse pregnancy outcomes in dyslipidemia patients diagnosed by the three different references were compared by Pearson's chi-squared (χ^2) test.

Results: The prevalence of dyslipidemia were 15.26% by the references of our research, 11.53% by WO24, and 17.45% by Wang, respectively. TC level was the risk factor of preterm birth (PTB); and TG level was associated with the risk of gestational diabetes mellitus (GDM) and PTB. The odds radio (OR) for GDM in patients with abnormal TG levels were 4.28[1.28-14.28] by WO24's, 3.06[1.43-6.57] by ours, and 2.62[1.13-6.11] by Wang's. The OR for PTB in patients with abnormal TG levels were 4.22[1.21-14.69] by WO24's,

3.04[1.22-7.62] by Wang's, and 2.31 [0.95-5.63] by ours. A increased risk of macrosomia was only seen in patients with abnormal TC level by Wang's reference (OR 3.67 [1.12-12.06]).

Conclusions: Dyslipidemia during pregnancy is associated with the increases of pregnant complications. The reference by Wang et al were more applicable in Southern China.

Keywords: Dyslipidemia; Pregnancy; Complication; Reference Range

Abbreviations: WO24: Williams Obstetrics 24th Edition; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipid Cholesterol; LDL-C: Low-Density Lipid Cholesterol; p-BMI: Pre-Pregnancy Body Mass Index; GDM: Gestational Diabetes Mellitus; PIH: Pregnancy-Induced Hypertension; PE: Preeclampsia; PTB: Preterm Birth

1. Introduction

The levels of serum lipids physiologically raise throughout pregnancy due to unique physiological state and necessary metabolism functional adjustments [1-3]. The significant changes of lipid concentration can be observed from the second trimester of pregnancy [4]. However, evidences suggested that the increased maternal lipid levels are associated with adverse pregnancy outcomes, including gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preterm birth (PTB), preeclampsia (PE), and macrosomia [5-9]. In addition, dyslipidemia during pregnancy may lead to postpartum dyslipidemia and postpartum impaired glucose tolerance in mothers [10-14] and metabolic disorders in offsprings [15].

However, there is no consensus about normal maternal lipid values during pregnancy. One of the most used

reference criteria for lipids during pregnancy was from "Williams Obstetrics 24th Edition" (WO24) [16]. These reference values were calculated according to the 2.5th or 5th percentiles of lipid values from pregnant women mainly from Porto (Portugal), Graz (Austria) and Warsaw (Poland) studies. Recently, a study by Wang et al [17] propose a lipids reference for Northern Chinese pregnant women by calculated the 5th percentiles. The baseline characteristics were mostly similar for dyslipidemia people diagnosed by those two references, including maternal age, p-BMI, family history of diabetes and hypertension. However, it has been shown that the normal blood lipid ranges are different between Western and Eastern populations [18]. Therefore, the reference ranges of blood lipids during pregnancy might also vary from ethnic and regional groups. In this study, we analyzed the lipid profile in the Southern Chinese pregnant women of middle stage. The reference values of pregnant lipid were calculated by the 5th percentiles. And the pregnant complications were compared among the cohorts by three different diagnostic references, for the purpose to address the proper reference values of pregnant lipid in Southern Chinese women.

2. Methods

2.1 Data sources

This retrospective study was performed at one of the largest regional university hospitals in South China (The First Affiliated Hospital of Sun Yat-sen University). A total of 860 pregnant women who delivered at our institution between January 2018 and April 2018 were recruited. Approval was obtained from Institutional Review Board. Informed consent was waived because this study was retrospective. Women were excluded if they met the following conditions: (1) diagnosed of diabetes or hypertension before pregnancy; (2) patients with hypothyroidism or hyperthyroidism; (3) patients with chronic kidney disease or hepatic dysfunction damage; (4) multiple pregnancy; (5) missing data of blood lipids

in the second trimester. Overall, 642 cases were included in the final analysis.

2.2 Data collection

Since lipid levels raise significantly from 12th week of pregnancy and both of those two researches had recommended reference of dyslipidemia in second trimester, we compared the reference in the second trimester of pregnancy. The following data were collected from medical records: maternal age, pre-pregnancy body mass index (p-BMI), family history of diabetes and family history of hypertension, and results of pregnancy lipids, pregnancy complications including GDM, PIH, PE, PTB, and macrosomia. In "Williams Obstetrics 24th Edition" [16], the recommended reference unit for blood lipids was mg/dL. We converted the unit to mmol/l according to the conversion factors described in the instructions of the blood fat detection kit provided by Roche Diagnostics GmbH.

2.3 Measures

All blood samples were measured in the laboratory of the Department of Biochemistry of the First Affiliated Hospital of Sun Yat-sen University. Lipid levels were measured with standard enzymatic procedures on an automatic chemistry analyzer (Abbott Aeroset, Chicago, IL, USA). Reference values of the lipids were calculated with 95% confidence interval (CI). Abnormal TC, TG and LDL-c level were diagnosed with the value above the 95% percentiles, and abnormal HDL-c level was diagnosed with the value below the 5% percentiles.

2.4 Definitions of adverse pregnancy outcomes

The diagnosis of GDM was based on the International Association of Diabetes and Pregnancy Study Groups criteria [19], in which any of the three items following 75-g OGTT were reached: FPG levels > 5.1 mmol/L and < 7.0 mmol/L, 1 h PG levels ≥10.0 mmol/L, and 2 h

PG levels ≥8.5 mmol/L and < 11.1 mmol/L. Pregnancy induced hypertension (PIH) included both gestational hypertension and PE. Gestational hypertension was defined as blood pressure elevation (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) at > 20 weeks' gestation in the absence of proteinuria [20]. PE was defined as new-onset hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and new-onset proteinuria (300 mg of protein in 24 h or a urine protein/creatinine ratio of 0.3 mg/dl) after 20 weeks of gestation, in a previously normotensive woman [20]. PTB was defined as gestational age of less than 37 weeks at delivery. Macrosomia was diagnosed when foetal birth weight ≥ 4000 g, regardless of gestational age.

2.5 Statistical analysis

Data analysis was performed by SPSS version 24.0. Continuous data were expressed as means ± standard deviation. Data between groups were compared using Student's t-test for continuous variables. Categorical data, presented as a frequency were compared with Pearson's chi-squared (χ^2) test or Fisher's exact test. Multivariate analysis was performed by logistic regression analysis. All statistical tests were two-sided, and P value <0.05 was considered to demonstrate statistical significance.

3. Results

3.1 Basic characteristics

Data of a total of 642 pregnant women of the mid-trimester were collected. The mean age were 32.70 ± 0.18 years. 6.54% of these women had a family history of diabetes and 10.44% had a family history of hypertension. The average lipid levels were presented in Table 1. The prevalence of dyslipidemia were 11.53% by WO24 reference value and 17.45% by Wang's reference value (P<0.001). There was a trend of

increase of TC, TG and LDL-c levels as the pregnant week increase, while the levels of HDL-c remanded stable during the whole pregnancy. The TC and LDL-c levels raised significantly between 16 to 20 weeks and maintained a smooth stage thereafter. However, the TG levels have shown continuous increase in the whole stages (as shown in Figure 1).

3.2 Referent range and risks of adverse pregnancy outcomes

The referent range of the lipids of our cohort were shown in table 2. The prevalence of dyslipidemia was 15.26% by the references of our research. After adjusted by maternal age, p-BMI, and gestational age at the time of lipid measurement, The relation between the lipid levels in second trimesters and the risk of pregnant complications were analyzed by logistic regression analysis. It was observed that increase of TC concentration was associated with increased risk for PTB (odd ratios [OR]: 1.150), increase of TG concentration was associated with increased risk for GDM (OR: 1.494) and PTB (OR: 1.415), and increase of HDL-C concentration was a protective factor for PIH (OR: 0.124) and PE (OR: 0.086). However, when we turned HDL-c concentration into a categorical variable, the protective effect was diminished. The level of LDL-c showed no statistic association with GDM, PIH, PE, PTB, and macrosomia (Table 2).

3.3 The adverse pregnant outcomes of dyslipidemia

The reference values of abnormal lipid levels were presented in table 3 according to the 95th percentiles of the distributions. There was no significant differences in the prevalences of any kind adverse pregnant outcomes of abnormal lipid levels diagnosed by the three reference values. The prevalence of PTB among women with abnormal level of TC were 17.65% by ours, 15.79% by WO24's, and 14.75% by Wang's, respectively (table 4). The prevalence of GDM and PTB were more closer with abnormal level of TG diagnosed by our research (39.39% , 21.21%) and Wang's (37.04%, 25.93%). And the prevalence of PIH and PE were also more closer with abnormal level of HDL-c diagnosed by our research (8.82%, 2.94%) and Wang's (8.82% , 2.94%).

According to the results of logistic regression analysis (table 4), the occurrence of PTB showed no correlation with the abnormal TC level from our research (*P*>0.05), neither WO24 and Wang et al. The risk of GDM increased in women with abnormal TG levels diagnosed by the three references, while the odds ratio in our research (3.06 [1.43-6.57]) were more closer to Wang et al (2.62 [1.13-6.11]) than WO24 (4.28 [1.28-14.28]). The odds radio for PTB raised significantly in those with abnormal TG level by Wang et al (3.04 [1.22-7.62]) and WO24 (4.22 [1.21-14.69]), and there was a trend of raised risk of PTB in abnormal TG level by our research (2.31 [0.95-5.63]). No significant differences in the risks of PIH and PE were observed in people with or without abnormal levels of HDL-c.

Characteristics	Mean ± SD
Maternal age (year)	32.70 ± 0.18
p-BMI (kg/m^2)	21.07 ± 0.11
TC (mmol/L)	6.09 ± 0.04
TG (mmol/L)	2.12 ± 0.03
HDL-c (mmol/L)	1.94 ± 0.14

LDL-c(mmol/L)	3.48 ± 0.03

Abbreviations: p-BMI, pre-pregnancy body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipid cholesterol; LDL-C, low-density lipid cholesterol

Table 1: Basic characteristics of pregnant women.
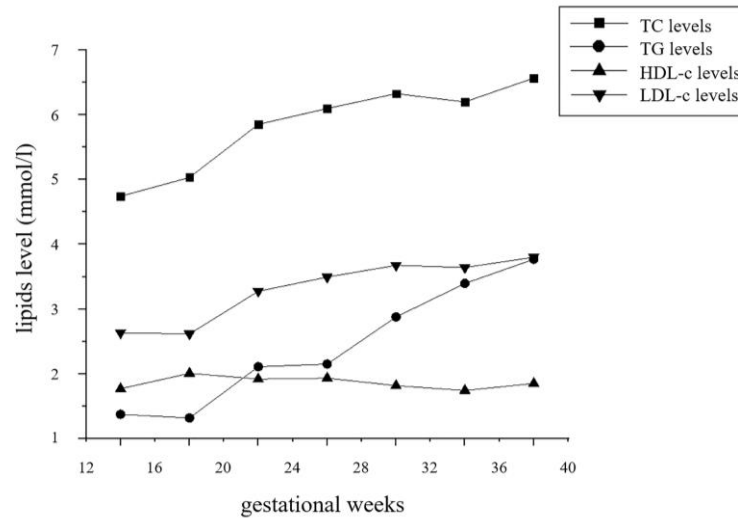
TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipid cholesterol; LDL-C, low-density lipid cholesterol

Figure 1: The changing curve of lipids level during pregnancy.

	95% CI	Adverse pregnancy outcomes									
		GDM		PIH		PE		PTB		Macrosomia	
		OR (95% CI)	P values	OR (95% CI)	P values	OR (95% CI)	P values	OR (95% CI)	P values	OR (95% CI)	P values
TC	4.40-7.90	0.981 (0.794-1.213)	0.861	0.940 (0.622-1.420)	0.769	0.937 (0.555-1.583)	0.808	1.150 (1.000-1.477)	0.050	1.403 (0.885-2.224)	0.150
TG	1.19-3.51	1.494 (1.164-1.919)	0.002	1.243 (0.846-1.827)	0.268	1.340 (0.861-2.087)	0.195	1.415 (1.083-1.848)	0.011	1.075 (0.629-1.837)	0.792
HDL-c	1.38-2.54	0.727 (0.381-1.388)	0.334	0.124 (0.031-0.504)	0.004	0.086 (0.014-0.535)	0.009	0.485 (0.220-1.070)	0.073	3.291 (0.755-14.344)	0.013
LDL-c	2.34-4.78	0.983 (0.728-1.326)	0.909	1.135 (0.643-2.001)	0.661	1.251 (0.615-2.545)	0.536	1.410 (0.998-1.991)	0.051	1.415 (0.734-2.727)	0.300

Adjusted for maternal age, pre-pregnancy body mass index, and gestational age at the time of lipid measurement. OR (95% CI) and *P* values were calculated by logistics regression analysis. TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipid cholesterol; LDL-C, low-density lipid cholesterol; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PE, preeclampsia; PTB, Preterm birth

Table 2: Referent ranges and risk of adverse pregnancy outcomes.

	TC (mmo/l)	**TG (mmo/l)**	**HDL-c (mmo/l)**	**LDL-c (mmo/l)**
WO24[1]	< 7.74	<4.32	>1.35	<4.77
Wang et al.[2]	<7.50	<3.56	>1.41	<4.83
Our research[3]	< 7.90	<3.51	>1.38	<4.78

[1]WO24: reference from "Williams Obstetrics 24th Edition"

[2]Wang et al.: reference from Wang et al.

[3]Our research: 95th percentage from our population

TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipid cholesterol; LDL-C, low-density lipid cholesterol

Table 3: Reference values for lipids level in middle pregnancy.

Serum Lipid		TC	TG		HDL-c	
Adverse pregnancy outcomes		PTB	GDM	PTB	PIH	PE
Our research[1]	prevalence	17.65%	39.39%	21.21%	8.82%	2.94%
	OR (95% CI)	2.14 (0.84-5.44)	3.06 (1.43-6.57)	2.31 (0.95-5.63)	2.25 (0.62-8.22)	1.10 (0.13-8.93)
	P values[a]	0.052	0.004	0.066	0.219	0.926
WO24[2]	prevalence	15.79%	50.00%	33.33%	4.35%	NC[#]
	P values[b]	0.833	0.524	0.448	0.641	1.000
	OR (95% CI)	1.79 (0.71-4.50)	4.28 (1.28-14.28)	4.22 (1.21-14.69)	0.95 (0.12-7.54)	NC[#]
	P values[a]	0.166	0.025	0.034	0.193	NC[#]
Wang[3]	prevalence	14.75%	37.04%	25.93%	8.82%	2.94%
	P values[b]	0.711	0.852	0.668	1.000	1.000
	OR (95% CI)	1.66 (0.77-3.57)	2.62 (1.13-6.11)	3.04 (1.22-7.62)	2.06 (0.56-7.50)	1.03 (0.13-8.36)
	P values[a]	0.198	0.025	0.018	0.275	0.975

[a] *P* values of OR (95% CI). OR (95% CI) and *P* values[a] were calculated by logistics regression analysis

[b]Compare with our research, calculated by Fisher exact test

[#] No case observed

[1] 95th percentage from our population

[2] reference from "Williams Obstetrics 24th Edition"

[3] reference from Wang et al.

TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipid cholesterol; LDL-C, low-density lipid cholesterol; PTB,

Preterm birth; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PE, preeclampsia

Table 4: Prevalences and risk of adverse pregnancy outcomes in people with abnormal lipids levels.

4. Discussion

It has been demonstrated that lipid levels raised significantly during middle pregnancy and abnormally elevated lipid levels were associated with adverse pregnant outcomes [6-7]. However, the recommended normal range of serum lipid level during pregnancy is still controversial. In the current study, we for the first time evaluated the different reference values of lipid levels in the second trimester pregnancy among southern Chinese women. Our study found that there were no significant differences between the reference values of lipid levels at mid-trimester pregnancy by WO24 and by Wang et al. However, the prevalence of dyslipidemia was significantly higher by Wang et al (17.45%) than that by WO24 (11.53%, vs Wang's $P<0.001$). Our data has confirmed that abnormally elevated lipid levels were associated with increases of adverse pregnant outcomes. After adjusted by maternal age, p-BMI, and gestational age at the time of lipid measurement, TC levels was associated with an increased risk of PTB, and TG levels was associated with an increased risk of GDM and PTB.

There were no significant differences of prevalence or ORs of the abnormal pregnant outcomes were observed among the dyslipidemia pregnant women diagnosed with the three different reference values. Risk of GDM raised in women with abnormal level of TG by the three references, and risk of PTB raised in women with abnormal level of TG by WO24 and Wang et al., while risk of macrosomia was only raised in women with abnormal level of TC by Wang et al. There were no significant differences in the prevalence of GDM, PTB, PIH, PE, and macrosomia in women with abnormal levels of TC, TG, HDL-c and LDL-c

diagnosed by the references of our research, WO24's, and Wang's. However, the prevalence and the ORs of adverse pregnancy outcomes were more closer in dyslipidemia people diagnosed by our research and Wang et al than that by WO24 (Table 4). Considering that Caucasians were the main objects of WO24 study and it has been indicated that lipid levels were different between Asian pregnant women and European pregnant women [4], the differences of culture and ethnicity might account for the above differences.

This study found that every 1 mmol/l elevation in HDL-c concentration in second trimester was associated with a significant decreased risk of PIH and PE. However, when we turned HDL-c concentration into a categorical variable, the protective effect was diminished. Together with that there was no significant changes of HDL-c levels during the whole pregnancy, we consider the levels of HDL-c play a limited role in the adverse pregnant outcomes. Same is the LDL-c level as we found no statistic association between LDL-c level and any kind of adverse pregnant outcomes. TG was the lipid with the most obvious increase during pregnancy and was significantly associated with both the increase of GDM and PIH. TC levels raised significantly at 16 to 20 pregnant weeks and stabled in the following stages. It is also associated with increased risk of PIH. Taken together, attentions should be paied on the abnormally increases in the TG and TC levels during the second trimester of pregnancy, as it may be a mark of metabolic syndrome developed in pregnant mother that relates to the long term postpartum metabolic disorders in both mother and offsprings.

Our study showed that both WO24 and Wang's study

provided applicable serum lipid reference values to the pregnant women in Southern China. The reference by Wang et al may be more applicable as the prevalence of dyslipidemia and the ORs of adverse outcomes were more similar with ours. Abnormally increased TG and TC levels at mid-stage of pregnacy play important role in the adverse pregnant outcome and may be associated with long term postpartum metabolic statements. There were several limitations in our study. First, the limited sample size of our study might weaken its power of presentative of women in Southern China. Second, the risk of selection bias is unavoidable in observational study. Therefore, further prospective multicenter randomized controlled investigations for lipid reference during the whole pregnancy are needed.

5. Conclusion

In conclusion, this study showed that dyslipidemia during pregnance is associated with the increases of pregnant complications. Futhermore, both the pregnant serum lipid references of WO24 and Wang's study are applicable to pregnant women in Southern China. However, the reference by Wang et al provided a trend of more applicable. This finding provides evidence for lipids screening during pregnancy.

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