Postpartum dyslipidemia and the potential predictors in women with history of gestational diabetes mellitus

Ling Pei  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology  
Huangmeng Xiao  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology  
Fenghua Lai  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology  
Zeting Li  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology  
Zhuyu Li  
Sun Yat-sen University First Affiliated Hospital Department of obstetrics and gynecology  
Shufan Yue  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology  
Haitian Chen  
Sun Yat-sen University First Affiliated Hospital Department of obstetrics and gynecology  
Yanbin Li  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology  
Xiaopei Cao  
Sun Yat-sen University First Affiliated Hospital Department of Endocrinology

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Abstract

**Aims/Introduction:** To analyze the incidence of early postpartum dyslipidemia and the potential predictors among women with history of gestational diabetes mellitus (GDM).

**Materials and Methods:** This was a retrospective study. 589 women diagnosed with GDM were recruited and followed up at 6-12 weeks after delivery. The general demographic and metabolic data during pregnancy were collected. Participants were divided into the normal lipid group and dyslipidemia group according to the postpartum lipid level. Demographic and metabolic parameters were compared. Multivariate logistic regression was performed to analyze the potential predictors for the early postpartum dyslipidemia. Receiver operating characteristic (ROC) curve was conducted to determine the cut-off values.

**Results:** 38.5% of the 589 women developed dyslipidemia in early postpartum and 60% of them had normal glucose metabolism. Delivery age, systolic blood pressure (SBP), glycated hemoglobin (HbA1c) and low-density lipoprotein cholesterol (LDL-C) were independent predictors of early postpartum dyslipidemia in women with history of GDM. The cut-offs of maternal age, SBP, HbA1c and LDL-C were 35 years, 5.1% and 3.56 mmol/L, respectively. LDL-C achieved a balanced mix of high sensitivity (63.9%) and specificity (69.2%) with highest area under the receiver operating characteristic curve (AUC) (0.696). When LDL-C was combined with age, SBP and HbA1c, the AUC reached to 0.733.

**Conclusions:** Women with history of GDM should be screened lipid metabolism after delivery, particularly those with maternal age >35 years, SBP>123mmHg before labor, HbA1c>5.1%, or LDL-C>3.56mmol/L in the second trimester of pregnancy.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in nowadays. It accounted for up to 40% of all deaths in both urban and rural population in China\footnote{1}. It has been reported that there was a stagnation trend of cardiovascular mortality rates in young adults, especially in women even though the overall cardiovascular mortality were marked decreased over the past decades \footnote{2}. Therefore, the recommendation for the screen of CVD risk was to be started at age of 20 year, and revisited every 4–6 years for the purpose to prevent cardiovascular events \footnote{3, 4}.

Gestational diabetes mellitus (GDM) is a common pregnant complication that is strongly associated with adverse maternal and offspring events. Currently, the total incidence of GDM in mainland China was 14.8\%-17.6\% \footnote{5, 6}. Women with history of GDM have much higher risk of postpartum diabetes \footnote{7, 8} as well as other CVD-related risk factors, including dyslipidemia \footnote{9-12} and metabolic syndrome \footnote{13}. As a result, the incidence of CVD among women with history of GDM was 2-3fold increased than those without GDM \footnote{14-17}. Dyslipidemia is a key independent modifiable risk factor of atherosclerosis. It has showed that the prevalence of postpartum dyslipidemia in GDM women was 52 % \footnote{10} and women with GDM had a 1.4-1.8-fold risk for dyslipidemia, compared with their peers \footnote{11}, indicating that postpartum dyslipidemia was also a serious health problem in women with GDM. Professional guidelines recommend all GDM women to
screen glucose metabolism 4-12 weeks after delivery while the risk of postpartum dyslipidemia has not been put on the agenda [18]. Up to date, studies relative to the risk of postpartum dyslipidemia are few. And the potential predictors were seldomly reported. Thus, the aim of this study was to explore the potential risk factors during pregnancy affecting abnormal postpartum lipid metabolism from a retrospective study.

**Materials And Methods**

**Participants**

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committees for clinical research and animal trials of the First Affiliated Hospital, Sun Yat-sen University (ethical approval number: [2017] 124 and [2020] 048).

Women who diagnosed with GDM according to the 75g 2-h oral glucose tolerance test (OGTT) performed between 24-28 weeks during pregnancy were recruited. All of them have received intensive life style intervention and insulin were used for those who were failed in life style intervention. Participants were followed up at 6-12 weeks after delivery. Inclusion criteria were: (1) age 18-45 years old, (2) diagnosed GDM with a 75g 2-h oral glucose tolerance test (OGTT) during 24-28 pregnant week; (3) at lease one plasma lipids were measured at the second or third trimester; (4) received a 75g 2-h OGTT and plasma lipids measurements between 6-12 weeks after delivery. Exclusion criteria were: (1) patients diagnosed with overt diabetes during pregnancy; (2) patients suffered from subclinical or overt hyperthyroidism/hyptothyroidism; (3) patients complicated by chronic liver and kidney diseases.

**Data Collection**

The demographic characteristics, basic anthropometry, glucose and lipid levels during pregnancy and after delivery were recorded, including gestational age, past medical history, the history of family diabetes, prepregnancy weight, weight gain during pregnancy, systolic blood pressure (SBP)/diastolic blood pressure (DBP) before labor, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) /1hour plasma glucose (1h PG) / 2hour plasma glucose (2h PG) of a 75 g glucose tolerance test (OGTT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

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**Definition of GDM and Dyslipidemia**
The diagnosis of GDM was based on the IADPSG criteria\cite{19}: any of the three following 75 g OGTT results were reached: 5.1 mmol/L ≤ FPG < 7.0 mmol/L, 1 h plasma glucose (1h PG) ≥ 10.0 mmol/L, and 8.5 mmol/L ≤ 2 h plasma glucose (2 h PG) < 11.1 mmol/L.

Postpartum dyslipidemia was defined according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report (NCEP-ATP III)\cite{20}: TC ≥ 6.22 mmol/L; TG ≥ 2.26 mmol/L; LDL-C ≥ 4.14 mmol/L and HDL-C ≤ 1.04 mmol/L.

WHO 1999 criteria\cite{21} were used to assess postpartum glucose metabolism of subjects, diabetes was diagnosed when FBG ≥ 7.0 mmol/l or 2hPG ≥ 11.1 mmol/l or random venous blood glucose ≥ 11.1 mmol/L. Subjects without typical symptoms of diabetes were tested again on the following day; impaired fasting glucose(IFG) was diagnosed as 6.1 mmol/L ≤ FPG < 7.0 mmol/L, and 2 h PG < 7.8 mmol/L; impaired glucose tolerance (IGT) was defined as FPG < 6.1 mmol/L and 7.8 mmol/L ≤ 2h PG < 11.1 mmol/L.

Statistical analysis

Statistical analysis was carried out using SPSS 22.0 software (IBM, Armonk, NY, USA). Continuous data were summarized as either mean ± standard deviation or median and inter-quartile range (IQR), and categorical data were expressed as percentages. Data were compared by unpaired t-test or Mann–Whitney U tests where appropriate. Categorical variables were compared using the Chi-square test. Logistic regression models were used to assess the potential predictors and receiver operating characteristic (ROC) curve was performed to determine the cut-off values of postpartum dyslipidemia in GDM women. We assessed the overall predictability of the predictors using the receiver operating characteristic area under the curve (AUC). P<0.05 was considered statistically significant.

Results

A total of 589 GDM pregnant women were enrolled and finished the postpartum visit in this study. 227 of those 589 women (38.5%) were diagnosed with dyslipidemia and 209 (35.5%,32.4% in prediabetes and 3.1% in diabetes) were diagnosed with abnormal glucose tolerance at 6–12 weeks after delivery. 23.1% of participants had dyslipidemia with normal glucose tolerance which accounted for up to 60% (23.1%/38.5%) of dyslipidemia. 15.49% (13.6% in prediabetes and 1.89% in diabetes) of participants had both postpartum glucose intolerance and dyslipidemia (Fig 1a). Of which 195 (33.1%) abnormal TC, 33 (5.6%) abnormal TG, 15 (2.5%) abnormal HDL-C and 127 (21.6%) abnormal LDL-C. 42.3% of them presented with only one type of dyslipidemia (Fig 1b). Compared to women with normal postpartum lipids, women with dyslipidemia had older delivery age, higher pregnant SBP, HbA1c, 1 h PG, TC, TG, LDL-C, and TG/HDL-C ratio, higher postpartum glucose levels and higher incidence of postpartum glucose intolerance (table 1).

Logistic regression analysis has shown that age, pregnant SBP, 1h PG, HbA1C, lipid profiles (TC, TG, HDL-C, LDL-C) and TG/HDL-C ratio were significantly associated with postpartum lipid outcome. The ORs for
them was 1.047-2.551, respectively. Multivariate logistic regression analysis further showed age (OR = 1.06, 95% CI: 1.014-1.109, P = 0.11), SBP (OR = 1.022, 95% CI: 1.006-1.038, P = 0.006), HbA1c (OR = 1.897, 95% CI: 1.119-3.215, P = 0.017) and LDL-C (OR = 3.671, 95% CI: 1.386-9.724, P = 0.009) were independent predictors of abnormal postpartum lipid metabolism. Receiver operating characteristic (ROC) curves were used to determine overall to predict dyslipidemia. Sensitivity in the prediction of incident dyslipidemia of each predictor varied from 47.1% (age) to 63.9% (LDL-C), with specificity decreasing from 69.6% (SBP) to 57.4% (HbA1C) across these categories. The cut-offs of age, SBP, HbA1c and LDL-C were 35 years, 123mmHg, 5.1% and 3.56 mmol/L respectively. AUC was 0.56-0.696 (Table 2).

Table 2: Logistic analysis of the factors during pregnancy associated with postpartum abnormal lipid metabolism

|                  | OR     | 95%CI      | P value | sensitivity | specificity | AUC     | Cut-off     |
|------------------|--------|------------|---------|-------------|-------------|---------|-------------|
| age              | Univariate | 1.047     | 1.007-1.088 | 0.02   | 51.4     | 58      | 0.56       | 35 years   |
|                  | Multivariable | 1.06     | 1.014-1.109 | 0.011 |          |         |            |            |
| SBP              | Univariate | 1.023     | 1.008-1.038 | 0.02   | 47.1     | 69.6    | 0.593      | 123mmHg    |
|                  | Multivariable | 1.022     | 1.006-1.038 | 0.006 |          |         |            |            |
| 1h PG, HbA1c     | Univariate | 1.172     | 1.03-1.333 | 0.016 | -        | -       | -          | -          |
|                  | Multivariable | 1.897     | 1.119-3.215 | 0.017 |          |         |            |            |
| TC               | Univariate | 1.949     | 1.629-2.331 | 0.00   | -        | -       | -          | -          |
| TG               | Univariate | 1.566     | 1.272-1.928 | 0.00   | -        | -       | -          | -          |
| HDL-C            | Univariate | 1.716     | 1.11-2.654 | 0.015 | -        | -       | -          | -          |
| LDL-C            | Univariate | 2.551     | 1.969-3.304 | 0.00   | 63.9     | 69.2    | 0.696      | 3.56mmol/l |
|                  | Multivariable | 3.671     | 1.386-9.724 | 0.009 |          |         |            |            |
| TG / HDL-C ratio | Univariate | 1.4       | 1.085-1.087 | 0.01   | -        | -       | -          | -          |
Univariate = Univariate logistic regression analysis; Multivariable = Multivariate logistic analysis; OR = odds ratio; CI = confidence interval; SBP = Systolic blood pressure; TC = total cholesterol; TG = triglycerides. LDL-C = low-density lipoprotein cholesterol; 1h PG = 1h plasma glucose.

In general, LDL-C achieved a balanced mix of high sensitivity and specificity with highest area under the receiver operating characteristic curve (AUC) (0.696). To improve the overall predictability, the AUC was up to 0.733 when combined all the independent predictors (figure 2).

Discussion

We for the first time analyzed the prevalence of early postpartum dyslipidemia among Chinese GDM women. Our data showed that 38.5% women aged 18–45 years who has history of GDM developed dyslipidemia at 6–12 weeks postpartum and about 40% of them presented with only one type of dyslipidemia. Age, SBP before labor, HbA1c and LDL-C level at gestational 24–28 weeks were significant independent predictors of the early postpartum dyslipidemia. Among them, the cut-offs were 35 years, 123 mmHg, 5.1% and 3.56 mmol/L, respectively. The overall predictability (AUC) of LDL-C was 0.696. When LDL-C was combined with age, SBP and HbA1c, the AUC reached to 0.733. The present findings indicated that lipids levels during pregnancy were associated with increased risk of dyslipidemia after delivery which was consistent with two other studies that also presented the relationship between hypertriglyceridemia in pregnancy and 6 to 12 months postpartum [22,23].

In this study, the incidence of early postpartum dyslipidemia and hyperglycemia were 38.5% and 35.5%, respectively. The proportion of the different types of dyslipidemia in our study was similar to another multi-ethnic study, which presented the overall postpartum dyslipidemia prevalence of 52% at 6 weeks postpartum [10]. Moreover, there were 23.1% of participants with dyslipidemia but normal postpartum glucose tolerance, suggesting about one of the four women with history GDM were mistakenly considered as “normal” if only the postpartum glucose metabolism were screened. Further, nearly one of the six women has both postpartum abnormal glucose tolerance and abnormal lipid profile, indicating a startling risk of CVD among those young mothers. Previous studies have shown that full adherence to the ATP III Primary Prevention Guidelines would prevent 20,000 myocardial infarctions and 10,000 deaths from coronary heart disease per year in adults [24]. And 1 mmol/L reduction of LDL-C could prevent 11 per 1000 major vascular events over 5 years for individuals with 5-year risk of major vascular events lower than 10% [25]. It was important to note that more preventive efforts need to be taken for young patients with multiple risk factors for CVD, who would benefit most from early cardioprotective interventions [26]. Accordingly, screening and management of dyslipidemia among those young mothers with history of GDM at early postpartum could also be beneficial lots for them to prevent long-term cardiovascular disease.

However, GDM women had poor compliance with postpartum evaluation and the rates of postpartum review were low [27,28]. Therefore, we explored predictors during pregnancy to dyslipidemia in early postpartum women for the purpose to raise the awareness management of early postpartum dyslipidemia. In line with previous studies [29,30], our data showed age and SBP were the independent risk factor for
postpartum dyslipidemia. Age may be a predisposing factor for dyslipidemia due to TC–TG and other lipoprotein levels increased with ageing\cite{31,32}. Remarkably, ageing was associated with insulin resistance and reduced pancreatic beta-cell reserve, which appeared to cause exacerbated adipose tissue lipolysis\cite{33}. Hypertensive disorders of pregnancy (HDP) was also a recognized risk on adverse lipid profile after pregnancy\cite{29}, as a result, guidelines recommended that lipid screening for all women with HDP history\cite{34}. Moreover, our findings also indicated HbA1c and LDL-C at gestational 24–28 weeks were the independent risk factor and LDL-C was the most important predictor. Patients with LDL-C $>3.56$ mmol/L with relatively balanced sensitivity (63.9%) and specificity (69.2%), coupled with best AUC (0.696). The observed associations are plausible, although precise mechanisms remain to be elucidated.

Management of glucose and lipid during pregnancy may provide a chance to reduce the development dyslipidemia postpartum. The ORs for age, SBP, HbA1c and LDL-C were 1.06, 1.022, 1.897 and 3.671, respectively. So LDL-C levels during pregnancy have the most relevant to the onset of dyslipidemia after delivery, followed by HbA1c. Plasma LDL-C can be measured directly or calculated using the Friedewald formula: LDL-C = TC - HDL-C - (TG/2.2) in mmol/L, and the outcome were same in the absence of high TG\cite{35}. LDL-C induced apoptosis and decreased both proliferation and maximal glucose-stimulated insulin secretion in murine and human β-cells\cite{36}. In addition, a multiple stepwise regression analysis also revealed LDL-C and HbA1c were independent risk factors for the development of insulin resistance after delivery in Chinese women with history of GDM\cite{37}. Hence, optimal levels of glucose and lipid during pregnancy were attribution to reduce insulin resistance and improved pancreatic β-cell function, so as to decrease postpartum dyslipidemia. More data were needed to further verify our hypothesis in future.

The present study has a few limitations. First, our results were based on a fairly short follow-up period and all participants were from a single center. Second, as a retrospective study may result in selective bias and incomplete clinical data. Last, some characteristics of the subjects were missed, such as breastfeeding, diet and physical activity, which maybe affect glucolipid metabolism during pregnancy and postpartum. Therefore, it is necessary that a long-term follow-up and larger-scale validation study from multicenter to be performed in future.

In summary, our research highlighted a high prevalence of dyslipidemia among women with history of GDM in the early postpartum period and indicated that postpartum lipid screening might be warranted, particularly those with maternal age $>35$ years, SBP $>123$mmHg before labor, HbA1c $>5.1\%$ or LDL-C $>3.56$ mmol/L in the second trimester of pregnancy. Simultaneously, optimal management of glucose, lipid and blood pressure during pregnancy may be beneficial to the postpartum metabolism in GDM women.

Declarations

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All authors contributed to study design and interpretation. Ling Pei performed statistical analyses and wrote the first draft of the manuscript. Huangmeng Xiao, Zeting Li, Zhuyu Li, Shufan Yue and Haitian Chen were involved in data collection and processing. Fenghua Lai, Yanbing Li and Xiaopei Cao read, commented on, and approved the final manuscript. Xiaopei Cao is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURE

The authors declare no conflict of interest.

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**Tables**

**Table 1 Basic characteristics of women with history of GDM**
|                          | Postpartum normal lipid group | Postpartum dyslipidemia group | p     |
|--------------------------|------------------------------|-----------------------------|-------|
|                          | n=362                        | n=227                       |       |
| Age (years) median (IQR) | 33[30-36]                   | 34[30.5-38]                 | 0.019*|
| age ≥35, n/%             | 149 /41.2%                  | 114/50.2%                   | 0.057 |
| Pre-pregnancy BMI (kg/m²), median (IQR) | 21.49[19.59-23.89]          | 21.99[20.04-23.82]          | 0.082 |
| Pre-pregnancy BMI ≥24kg/m², n /% | 81/24.6%               | 57/23.9%                    | 0.375 |
| Weight gain during whole pregnancy (kg), median (IQR) | 11(8-14)                  | 11(8.8-14.42)               | 0.384 |
| Family history of diabetes, n/% | 93 /63.3%              | 54/36.7%                    | 0.582 |
| SBP (mmHg), median (IQR) | 117 (110-125)               | 122 (122-129)               | 0.01* |
| DBP (mmHg) median (IQR)  | 74[68-79]                   | 74[68-80]                   | 0.299 |
| 24-28 weeks during pregnancy |                           |                             |       |
| FPG (mmol/L), median (IQR) | 4.6[4.3-4.9]              | 4.6[4.3-5.0]                | 0.422 |
| 1h PG (mmol/L), median (IQR) | 9.8[8.8-10.4]             | 10.0[9.1-10.6]              | 0.01* |
| 2h PG (mmol/L), median (IQR) | 8.8[8.4-9.3]              | 8.8[8.35-9.6]               | 0.194 |
| HbA1C(%), median (IQR)   | 5.0 (4.8-5.2)               | 5.1 (4.8-5.3)               | 0.03* |
| TC (mmol/L), median (IQR) | 6.0[5.3-6.6]               | 6.7[6.0-7.5]                | 0.00* |
| TG (mmol/l), median (IQR) | 2.15[1.78-2.7]             | 2.47[1.91-3.17]             | 0.00* |
| HDL-C (mmol/L), median (IQR) | 1.92[1.72-2.16]           | 1.96[1.69-2.27]             | 0.06  |
| LDL-C (mmol/L), median (IQR) | 3.28[2.82-3.69]           | 3.76[3.29-4.29]             | 0.00* |
| TG / HDL-C ratio         | 1.13[0.85-1.51]            | 1.28[0.91-1.75]             | 0.003*|
| At 6–12 weeks postpartum |                             |                             |       |
| FPG (mmol/l), median (IQR) | 4.7[4.4-5.0]              | 4.8[4.6-5.2]                | 0.00* |
| 1h PG (mmol/l), median (IQR) | 8.5[7.6-9.4]              | 9.1[8.0-9.9]                | 0.02* |
| 2h PG (mmol/l), median (IQR) | 6.9[5.8-8.2]              | 7.4[6.4-8.4]                | 0.029*|
* P ≤ 0.05. IQR, inter-quartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides. HDL-C high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; PG, plasma glucose.

Figures

Figure 1

Glucose and lipid metabolism at 6-12 weeks postpartum in women with GDM. a. The incidence of dyslipidemia among normal glucose, prediabetes and diabetes were 35.8%, 42.0% and 61.0%, accounted for the whole participants 23.1%, 13.6% and 1.89%, respectively. TC = high TC according to the dyslipidemia definition, TG = high TG according to the dyslipidemia definition, HDL-C = high HDL-C according to the dyslipidemia definition, LDL-C = high LDL-C according to the dyslipidemia definition; Mix = high TC and high TG according to the dyslipidemia definition. Single = presented only one type of dyslipidemia accounted for the whole postpartum dyslipidemia.
Figure 2

ROC curves showing the capacity to predict incident dyslipidemia of age, SBP before labor, HbA1c, LDL-C at gestational 24–28 weeks and combined overall. ROC=receiver operating characteristic. AUC=area under the ROC curve. SBP=Systolic blood pressure. LDL-C= low-density lipoprotein cholesterol. combined=age +SBP +HbA1c+LDL-C.