The small dense LDL particle/large buoyant LDL particle ratio is associated with glucose metabolic status in pregnancy

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Abstract
Background: The lipoprotein subfraction particle profile can be used to improve clinical assessments of cardiovascular disease risk and contribute to early detection of atherogenic dyslipidemia. Lipid alterations in gestational diabetes have been extensively studied, but the results have been inconsistent. Here, we investigated serum lipoprotein subfraction particle levels and their association with glucose metabolic status in pregnancy.

Methods: Twenty-eight pregnant women with gestational diabetes and 56 pregnant women with normal glucose tolerance matched for body mass index were enrolled in this study. We assessed fasting serum lipid concentrations and lipoprotein subfraction particle levels in participants between 24 and 28 weeks of gestation.

Results: The level of low-density lipoprotein (LDL) cholesterol was significantly lower in women with gestational diabetes than in those with normal glucose tolerance, but the triglyceride and high-density lipoprotein (HDL) cholesterol levels of the two groups were similar. Lipoprotein particle analysis showed that very-low-density lipoprotein (VLDL) particle number and the small dense LDL particle/large buoyant LDL particle (sdLDL-P/lbLDL-P) ratio were significantly higher in women with gestational diabetes than in those with normal glucose tolerance (P = 0.013 and P = 0.015, respectively). In multivariate analysis, fasting glucose was independently and positively associated with sdLDL-P/lbLDL-P ratio even after adjustment for maternal age, gestational weight gain, BMI and LDL cholesterol (standardized Beta = 0.214, P = 0.029).

Conclusions: The sdLDL-P/lbLDL-P ratio is higher in GDM compared with non-diabetic pregnant women, and positively and independently associated with fasting glucose in pregnant women.

Keywords: Lipoprotein particle, Gestational diabetes mellitus, Pregnancy, Insulin resistance

Background
Lipoproteins are comprised of multiple subfractions according to their size, density, and physicochemical properties. Determination of lipoprotein particle subfractions improves the clinical evaluation of individuals at high risk of cardiovascular diseases (CVD) and type 2 diabetes [1, 2]. Low-density lipoprotein (LDL) cholesterol is universally known as a major risk factor for CVD and type 2 diabetes, whereas LDL particle is more valuable as a risk indicator of LDL-attributable atherosclerosis [3]. Further, the small dense LDL (sdLDL) subfraction shows a positive association with coronary artery disease and is thought to be an atherogenic lipoprotein [4, 5]. Moreover, the protective effect of high-density lipoprotein (HDL) cholesterol on the incidence of type 2 diabetes is largely attributable to high HDL2 cholesterol subfractions [6].

Gestational diabetes mellitus (GDM), which is defined as impaired glucose tolerance that first appears during pregnancy, is associated with insulin resistance and beta-cell decompensation during pregnancy. There is a substantially increased risk of postpartum diabetes and CVD in GDM patients due, in part, to aberrant metabolic disturbances during pregnancy [7, 8]. In addition to dysglycemia, multiple metabolic and inflammatory factors are altered in women with GDM. Lipid alterations in GDM compared with normal pregnancy have been extensively studied, but the results have been inconsistent, especially those...
concerning LDL cholesterol [9]. The characterization of changes in lipoprotein particle levels in GDM may help identify lipid metabolic changes and potentially improve predictions of the risks of adverse pregnancy outcomes and postpartum metabolic diseases. Previous data obtained in American and Mediterranean populations indicated that women with GDM show remarkable changes in LDL particle distribution [10, 11]. However, the lipoprotein particle diameter differs according to ethnicity [12], and there are no published studies that describe the lipoprotein particle profile of the Chinese Han population with GDM. Thus, the objective of this study was to investigate differences in lipoprotein particle profile of GDM patients and healthy pregnant women and to examine the relationship between lipoprotein subfraction particles and the parameters of glucose metabolism during pregnancy.

**Methods**

This study was conducted at Women’s Hospital Schools of Medicine Zhejiang University. Approval from the Institutional Ethics Committee at Women’s Hospital School of Medicine Zhejiang University was obtained, and all subjects provided informed consent. Twenty-eight singleton pregnant women with GDM were included in the present study. As controls, we selected 56 singleton pregnant women with normal glucose tolerance, matched for body mass index (BMI) and gestational age. GDM was diagnosed between the 24th and 28th weeks of gestation if one or more of the blood glucose levels measured during the one-step 75-g oral glucose tolerance test (OGTT) met or exceeded the following criteria: fasting, 5.1 mmol/L; 1-h, 10.0 mmol/L; and 2-h, 8.5 mmol/L. All participants resided in the Zhejiang Province and were of Han ethnicity. We excluded patients with obesity (BMI > 30 kg/m²), diabetes, thyroid disease, hypertensive disorders, renal diseases, hepatitis or other serious medical condition. In addition, any participant who had smoked or received the lipid lowering drugs, diabetic drugs during pregnancy was also excluded.

Blood samples were collected from participants at 24–28 weeks of gestation after a 12-h fast. Lipoprotein component analysis was performed using the lipoprotein subgroup particle number analysis method (SpectraCell Laboratories; Houston, TX, USA) according to a patented procedure (Patent No.: US 7,856,323 B2) [13]. The serum samples were mixed with a fluorescent dye and a gradient material and then separated in a continuous gradient (d = 1.000–1.300 g/cm³) through analytical ultracentrifugation. Then, the fluorescence of the lipoprotein particles was measured in a high-performance liquid chromatography–type flow system and normalized to a cholesterol scale using a proprietary algorithm. The lipoprotein particle profile included the quantitation of the levels of very-low-density lipoprotein particle (VLDL-P), total LDL particle (LDL-P), remnant lipoprotein particle (RLP), LDL III particle (LDL_{III}-P), LDL IV particle (LDL_{IV}-P), total HDL particle (HDL-P), large buoyant HDL 2b particle (lbHDL 2b-P), and non-HDL particle. Small dense LDL particle (sdLDL-P) levels were calculated as follows: sdLDL-P = LDL_{III} particle + LDL_{IV} particle. Large buoyant HDL particle (lbHDL-P) number was calculated by subtracting sdLDL-P and RLP from total LDL particle. The coefficient of variation for lipoprotein particle analysis using known standards has been reported as ranging from 2% to 3%. Serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin, lipoprotein(a) (Lp(a)), homocysteine, and high-sensitivity C-reactive protein (hsCRP) levels were determined using an Olympus AU400e chemistry immune analyzer (Tokyo, Japan). Blood glucose was measured using an Architect c16000 automated analyzer (Abbott Laboratories, Abbott Park, IL, USA). The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated as follows: HOMA-IR = [fasting glucose (mmol/L) × fasting insulin (μIU/mL)]/22.5.

Distribution of continuous variables was tested for normality using the Shapiro–Wilkinson test, and data showing a normal distribution were subjected to independent-sample t-tests. When the distribution was asymmetric, the two-sample Mann–Whitney U test was performed. The chi-square test was used for categorical variables. Correlation analyses between two parameters were evaluated using the Pearson correlation tests, after square root or logarithmic transformation of variables (whenever necessary). To evaluate the contribution of different variables to sdLDL-P/lbLDL-P ratio and VLDL-P, multivariate linear regression analyses were performed, using stepwise selection. Maternal age, gestational weight gain, BMI at OGTT, progesterone treatment history, FBG and LDL cholesterol were included as independent variables in the sdLDL-P/lbLDL-P ratio regression model. Maternal age, gestational weight gain, BMI at OGTT, progesterone treatment history, FINS and 2-h–OGTT were included as independent variables in the VLDL-P regression model. Two-sided p-value <0.05 was considered to indicate statistical significance. All tests were performed using the SPSS statistics version 20 (SPSS Inc., Chicago, IL, USA). The post hoc analysis was performed on the correlations to assess the appropriateness of the total sample size by determining the correlation coefficient that could be detected with 75% power using two-sided comparison with alpha = 0.05 [14].

**Results**

The characteristics of the study population are described in Table 1. The maternal age of the GDM group was significantly higher (P = 0.005), whereas the prevalence of mothers aged ≥35 years did not significantly differ between the two groups. The history of progesterone treatment in the early gestation were found in two women
Table 1 Clinical and Laboratory characteristics of the GDM and normal pregnant groups

| Characteristics                        | Control (n = 56) | GDM (n = 28) | p value   |
|---------------------------------------|-----------------|-------------|-----------|
| Age (years)                           | 30.0 (28.0, 33.0) | 33.0 (30.3, 36.0) | 0.005*    |
| Advanced maternal age (≥ 35 years), n (%) | 10 (17.8%) | 9 (32.1%) | 0.140     |
| Gestational age (weeks)               | 25 (24, 27) | 25 (24, 26) | 0.817     |
| Pre-pregnancy BMI (kg/m²)             | 20.1 ± 2.2 | 20.6 ± 2.5 | 0.392     |
| BMI at OGTT (kg/m²)                   | 23.3 ± 2.5 | 24.0 ± 2.5 | 0.148     |
| Progesterone treatment history        | 1 (1.79%) | 2 (7.14%) | 0.257     |
| Fasting blood glucose (mmol/L)        | 4.39 (4.20, 4.65) | 4.66 (4.46, 5.01) | 0.001*    |
| 1-h blood glucose (mmol/L)            | 7.24 ± 1.31 | 10.63 ± 1.44 | <0.001*   |
| 2-h blood glucose (mmol/L)            | 6.35 ± 0.95 | 8.67 ± 1.29 | <0.001*   |
| Fasting insulin (μIU/mL)              | 8.1 (5.2, 11.7) | 10.0 (7.0, 14.1) | 0.033*    |
| HOMA-IR                               | 1.55 (1.01, 2.35) | 2.17 (1.39, 2.94) | 0.012*    |
| Total cholesterol (mg/dL)             | 240.59 ± 42.69 | 222.96 ± 36.21 | 0.065     |
| LDL cholesterol (mg/dL)               | 115.00 ± 35.78 | 96.61 ± 28.65 | 0.020*    |
| HDL cholesterol (mg/dL)               | 84.79 ± 18.96 | 79.43 ± 17.35 | 0.213     |
| Non-HDL cholesterol (mg/dL)           | 155.80 ± 37.75 | 143.54 ± 27.69 | 0.131     |
| Triglyceride (mg/dL)                  | 185.0 (146.5, 236.0) | 219.5 (175.8, 285.3) | 0.055     |
| Lipoprotein(a) (mg/dL)                | 6.2 (2.5, 11.6) | 6.0 (2.5, 12.5) | 0.906     |
| hsCRP (mg/L)                          | 2.1 (1.2, 4.0) | 1.8 (1.1, 3.9) | 0.632     |
| Homocysteine (μmol/L)                 | 4.0 (3.7, 4.7) | 4.8 (3.7, 5.9) | 0.049*    |
| TG/HDL cholesterol ratio              | 2.16 (1.64, 3.10) | 2.96 (2.14, 3.84) | 0.029*    |

Data are presented as median (interquartile range) or n (%) or mean ± SD. BMI, body mass index; OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein. Values in bold indicate significant differences (P < 0.05).
Discussion

In the current study, we investigated lipid profiles, including conventional lipid measurements and lipoprotein particle levels, in women with GDM and in pregnant women with normal glucose tolerance. The results indicated that the VLDL-P number and sdLDL-P/lbLDL-P ratio of those with and without GDM significantly differed and were both correlated with glucose metabolic parameters.

There is evidence that maternal lipid levels become abnormal in the context of GDM. A recent meta-analysis reported that GDM patients had higher triglyceride and lower HDL cholesterol levels than pregnant women with normal glucose tolerance in the second trimester; yet, both total cholesterol and LDL cholesterol levels were inconsistent [9]. Our results showed a significant decrease in LDL cholesterol with GDM, which was counterintuitive but in agreement with some previous studies [10, 15, 16]. Moreover, White et al. [17] previously reported that increased LDL cholesterol levels were associated with a lower risk of type 2 diabetes. Several genetic variants that have been associated with reduced LDL cholesterol have also been associated with increased risk of diabetes [18]. These studies help explain the phenomenon of decreased LDL cholesterol during GDM with the increased risk of developing diabetes postpartum.

Although three studies have investigated the relationship between LDL subfractions and GDM, there is no data concerning lipoprotein particle levels in the Chinese Han population. Rizzo et al. [11] reported an increased number but decreased average size of small dense LDL particles in Mediterranean women with GDM whose triglyceride and LDL cholesterol were similar to those of normal pregnant women. In a study conducted by Qiu et al. [10], American patients with GDM showed higher triglyceride and lower LDL cholesterol as well as smaller LDL particle size compared with pregnant women with normal glucose tolerance. Additionally, Han et al. [19] found that women had a smaller LDL peak diameter size and a higher level of the small dense LDL subfraction years before developing GDM. In this study, we used a different lipoprotein particle subfraction parameter, the

| Table 2 Lipoprotein particle numbers of subjects included in the study |
|---------------------------------|---------------------------------|----------------|
|                                | Control (n = 56) | GDM (n = 28) | p value |
| VLDL-P (nmol/L)                | 76 (53, 107)     | 97 (72, 142) | 0.013*  |
| Total LDL-P (nmol/L)           | 1160 ± 227       | 1042 ± 207   | 0.024*  |
| RLP (nmol/L)                   | 145 (113, 199)   | 175 (107, 226) | 0.286 |
| lbLDL-P (nmol/L)               | 401 (299, 509)   | 282 (227, 441) | 0.005*  |
| LDLIII-P (nmol/L)              | 395 (316, 467)   | 380 (317, 462) | 0.690 |
| LDLIV-P (nmol/L)               | 175 (150, 209)   | 163 (132, 184) | 0.064 |
| LDLIV-P/Total LDL-P ratio      | 0.16 (0.13, 0.18) | 0.15 (0.13, 0.18) | 0.690 |
| sdLDL-P (nmol/L)               | 575 (509, 644)   | 526 (485, 629) | 0.107 |
| sdLDL-P /Total LDL-P           | 0.51 ± 0.08      | 0.53 ± 0.06  | 0.271 |
| sdLDL-P /lbLDL-P               | 1.40 (1.14, 1.95) | 1.90 (1.33, 2.55) | 0.015*  |
| Total HDL-P (nmol/L)           | 8062 ± 731       | 8250 ± 734   | 0.271 |
| lbHDL2b-P (nmol/L)             | 3661 ± 592       | 3543 ± 596   | 0.391 |
| lbHDL2b-P /Total HDL-P ratio   | 0.46 ± 0.05      | 0.43 ± 0.05  | 0.0098* |
| Non-HDL-P (nmol/L)             | 1241 ± 231       | 1146 ± 208   | 0.070 |

Data are presented as median (interquartile range) or mean ± SD. VLDL-P, very-low-density lipoprotein particle; RLP, remnant lipoprotein particle; lbLDL-P, large buoyant low-density lipoprotein particle; sdLDL-P, small dense low-density lipoprotein particle; lbHDL2b-P, large buoyant high-density lipoprotein particle. P values in bold indicate significant differences (P < 0.05)

| Table 3 Pearson correlations between lipoprotein particle profile and glucose metabolic parameters |
|---------------------------------|---------------------------------|----------------|
|                                | FBG#                             | FINS#                  | 2-h OGTT glucose | HOMA-IR#               |
| VLDL-P (nmol/L)                | 0.209                            | 0.293**                | 0.286**          | 0.308**                |
| Total LDL-P (nmol/L)           | −0.136                           | −0.062                 | −0.097           | −0.080                 |
| lbLDL-P (nmol/L)               | −0.261*                          | −0.197                 | −0.178           | −0.227*                |
| sdLDL-P /lbLDL-P ratio         | 0.297**                          | 0.236*                 | 0.158            | 0.270**                |
| HDL2b-P (%)                    | 0.029                            | 0.098                  | 0.015            | 0.096                  |

P values in bold indicate significant differences. *, P < 0.05; **, P < 0.01

#Skewed variables were logarithmically transformed before testing

#Skewed variables were square root transformed before testing
skewed variables were logarithmically transformed before testing. *, P < 0.05, ***, P < 0.001

Table 4 Multivariate regression analysis with sdLDL/lbLDL ratio as dependent variable$^a$

| Independent variables | \( \beta \)  | \( P \)  |
|-----------------------|-------------|---------|
| Age$^a$               | −0.062      | 0.544   |
| BMI                   | 0.068       | 0.496   |
| Gestational weight gain | 0.009   | 0.930   |
| Progesterone history  | 0.003       | 0.971   |
| FBG$^b$               | 0.214       | 0.029*  |
| LDL cholesterol       | −0.450      | <0.001 *** |

$^a$Standardized \( \beta \)-coefficients and \( P \) values are given
$^b$Skewed variables were logarithmically transformed before testing. *, \( P < 0.05 \), ***, \( P < 0.001 \)

sdLDL-P/lbLDL-P ratio, to reflect LDL particle mean size. Although the number of total LDL particles was decreased in the GDM group, the sdLDL-P/lbLDL-P ratio was significantly increased, which indicated a tendency toward the predominance of small dense LDL particles.

Previous studies have reported that the ratio of small dense LDL to large buoyant LDL is a potent marker for evaluating lipid metabolic status. A recent study by Lee et al. [20] determined that the sdLDL/lbLDL ratio increases during the development of impaired fasting glucose and is strongly associated with insulin resistance, suggesting atherogenic dyslipidemia from a pre-diabetic stage. A high sdLDL/lbLDL ratio has also been shown to be associated with lipid metabolic disturbance in patients with metabolic syndrome and human immunodeficiency virus (HIV)-associated lipodystrophy [21, 22]. Although a different analytic methodology was used to measure the number of lipoprotein particle in this study, the sdLDL-P/lbLDL-P ratio in pregnant women was positively correlated with fasting glucose after adjusting for age and BMI, two factors known to affect lipid metabolism. It seems plausible that alteration in LDL particle size would be linked to glucose metabolic status.

The causal relationship between abnormal lipoprotein patterns and CVD has been firmly established, and the lipoprotein profile has also been well studied in type 2 diabetes. The exacerbation of lipoprotein patterns and CVD has been firmly established, and the particle size would be linked to glucose metabolic status. It seems plausible that alteration in LDL particle size would be linked to glucose metabolic status.

With aggravating insulin resistance, the concentration and mean size of VLDL-P increase, whereas LDL and HDL particle sizes decrease [23]. Abnormal lipoprotein profiles, including higher small dense LDL and lower large buoyant HDL fractions, indicate poor glycemic control in overweight adolescents with type 2 diabetes [24]. A recent article by Mackey et al. [25] described the association between lipoprotein particles and the incidence of type 2 diabetes in a multicenter prospective cohort study, indicating that the number and size of VLDL-P were significantly associated with the incidence of type 2 diabetes in patients with atherosclerosis. Thus, it is justifiable to speculate aberrant lipoprotein particle profile existing at the early gestation in the subjects who developing gestational diabetes. The sdLDL-P/lbLDL-P ratio and VLDL-P number may be potential as biomarkers to improve early intervention of gestational diabetes.

Nutraceuticals have been shown a peculiar role in ameliorating dyslipidemia, also in pregnant women [26]. It was recently reported that omega-3 fatty acids and vitamin E co-supplementation had beneficial effects on glucose homeostasis parameters, serum triglycerides and VLDL cholesterol in GDM women [27]. Moreover, vitamin D and symbiotic supplementation were of some use for improve lipid profile among GDM patients [28, 29]. These data suggest that nutraceuticals and dietary intervention may modulates maternal glucose and lipid metabolism, but more randomized trials are needed to evaluate the effects of nutraceuticals [30]. In our study, as the subjects received similar dietary advice at obstetric clinic, we have not assessed nutraceutical intakes or taken this into account as a confounding variable.

Our study has several limitations. Firstly, because of its cross-sectional design, we were unable to determine whether abnormal lipoprotein subfractions are a cause or a consequence of impaired glucose metabolic status. Secondly, the relatively small sample size may have limited the generalization of our current findings. However, we were able to identify the correlations between lipoprotein parameters and glucose metabolic parameters. Meanwhile, the post hoc analysis showed that the study had a power of 75% to detect a correlation coefficient with \( r \geq 0.285 \), implying that statistical power should not be a serious problem. Further cohort studies with a larger sample size and participants in their three trimesters of pregnancy and postpartum period are warranted to investigate the dynamic alterations of lipoprotein subfraction profiles in the perinatal period.

### Conclusion

In conclusion, our study described the lipoprotein subfraction particle profile in pregnant women and its relationship to glucose metabolic parameters. The sdLDL-P/lbLDL-P ratio is independently and positively associated...
with fasting glucose in pregnant women. Our study suggests that GDM patients have a tendency toward the predominance of small dense LDL particles, which may contribute to an increased risk for atherosclerosis and CVD in the postpartum period.

Abbreviations
BMI: Body mass index; CVD: Cardiovascular diseases; FINS: Fasting insulin; GDM: Gestational diabetes mellitus; HDL: High-density lipoprotein; HOMA-IR: The homeostatic model assessment of insulin resistance; LDL: Low-density lipoprotein; lbHDL-2b-P: Large buoyant high-density lipoprotein 2b particles; lbLDL-P: Large buoyant low-density lipoprotein particles; LDL: Low-density lipoprotein; OGTT: Oral glucose tolerance test; RLP: Remnant lipoprotein particles; sdLDL-P: Small dense low-density lipoprotein particles; VLDL: Very-low-density lipoprotein

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors’ contributions
YM Chen analyzed and interpreted the patients’ data, and also wrote the manuscript in collaboration with coauthors. MK Du helped with participant recruitment, acquisition of data, and oversaw the laboratory work. JY Xu provided input on the study plan and edited the manuscript. DQ Chen designed the study and critically revised the manuscript. All authors have provided input on the study plan and edited the manuscript. MK Du helped with participant recruitment.

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Committee at Women's Hospital School of Medicine Zhejiang University.

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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