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Cardiovascular biochemical risk factors among women with spontaneous preterm delivery

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Abstract

Objective: To determine whether women delivering preterm have unfavorable cardiovascular profiles as compared with women who deliver at term.

Methods: A prospective observational cohort study enrolled 165 women with spontaneous preterm delivery (sPTD) at 24⁺⁰ and 36⁺⁶ gestational weeks in three perinatal care centers in The Netherlands between August 2012 and August 2014. Total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, apolipoprotein, glucose, and homocysteine were measured within 24 hours after delivery. Lipids and cardiovascular biochemical risk factors were compared between women with sPTD and an external comparison group of 30 women with term delivery via analysis of covariance.

Results: Mean gestational age at delivery was 30.7 ± 3.6 weeks in the sPTD group and 40.3 ± 1.3 weeks in the reference group. Data were adjusted for body mass index, age, and center. As compared with the reference group, total cholesterol and LDL-cholesterol levels were lower and glucose levels were higher among women with sPTD.

Conclusion: An association between sPTD and unfavorable lipids and cardiovascular biochemical risk factors was not established. The higher levels of glucose in the sPTD group might be due to increased insulin resistance, which is associated with a higher risk of sPTD.

KEYWORDS

Biochemical marker; Cardiovascular risk factors; Corticosteroids; Glucose; Hyperglycemia; Lipids; Preterm birth; Preterm delivery

1 | INTRODUCTION

Spontaneous preterm delivery (sPTD), defined as delivery before 37 gestational weeks, is the leading cause of neonatal morbidity and mortality worldwide.¹ It has a worldwide prevalence of 5%–13%, and affects approximately 12.9 million pregnancies annually.² The burden of disease due to sPTD is associated with high expenditure

for medical care, special education, and institutionalized care for disabled infants.

Two-thirds of preterm deliveries occur as a result of spontaneous labor or preterm pre-labor rupture of membranes (PPROM).³ The mechanisms that initiate the inappropriate activation of uterine contractions and/or PPRM are largely unknown. Risk factors for sPTD include uterine overdistension (i.e., multiple gestations and

polyhydramnios), blood loss, previous sPTD, and infection, among others.³ Cardiovascular pathology has also gained interest as a risk factor for sPTD: women who deliver preterm with spontaneous onset have been shown to have increased risk of type 2 diabetes and cardiovascular disease later in life.^{4,5} The pathways that might link sPTD with this increased risk of maternal cardiovascular disease are not well understood. However, pregnancies are metabolically stressful and, if the woman is predisposed to cardiovascular disease, she might have a reduced ability to adapt appropriately to the gestational vascular and metabolic changes that pregnancy induces, resulting in sPTD.

Over the past few years, several studies have tried to elucidate the relationship between sPTD and maternal lipid composition, homocysteine, and hyperglycemia⁶⁻⁸; however, they report conflicting results on the association between lipid levels and risk of sPTD. Moreover, the lipids were mainly measured before and in the first two trimesters of pregnancy. There are few data on lipids and other cardiovascular biochemical risk factors measured directly after delivery. This information might have the potential to clarify the mechanisms that initiate sPTD. The aim of the present study was to determine whether women who deliver preterm have unfavorable cardiovascular profiles shortly after delivery relative to women who deliver at term.

2 | MATERIALS AND METHODS

The PRELUDE study (Preterm Labour; Heart and Vascular Defects), a prospective observational multicenter cohort study to explore cardiac and vascular disease as a potential cause of sPTD, enrolled pregnant women with signs of threatening sPTD between August 1, 2012, and August 31, 2014, at three perinatal centers in The Netherlands: Academic Medical Center (AMC), Amsterdam; University Medical Center Groningen (UMCG), Groningen; and University Medical Center Utrecht (UMCU), Utrecht. The study protocol was approved by the ethics committee of the AMC (ref. no. MEC AMC 2011 299) and the management boards of all participating hospitals. All women provided written informed consent.

All women aged at least 18 years with a gestational age of 24–37 weeks were invited to participate in the study. The exclusion criteria were known HIV seropositivity, known maternal congenital heart disease, multiple pregnancy, uterine anomaly, and known fetal congenital or chromosomal anomaly. Women were subsequently enrolled in the study if they delivered before 37 weeks of gestation.

As a reference group, women with term delivery were selected from the Preeclampsia And Non-preeclampsia Database (PANDA; AMC approval ref. no. MEC AMC 05 133),⁹ which included 165 women with gestational hypertensive disease and 268 women with non-hypertensive pregnancies attending AMC between 2005 and 2010. The set-up and execution of PANDA conformed to the Dutch biobank regulations at that time. Maternal blood, umbilical cord blood, and placenta tissue combined with clinical information of

the mother and neonate were stored with informed consent. Frozen plasma samples (-80°C) were obtained at—or within 24 hours of—delivery.

Medical records were used to collect baseline data including demographic data (age, ethnicity); general medical history; medication; smoking (non-smoker, quit in first trimester, current smoker); obstetric history; length and weight before pregnancy; blood pressure before 12 gestational weeks; PPRM; treatment with tocolytic medication; treatment with corticosteroids (first and second course); route of delivery; additional pregnancy complications; gestational age at delivery; delivery weight; and neonatal outcome. Body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) was calculated for each woman by using height and weight recorded before pregnancy. For all women, gestational age was calculated on the basis of an ultrasound scan performed at 8⁺⁴ to 12⁺⁶ gestational weeks.

The following pregnancy complications were defined: gestational diabetes mellitus (GDM; blood glucose, ≥ 6.1 mmol/L at fasting; and ≥ 7.8 mmol/L after 75-g oral glucose tolerance test); pregnancy-induced hypertension (PIH; systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg in the absence of proteinuria, measured at two different times with a minimum interval of 4 hours, occurring for the first time after ≥ 20 gestational weeks) and pre-eclampsia (PIH with ≥ 0.3 g/24 hours proteinuria or PIH with protein/creatinine ratio ≥ 30 mg/mmol).

Blood samples were collected within 24 hours after delivery. The women did not routinely fast before sample collection because fasting has little impact on lipid levels.¹⁰ The following biomarkers were measured: total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), apolipoprotein B (ApoB), non-fasting glucose, and homocysteine. All blood samples were centrifuged immediately after collection and analyzed by standard procedures at the clinical chemistry laboratories of the three participating centers. Homocysteine specimens were placed on ice and transported to the laboratory within 30 minutes of collection.

At the AMC, total cholesterol, triglycerides, HDL-c, and glucose were measured by a Cobas 8000 analyzer (Roche, Mannheim, Germany). ApoB was measured by an Architect C8000 analyzer (Abbott, Abbott Park, IL, USA). Homocysteine was measured by a Premier XE mass spectrometer (Waters, Milford, MA, USA). At the UMCG, total cholesterol, triglycerides, HDL-c, glucose, and LDL-c were measured by a Modular of Cobas chemical analyzer (Roche). ApoB was measured by a BN2 analyzer (Siemens Healthcare Nederland, The Hague, The Netherlands). Homocysteine was measured by an Architect analyzer (Abbott). At the UMCU, total cholesterol, triglycerides, HDL-c, LDL-c, ApoB, glucose, homocysteine were measured by a Vitros (Ortho, Mulgrave, Vic., Australia) or DxC800 (Beckman Coulter, Brea, CA, USA) analyzer. At all centers, LDL cholesterol was calculated by using the Friedewald formula. The same analyses were performed for the reference plasma samples at the UMCU.

Incomplete case analyses lead to loss of statistical power; therefore, the present analyses were first done without imputation of

missing covariates. Because no differences in data were found, missing values of key covariates in both groups (BMI, $n=26$; blood pressure, $n=44$; current smoking, $n=9$; ethnicity, $n=30$), and missing data on lipids and other cardiovascular biochemical risk factors of the sPTD group (total cholesterol, $n=1$; LDL-c, $n=4$; ApoB, $n=2$; homocysteine, $n=28$; glucose, $n=1$) were imputed by using a multivariate normal imputation technique (10 imputation sets) in SPSS version 21.0 (IBM, Armonk, NY, USA).

All statistical analyses were performed by SPSS version 21.0. Baseline variables were expressed as mean \pm SD or number (percentage) as appropriate. Lipid levels and biochemical cardiovascular indices were compared between the sPTD and reference group by analysis of covariance using the covariates age, BMI, and center, and are reported as mean (95% confidence interval). Subgroup analysis was conducted to compare administration of corticosteroids within the 2 days before delivery, administration of corticosteroids more than 2 days before delivery, and no administration of corticosteroids. The same analysis was repeated for a cut-off of 3, 4, and 5 days, because the glycemic effect of steroids begins approximately 12 hours after the first dose and lasts up to 5 days.¹¹ Subgroup analysis was also performed for mode of delivery (vaginal vs cesarean), severity of PTD (24–30, 30–34, and 34–37 gestational weeks), and start of delivery (ruptured vs intact membranes). A two-tailed P value of less than 0.05 was considered to be statistically significant.

3 | RESULTS

During the 2-year study period, 188 women with sPTD met the study criteria and were enrolled in the study. Blood samples to assess lipids and other cardiovascular biochemical risk factors were subsequently available for 165 women, who were included in the final analysis. For the reference group, there were 81 normotensive singleton pregnancies for which three or more ampoules of frozen heparin plasma were available in the biobank; of these, 51 samples were excluded because of delivery before 37 or after 42 gestational weeks; cesarean delivery; multiple pregnancy; gestational diabetes; drug usage; maternal heart disease; thrombophilia disorder or reported pre-existing maternal disease; congenital neonatal abnormalities; or insufficient clinical data to judge these criteria. Thus, 30 reference samples were available and the frozen maternal plasma samples were obtained for the analysis of cardiovascular biochemical risk factors in the present study.

Baseline characteristics of the study and reference groups are summarized in Table 1. Intrinsic to the nature of the study groups, mean gestational age at delivery and delivery weight were differed between the two groups (both $P<0.001$). Most women in both groups were white (sPTD group, 81.8%; reference group, 83.3%).

Table 2 presents the crude and adjusted lipid levels and cardiovascular biochemical risk factors in the sPTD and reference groups. Women with sPTD had lower levels of cholesterol and LDL-c relative

TABLE 1 Characteristics of the study women by presence of sPTD.^a

Characteristic	sPTD (n=165)	Reference group (n=30)	P value
Maternal age, y	31.5 \pm 5.3	29.8 \pm 5.1	0.102
White	135 (81.8)	25 (83.3)	0.837
Pre-pregnancy BMI	23.7 \pm 4.3	24.5 \pm 5.5	0.173
Diabetes mellitus	4 (2.4)	0	
Nulliparous	100 (60.6)	16 (53.3)	0.461
Smoking during pregnancy	20 (12.1)	3 (10)	0.393
Systolic BP at ≤ 12 wk, mm Hg	112 \pm 12	111 \pm 11	0.380
Diastolic BP at ≤ 12 wk, mm Hg	66 \pm 9	65 \pm 11	0.203
PPROM	70 (42.4)	NA	
Corticosteroids	132 (80.0)	0	
Hypertensive complications (PIH or PE)	2 (1.2)	0	
Gestational diabetes	7 (4.2)	0	
Gestational age at delivery, d	215 \pm 25	282 \pm 9	<0.001
Delivery weight, g	1712 \pm 704	3605 \pm 440	<0.001
Cesarean delivery	33 (20.0)	NA	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DM, diabetes mellitus; BP, blood pressure; PPRM, preterm pre-labor rupture of membranes; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; sPTD, spontaneous preterm delivery; NA, not applicable.

^aValues are given as mean \pm SD or number (percentage).

to the reference group. Glucose levels were significantly higher among women with sPTD, even after additional adjustment for administration of corticosteroids (data not shown).

Corticosteroids were administered to 132 (80%) women with sPTD, 14 of whom received a second course. In Table 3, levels of lipids and biochemical cardiovascular indices are stratified by women who received corticosteroids within the 2 days before delivery, those who received them more than 2 days before delivery, and those who did not receive these drugs. No differences were found between these groups. Similar results were found for a cut-off of 3, 4, and 5 days (data not shown).

For 33 women in the sPTD group, an emergency cesarean was performed for reasons of fetal distress ($n=21$), non-vertex presentation ($n=11$), and prior cesarean delivery ($n=1$). There were no differences between women who delivered preterm by cesarean and those who delivered vaginally. Within the sPTD group, no significant differences were observed regarding the severity of PTD (24–30, 30–34, or 34–37 gestational weeks) or status of membranes at start of delivery (ruptured or intact) (data not shown).

TABLE 2 Comparison of cardiovascular biochemical risk factors between women with and those without sPTD.^a

Risk factor	Crude analysis			Adjusted analysis ^b		
	sPTD (n=165)	Reference group (n=30)	P value	sPTD (n=165)	Reference group (n=30)	P value
Cholesterol, mmol/L	5.98 (5.78–6.19)	6.89 (6.40–7.37)	0.001	5.71 (5.44–5.99)	6.93 (6.45–7.41)	<0.001
Triglycerides, mmol/L	2.29 (2.05–2.53)	2.52 (1.96–3.08)	0.453	2.04 (1.74–2.34)	2.58 (2.02–3.13)	0.105
HDL-cholesterol, mmol/L	1.75 (1.68–1.81)	1.64 (1.50–1.79)	0.205	1.76 (1.68–1.84)	1.67 (1.53–1.82)	0.297
LDL-cholesterol, mmol/L	3.24 (3.07–3.42)	4.10 (3.69–4.52)	<0.001	3.16 (2.92–3.39)	4.10 (3.68–4.51)	<0.001
ApoB, g/L	1.20 (1.11–1.29)	1.36 (1.14–1.57)	0.194	1.17 (1.04–1.29)	1.35 (1.13–1.56)	0.172
Glucose, mmol/L	6.18 (5.91–6.45)	5.09 (4.45–5.72)	0.002	6.30 (5.95–6.66)	5.18 (4.56–5.80)	0.002
Homocysteine, μ mol/L	6.07 (5.42–6.72)	7.39 (6.10–8.68)	0.082	5.82 (4.80–6.66)	7.22 (5.93–8.52)	0.120

Abbreviations: ApoB, apolipoprotein; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sPTD, spontaneous preterm delivery.

^aValues are given as mean (95% confidence interval).

^bAdjusted for age, BMI, and center.

4 | DISCUSSION

The main finding of the present study is that peripartum women with sPTD had lower levels of total cholesterol and LDL-c and higher levels of non-fasting glucose as compared with those who delivered vaginally at term. However, the levels were within normal ranges. As a result, it was not possible to establish an association between sPTD and unfavorable lipids or biochemical cardiovascular indices. The differences in lipids might be explained by the physiologic increase in lipids that occurs during pregnancy. The higher levels of glucose in the sPTD group were not attributed to the effect of corticosteroids: the difference might be explained by increased insulin resistance, which is associated with a higher risk of sPTD.¹²

To predict the risk of sPTD, other studies have examined lipid levels before and in the first two trimesters of pregnancy.^{6–8,13–17} Both the design and results of those studies differ from the present analysis. For example, three studies on pre-pregnancy¹⁴ and second-trimester^{7,15} measurement of lipids found an association between increased levels of total cholesterol and sPTD risk, although four other studies did not confirm this.^{8,13,16,17} No association was observed between risk of sPTD and HDL-c or LDL-c.^{6–8,13,14,16,17} The strongest association has

been reported for high levels of homocysteine and sPTD measured at the second trimester⁸ and during delivery¹⁸; however, the current results indicate that this association does not persist shortly after delivery. In contrast to another study,¹⁹ the administration of corticosteroids did not seem to have an effect on levels of lipids or glucose in the present study.

Normal gestation is characterized by an increase in lipids in maternal circulation to ensure healthy fetal development.²⁰ Owing to preterm delivery, lipid levels in the sPTD group were measured at an earlier stage of pregnancy relative to the reference group; thus, the lower levels of total cholesterol and LDL-c observed in the sPTD group might be the result of a smaller physiologic increase in lipids due to the shorter gestation.²⁰

Gestational diabetes mellitus is associated with significantly increased risks of adverse perinatal outcomes.²¹ Milder hyperglycemia that does not meet the diagnostic criteria for GDM also amplifies the risk of adverse outcomes, including sPTD.¹² Moreover, women with a history of sPTD have an increased risk of developing type 2 diabetes later in life.⁵ Consistent with this, women with sPTD had higher levels of glucose as compared with women who delivered at term, independent of their BMI. Therefore, insulin resistance might play a role in

TABLE 3 Cardiovascular biochemical risk factors among women with sPTD by the interval between corticosteroid administration and delivery.^a

Risk factor	≤ 2 d CCS (n=64)	>2 d CCS (n=68)	P value	No CCS (n=33)	P value ^b
Cholesterol, mmol/L	5.92 (5.48–6.35)	5.47 (5.06–5.89)	0.136	5.85 (4.90–6.79)	0.937
Triglycerides, mmol/L	1.96 (1.39–2.52)	2.01 (1.47–2.56)	0.889	2.36 (1.78–2.93)	0.149
HDL-cholesterol, mmol/L	1.85 (1.73–1.97)	1.72 (1.60–1.83)	0.118	1.84 (1.57–2.10)	0.781
LDL-cholesterol, mmol/L	3.33 (2.95–3.70)	2.95 (2.59–3.31)	0.157	3.12 (2.29–3.94)	0.658
ApoB, g/L	1.16 (0.94–1.38)	1.16 (0.94–1.37)	0.954	1.17 (0.95–1.39)	0.880
Glucose, mmol/L	6.17 (5.62–6.73)	6.20 (5.67–6.74)	0.933	6.59 (5.24–7.94)	0.546
Homocysteine, μ mol/L	6.59 (5.10–8.08)	5.40 (3.89–6.91)	0.199	4.90 (1.50–8.31)	0.353

Abbreviations: ApoB, apolipoprotein B; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; CCS, corticosteroid administration; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sPTD, spontaneous preterm delivery.

^aAdjusted for age, BMI, and center.

^bVersus ≤ 2 d CCS.

the pathogenesis of sPTD in the present cohort and should be further studied. However, mechanisms by which insulin resistance might increase the risk of sPTD have not been elucidated.

The strengths of the study include its prospective design and inclusion of BMI as a confounder in the analysis. Nonetheless, some limitations must be considered. First, lipids were not measured in fasting samples, which might have influenced the levels observed. On the one hand, studies comparing fasting with non-fasting lipid levels show minimal differences (<5%) for total cholesterol, HDL-c, and LDL-c values, although triglycerides may be increased by 15% in the non-fasted state.¹⁰ On the other hand, non-fasting lipids may more appropriately reflect the physiologically relevant exposure.

Second, the term delivery group was relatively small and comprised women from another cohort with a different study protocol, in which samples were stored at -80 °C prior to analysis. Storage might lead to an underestimation of total cholesterol and triglycerides and an overestimation of HDL-c.²² If this is true for the present data, the differences between the lipid levels of the sPTD and reference group would increase, but the conclusions would remain the same.

Third, because the etiology of sPTD is multifactorial, the effect of different mechanisms of preterm delivery, such as infection, on lipid levels and other biochemical cardiovascular risk factors was not studied in the present cohort. However, there was no difference between women with PPROM, which is associated with infection, and those who presented with intact membranes and contractions.

Fourth, a power analysis was not carried out because the PRELUDE study was essentially a cohort study. Therefore, it is not clear whether the study was sufficiently powered enough to show a significant difference between the groups. Last, lipids were measured in the first 24 hours after delivery, and lipid levels decrease significantly in this period.²³ Although the levels of lipids reported possibly do not fully reflect late pregnancy levels, the decrease is likely to be similar in the sPTD and reference groups because sampling was performed in the first 24 hours after delivery in both groups.

In summary, the present results indicate a more favorable maternal cardiovascular lipid profile shortly after delivery in women with sPTD as compared with women with a term delivery. These differences might be explained by the physiologic increase in lipids that occurs during pregnancy. As a result, the previously reported association between sPTD and cardiovascular biochemical risk factors cannot be confirmed. Insulin resistance might play a role in the pathogenesis of sPTD and should be further studied.

AUTHOR CONTRIBUTIONS

KYH, MAK, and MAO conducted the study and performed data analysis. All authors were involved in study design and planning, and interpretation of the data. KYH and MAO drafted the manuscript. MAK, AF, MWdL, BJM, JAVdP, CMB, PGP, KMS, GTS, and CR revised the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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