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Association of Spontaneous Preterm Delivery and Future Maternal Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) risk factors are well established, however, little is known about a woman's cardiovascular response to pregnancy, which appears to be an early marker of future maternal CVD risk. Spontaneous preterm delivery (sPTD) has been associated with up to a three-fold increased risk of maternal CVD death later in life compared to having a term delivery. This review focuses on three key areas to critically assess the association of sPTD and future maternal CVD risk: 1) CVD risk factors, 2) inflammatory biomarkers of interest, and 3) specific forms of vascular dysfunction, such as endothelial function and arterial stiffness, and mechanisms by which each may be linked to sPTD. The association of sPTD with subsequent future maternal CVD risk suggests that a woman's abnormal response to pregnancy may serve as her first physiological "stress test." These findings suggest that future research is needed to understand why women with sPTD may be at-risk for CVD, in order to implement effective interventions earlier in a woman's life.

Keywords

Vascular Biology; Lipids and Cholesterol; Mechanisms women; pregnancy and postpartum; cardiac disease

Introduction

Cardiovascular disease (CVD) is the number one killer of women despite advancement in life-saving therapies.[1] Women who experience adverse pregnancy outcomes such as preterm

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delivery, preeclampsia, gestational hypertension, intrauterine growth restriction, and gestational diabetes are at increased risk of future CVD.[2-4] More recently, adverse pregnancy outcomes such as spontaneous preterm delivery (sPTD) have been identified as a risk factor for future CVD risk.[2, 3, 5]

Normal Pregnancy

Recent literature has suggested that an otherwise healthy woman who is unable to carry her baby full term has therefore experienced an abnormal physiological "stress test."[3] Hemodynamic changes occur in a woman's body during and after pregnancy.[6] Both blood volume and red blood cell mass increase during pregnancy, leading to increased preload. Cardiac output increases by 20–50%, starting as early as 5 weeks of gestation and peaking by mid- to late pregnancy. These gradual increases in cardiac output, heart rate and systolic blood pressure over months of pregnancy is in some way similar to the acute responses observed during exercise stress testing.[7, 8] Reversal can be seen as early as 2 weeks postpartum,[6] again comparable to those cardiovascular changes seen acutely during the recovery period of an exercise stress test.[6, 7] Hypothetically, the pregnancy response may serve as a window into future maternal CVD risk.

Preterm Delivery

Preterm delivery is a common adverse pregnancy outcome that affects 9.6% of women who give birth in the United States.[9] There are two primary types of preterm delivery: spontaneous and medically indicated. Approximately 75% of preterm deliveries are the result of sPTD.[10] Spontaneous preterm delivery results from either preterm labor which leads to delivery or premature spontaneous rupture of membranes (PROM) which lead to preterm delivery.[10] In contrast, medically indicated preterm delivery is an intended preterm delivery for maternal or fetal indications such as preeclampsia or non-reassuring fetal status.[10] Medically indicated preterm delivery has been associated with arterial stiffness and up to an eight-fold increased future maternal CVD risk.[2] For both sPTD and medically indicated preterm delivery there is an inverse relationship between gestational age at delivery and increased maternal CVD risk.[11] However, less is known about the association of sPTD with subsequent future maternal CVD risk.

In this focused review, we discuss potential mechanistic pathways that could account for this association between sPTD and subsequent CVD. We focus on three key areas that pertain to sPTD and future maternal CVD risk: 1) CVD risk factors 2) inflammatory biomarkers, and 3) specific forms of vascular dysfunction such as endothelial function and arterial stiffness.

Association of Preterm Delivery and Future Maternal CVD

sPTD vs. Medically Indicated Preterm Delivery and CVD

In a landmark population based cohort study, researchers reported that mothers with no preeclampsia but a preterm delivery experienced a 2.95- fold increased risk of CVD death compared to controls over a 25-year follow-up period.[2] In addition, women with preeclampsia were divided into two groups based on whether the mother delivered at term or preterm. Women with term preeclampsia were at a 1.65-fold increased risk of CVD death

compared to women without preeclampsia. While women with preterm delivery and preeclampsia experienced an 8.12-fold higher risk of CVD death, independent of lifestyle or other socioeconomic variations.[2]

Otherwise healthy women who present with preterm PROM or an early delivery (less than a gestational age of 37 weeks) have up to a three-fold increased risk of CVD-related death later in life.[2] More recent reports demonstrate increased rates of ischemic heart disease (IHD) and associated death, hospitalizations and CVD mortality in sPTD.[12-15] From 2000-2017 fourteen studies (Table 1) examined cardiovascular outcomes and demonstrated death rates to be 1.5-3 fold higher for women with all preterm delivery compared to women who deliver at term after adjusting for age, hypertensive disorders and diabetes.[14] Recent studies have further demonstrated increased maternal CVD risk in as little as five years postpartum.[25]

In comparing medically indicated preterm delivery and sPTD in their association with later maternal IHD risk, Hastie et al.[12] found that both sPTD and medically indicated preterm delivery had strong associations with subsequent IHD [hazard ratio (HR) 2.26, 95% confidence interval (CI) 1.88–2.71] and total IHD events (HR 1.58, 95% CI 1.47–1.71) with stronger associations related to medically indicated preterm delivery compared to spontaneous preterm delivery (P=0.005).[12] However, among sPTD the association with IHD mortality was much stronger for extreme (24-32 weeks gestation) pre-term delivery (HR) 3.23, 95% CI 2.17–4.80] than mild–moderate (33-36 weeks gestation) pre-term delivery (HR 1.85, 95% CI 1.41–2.44, P=0.022).[12]

Women with medically indicated preterm delivery tend to be older, more likely to have adverse pregnancy outcomes such as gestational hypertension and preeclampsia, and more likely to deliver smaller infants, while women with sPTD are more likely to be younger, do not have preeclampsia, more likely to deliver higher birthweight infants and more likely to be lower socioeconomic status. As the age at first IHD event decreased, the association between preterm delivery and an IHD event increased.[15] Kessous et al.[15] also investigated the relationship of preterm delivery with later increased risk for cardiovascular morbidity. At 10-year follow up, patients with preterm delivery had higher rates of CVD and higher rates of total CVD-related hospitalizations with linear association between the number of previous preterm deliveries and future risk for cardiovascular hospitalizations (5.5% for ≥2 preterm deliveries; 5.0% for 1 preterm delivery vs 3.5% in the comparison group; P <.001).[15] Most recently, Pariente et al.[26] reported that women who had sPTD were at an increased risk of subsequent long term maternal kidney disease, which, in turn, may interplay with mortality from CVD.[26]

CVD and Preterm Delivery Associated with other Adverse Pregnancy Outcomes

Adverse pregnancy outcomes have been identified as a CVD risk marker, both in U.S. and European cardiovascular guidelines.[27, 28] In addition to established adverse pregnancy outcomes such as preeclampsia, small for gestational age, gestational hypertension and gestational diabetes, sPTD is associated with maternal CVD risk whether sPTD is independent or compounded by other adverse pregnancy outcomes.[2] Bonamy et al. identified small for gestational age as a contributor to CVD risk in mothers with preterm

delivery.[11] Compared to mothers who delivered at term, mothers with preterm delivery complicated by small for gestational age had HR 1.39-2.57 higher risk of subsequent CVD (p<.001).[11] Mothers of very small for gestational age (based on the Swedish reference curve for intrauterine growth <0.75) infants experienced an elevated hazard ratio of 1.38 to 3.40. In addition, the earlier the delivery, the more significant the small for gestational age appeared to contribute to higher maternal CVD risk.[29]

In summary, we have compiled 14 studies (Table 1) with CVD outcomes including non-fatal myocardial infarction, revascularization, cardiovascular death, stroke, thromboembolism, ischemic heart disease related hospitalizations and death related to ischemic heart disease in women which includes medically indicated and spontaneous preterm delivery (sPTD), including studies which adjusted for risk factors at study entry and/or during follow-up. The totality of this evidence suggests that all cause preterm delivery (medically indicated and sPTD) is associated with a 1.5 to 3-fold independent, increased risk of cardiovascular morbidity and mortality after controlling for some cardiovascular related risk factors. The more recent, larger studies suggest that sPTD is an independent predictor of future cardiovascular disease risk despite better designs which controlled for multiple cardiovascular disease risk factors. Notably, the HR (1.4 to 1.9) strengthened as more CVD risk factors were controlled for in the analysis, suggesting that sPTD may be an independent CVD risk predictor.[13, 15]

CVD Risk Factors and Preterm Delivery

Currently there are 4 risk factors shared by preterm delivery and future maternal CVD risk. They include: 1) Smoking 2) Hypertension 3) Diabetes and 4) African American Descent. [30-32] In the 2011 Prevention of Cardiovascular Disease in Women Update, adverse pregnancy outcomes such as hypertension in pregnancy, preeclampsia and gestational diabetes were characterized as novel CVD risk predictors.[28] Less understood is the impact of known CVD risk biomarkers such as cholesterol and glucose in the setting of sPTD and subsequent future maternal CVD risk. These risk factors include total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG) which are measured for CVD risk prevention traditionally in non-pregnant, mid-life women. These important risk factors may potentially play a role in the earlier identification of women who experience sPTD and are at future increased CVD risk.

In uncomplicated pregnancy, a steady rise occurs in major lipoproteins, and these levels peak near term delivery.[33] In uncomplicated pregnancies, neither TC nor TG exceeds 250 mg/dL at any time during pregnancy.[33] Eleven studies have investigated the relationship of cholesterol levels to preterm delivery and sPTD. Mudd et al. found an increased incidence of sPTD among women with higher TC, elevated LDL and higher TG. Interestingly, they found positive associations of lower total cholesterol, HDL and LDL levels in the medically indicated preterm delivery cohort. [34] Magnussen et al. [35] prospectively evaluated the Norwegian population study known as the Nord-Trøndelag Health Study from the Medical Birth Registry of Norway. After adjusting for hypertensive disorders in pregnancy, they found a positive association with preterm delivery and pre-pregnancy dyslipidemia. TG above 141.6 mg/dL were associated with a 60% higher risk of preterm delivery, although

lower levels of TG (less than 62 mg/dL) were not associated with preterm delivery. Furthermore, higher levels of TC, TG and glucose correlated with lower gestational age at preterm delivery.[35] These are similar findings to Mudd et al., although Magnussen et al. included women with impaired glucose, a known maternal CVD risk factor. The general theme of these studies is that dyslipidemia is prevalent in women who experience preterm delivery either prior, during, or after pregnancy.

Dyslipidemia pre-pregnancy and during pregnancy have been associated with increased sPTD risk.[36-38] Catov et al.[36] reported that women with dyslipidemia in early pregnancy were 2.8 times more likely to deliver prior to 34 weeks after adjusting for race, body mass index (BMI), education and family history of hypertensive disorders of pregnancy.[36] There were significant linear trends for both TC and LDL as dyslipidemia progressed and sPTD severity increased.[36] In a subset of patients from the Coronary Artery Risk Development in Young Adults study, investigators reported a U – shaped relationship curve between pre-pregnancy cholesterol and preterm birth risk. Pre-pregnancy TG in the highest quartile (>195 mg/dl) was associated with preterm delivery <34 weeks in non-hypertensive women. Preterm birth risk was also seen in the lowest quartile (TC <156 mg/dl). These rates were independent of ethnicity, age, parity, BMI, hypertension during pregnancy, physical activity, and years from measurement to birth.[39]

Inflammatory Biomarkers and Preterm Delivery

Currently there is limited data on the applicability of inflammatory markers such as C-reactive protein (CRP) in the utility of predicting all preterm delivery (PTD) or CVD. This may be because parturition itself is an inflammatory process therefore questioning the utility of this widely used cardiovascular risk marker.[10] However, higher elevations of CRP have been suggested to correlate with PTD. Interleukin-6 (IL-6) has potential as an emerging biomarker in women with adverse pregnancy outcomes, however its applicability to women with sPTD is less understood.

C-Reactive Protein

Serum CRP is an inflammatory biomarker, acute-phase protein secreted by the liver in response to inflammation. In addition, there is limited clinical applicability in markers of inflammation for diagnosis or treatment in this patient population. Pitiphat et al.[40] investigated CRP in preterm women and matched controls.[40] They found an association among presence of infection, elevated CRP and subsequent development of sPTD.[40] Other studies confirmed the association of elevated CRP with increased risk of preterm delivery. These findings indicate that the higher CRP values are associated preterm delivery. Catov et al.[37] investigated CRP, cholesterol and their association with sPTD. They concluded that early onset inflammation and dyslipidemia during pregnancy were independently associated with sPTD from 34 to 37 weeks. Interestingly, the presence of both conditions increased risk of sPTD at < 34 weeks 6.4-fold (95% CI 1.7, 24.1).

C-Reactive Protein in the Years After Delivery

Mechanistically, there are different pathways responsible for elevated CRP later in life compared to during pregnancy and in the immediate postpartum setting where there may be an infection. Studies in this area have yielded mixed results. Hastie et al. completed a retrospective cohort study to compare later maternal CRP (mean period =13 years after delivery) among women who had previous sPTD, those who had medically indicated PTD, and those with term births. After adjusting for potential cofounders, investigators reported an elevation in CRP for the medically indicated preterm group compared to term births, but not for the sPTD group.[41] CRP levels in women with sPTD over time were not significantly higher than those of women with term deliveries. Catov et al. reported similar findings in longer term follow up. Women with a history of preterm delivery 4-12 years postpartum had no difference in CRP or IL-6.[42]

Interleukin-6

Dulay et al. [43] found that maternal blood IL-6 and CRP levels were higher in women with subclinical intra-amniotic infection compared to time matched controls. However, the investigators noted there was overlap with confidence intervals leading to difficulty in interpretation of these results clinically. A systematic review further suggested that IL-6 and CRP are measurable in mid-trimester cervicovaginal fluid, but not in maternal blood samples, suggesting a localized, not systemic inflammatory process.[44]

Vascular Function in Preterm Delivery

There are limited studies evaluating vascular function in preterm delivery, however those available indicate that an abnormal vascular response to pregnancy and subsequent delivery may be an early warning sign for development of future maternal CVD.[42, 45-47] Novel non-invasive methods to assess arterial stiffness, including pulse wave velocity and augmentation index, during normal pregnancy[48, 49] are now available to extend the initial work in women with adverse pregnancy outcomes through this non-invasive vascular function test.

Preterm Delivery and CVD Risk

Pulse wave velocity is considered the gold standard in assessment of arterial stiffness non-invasively. Pulse wave velocity directly measures the more elastic, aorto-iliac pathway and has been previously described as being most clinically relevant as the aorta and its branches are in closest proximity to the left ventricle and are mostly responsible for pathophysiological effects of arterial stiffness. Augmentation index measures atrial stiffness via vascular smooth muscle and smaller artery tone.[50] Pulse wave velocity and augmentation index are complimentary but not interchangeable. In an initial report of the use of non-invasive pulse wave velocity and augmentation index in the context of sPTD, Khalil et al.[46] studied arterial stiffness in women with all preterm delivery compared to controls at 11 to 13 weeks' gestation and compared three cohorts: 1) medically indicated preterm delivery, 2)sPTD, and 3) term deliveries. They found that women with medically indicated preterm delivery had significantly higher arterial stiffness (increased augmentation index but no difference in pulse wave velocity) than women with sPTD and term delivery,[46] and lower

augmentation index in sPTD <34 weeks.[46] There are limited data assessing differences in vascular stiffness in women with sPTD during pregnancy and the postpartum period. A potential hypothesis for Khalil's finding may be that sPTD has a different vascular response than other adverse pregnancy outcomes s indicating an alternative mechanistic pathway which warrants additional inquiry. Catov et al.[42] reported that women with a history of preterm delivery 4-12 years postpartum had no difference in pulse wave velocity or endothelial function, compared to controls. This data supports the findings that women with sPTD are less likely to have arterial stiffness and more likely have an alternative vascular mechanistic pathway.

Knowledge Gaps

Important knowledge gaps remain regarding the utility of adverse pregnancy outcomes in the prediction of CVD in women. We have identified the following unanswered questions to improve these gaps: a) to what extent does a history of pregnancy complications influence the need for an earlier CVD risk assessment? b) Whether lifestyle modification should be recommended to women who had preterm delivery? c) To what extent does a history of pregnancy complication or sPTD specifically predict CVD independently of all measured risk factors used in CVD risk scores? If fully independent, is it at a level to meaningfully alter risk score calculations? If not, which usual risk factors (via adjustments) best explain (i.e. via significant attenuation of HR) association of history of sPTD and CVD outcomes? d) Can any lifestyle intervention post pregnancy lead to lessening of the future risk of sPTD? Future research will advise further investigation in order to provide evidence to further shape current national guidelines.

Limitations

Reviews of the literature are limited by potential publication bias as negatively associated studies are generally not published and therefore not included in the current body of knowledge.

Conclusions

A growing body of evidence suggests that both medically indicated and sPTD are independent predictors of women at risk for future CVD.[11-13, 15] sPTD is associated with higher SBP and lower HDL. While these associations may be due to preexisting conditions exacerbated by pregnancy, it may also be related to differences in mechanistic pathways. In addition, sPTD may label high-risk women for more vigilant CVD lifestyle interventions. Further investigation is needed to understand the role of inflammatory biomarkers for early identification of CVD risk in sPTD women.

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Table 1

Preterm Delivery and Associated CVD Studies

Study	Type of PTD	PTD Sample (N)	CVD Variables*	HR	CI	Follow-Up (years)	Outcomes
Smith et al.[16]2000	PTD < 37 weeks	114	Hypertension during pregnancy	2.1	1.2-3.5	Retrospective 1954-1963	CV Death
Irgens et al.[2]2001	PTD < 36 weeks	5,157	Age, PreE	1.6	1.4-1.8	25 years	All Death
				3.0	2.1-4.1		CV Death
Smith et al.[17]2001	PTD < 36 weeks	7,315	Age, PreE, HTN	1.8	1.3-2.5	15-19 years	IHD Hospitalization or Death
				1.9	0.7-4.9		IHD Death
				1.5	1.2-1.8		All Death
Pell et al.[18]2004	PTD < 36 weeks	6,768	Age, PreE, HTN	1.9	1.4-2.7	14-19 years	Cerebrovascular Events
Nardi et al.[19]2006	PTD < 32 weeks (8 months)	23	Age, HTN, CHO, DM, body mass index, smoking status	2.1	1.1-4.1	Retrospective 1990-2000	Non-fatal myocardial infarction and Death as a result of IHD
Catov et al.[20]2007	PTD < 37 weeks	27	Age, race, BP, HDL, smoking status, statin use	2.9	1.2-6.9	Retrospective Prior PTD 57 years ago	CVD (myocardial infarction, stroke, angina, coronary artery bypass graft, angioplasty, peripheral vascular disease)
Catov et al.[21]2010	PTD < 37 weeks	25,688	Age, PreE, DM, GDM	2.0	1.7-2.3	Retrospective 1973-2006	CVD Mortality
Lykke et al.[22]2010 a.	PTD < 37 weeks	41,659	Age, Pre-pregnancy CVD, DM, PreE	2.0	1.6-2.4	Retrospective 1978-2007	CV Death
Lykke et al.[23]2010 b.	PTD < 37 weeks 2 deliveries (both PTD)	1, 608	Age, HTN, PreE	1.4	1.02-1.81	Retrospective 1978-2007	HTN, Thromboembolism, DM, IHD
Hastie et al.[12]2011	sPTD < 36 weeks	29,965	Age, HTN, PreE	1.5	1.31-1.72	22	IHD events
				1.9	1.34-2.71		IHD Death
Bonamy et al.[11]2011	PTD < 37 weeks	56,893	Age, prior CVD, DM, GDM, HTN, PreE, smoking status	1.4	1.2-1.64	Retrospective 1983-2005	CV hospitalizations or death (coronary heart disease, cerebrovascular events, heart failure
Kessous et al.[15]2013	sPTD <34 weeks	5,992	Age, PreE, DM, obesity	1.4	1.2-1.6	10-20	CV hospitalizations
Rich Edwards[13]et al. 2015	sPTD <37 weeks	33,230	Age, PreE, GDM, DM, smoking, obesity	1.9	1.6-2.2	24.8	CVD Mortality
Ngo et al.[24]2015	sPTD< 37 weeks	38,435	Age, GDM, smoking, HTN, GHTN	1.53	1.35-1.72	7.5	CVD

*All variables were matched, excluded or controlled for

CVD Variable List: Age, HTN, PreE, GHTN, GDM, DM, CHO, Statin Use, Smoking Status, Obesity, Diabetes

Definitions of terminology: Preterm Delivery (PTD), spontaneous preterm delivery (sPTD), cardiovascular disease (CVD), hypertension (HTN), preeclampsia (PreE), blood pressure (BP), gestational diabetes (GDM), gestational hypertension (GHTN) diabetes mellitus (DM), cholesterol (CHO), high density lipoprotein (HDL), hazard ratios (HR), confidence intervals (CI), cardiovascular (CV), ischemic heart disease (IHD).