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Early or recurrent preterm birth and maternal cardiovascular disease risk

Janet M Catov, PhD, **Chun Sen Wu, MD**, **Jorn Olsen, PhD**, **Kim Sutton-Tyrrell, DrPH**, **Jiong Li, PhD**, and **Ellen Aagaard Nohr, PhD**
Departments of Obstetrics, Gynecology & Reproductive Sciences and Epidemiology, University of Pittsburgh, Pittsburgh PA (Janet M Catov, Kim Sutton-Tyrrell) Department of Epidemiology, School of Public Health, University of Aarhus, Aarhus Denmark (Chun Sen Wu, Jorn Olsen, Jiong Li, Ellen Aagaard Nohr), Department Epidemiology, School of Public Health, University of California at Los Angeles, Los Angeles California (Jorn Olsen)

Abstract

Purpose—Preterm birth (PTB) has been associated with a later increased risk of maternal cardiovascular disease (CVD). We hypothesized a more pronounced relation between early or recurrent PTB and maternal CVD risk.

Methods—We related PTB severity (earlier gestational age at delivery) and recurrence (=2) among women with births from 1973–1983 in Denmark (n=427,765) to maternal CVD morbidity or mortality (1977–2006). Birth data were linked to CVD hospitalizations and deaths identified in national registers and data were analyzed using Cox proportional hazards models.

Results—Women with a prior PTB had excess CVD after adjustment for age, parity, and education (HR 1.36 [95% CI 1.31, 1.41]). This was only modestly attenuated when women with preeclampsia or small for gestational age births were excluded, and the relationship was stronger for CVD mortality (HR 1.98 [1.73, 2.26]). Recurrent PTB was associated with higher CVD morbidity compared to women with one PTB, particularly for ischemic events (HR 1.78 [1.40, 2.27] vs. 1.22 [1.09, 1.36]). Risk was similarly elevated among women with early, moderate, and late PTB. Sensitivity analysis suggested that confounding by smoking only partly explained these associations.

Conclusions—Women with PTB, especially recurrent PTB, were at increased risk for CVD, suggesting common causes of these conditions.

Keywords

Premature birth; cardiovascular disease; pregnancy; women

Women who have had preterm births with or without preeclampsia appear to have excess cardiovascular disease (CVD) risk later in life,(1–4) but the relationship between severity or recurrence of preterm birth (PTB) and maternal CVD risk has not yet been examined. A history of preterm birth is the single best marker of PTB risk in subsequent pregnancies, and recurrence

Corresponding author: Janet M. Catov, PhD MS; Department of Obstetrics, Gynecology & Reproductive Sciences; University of Pittsburgh; 300 Halket Street; Pittsburgh, PA 15213; phone 412.641.6217; fax 412.641.1133; catovjm@upmc.edu.

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risk increases as gestational age of the previous birth decreases.(5) A woman who was born preterm herself (6) or has sisters with preterm births(7) is at increased risk for preterm births in her own pregnancies. These findings suggest time stable family related causes of early or recurrent preterm birth, such as genetic factors.

Lower offspring birth weight is associated with higher maternal CVD prevalence,(2,4,8–11) and in one study women who delivered preterm 20 years in the past had excess CVD mortality independent of infant birth weight.(1) To follow-up on this and to explore the possibility of common causes of both PTB and CVD, we linked births of 427,765 women in Denmark between 1973–1983 to hospitalizations and deaths related to specific CVD conditions through 2006.

We predicted that an underlying predispostion to both preterm birth and CVD would be most pronounced for women with early or recurrent preterm births given the evidence that these are more likely to aggregate in families. We also explored the relation between PTB and specific cardiovascular conditions. First vs. subsequent preterm births were also evaluated, and we examined if the association between PTB and CVD was present in the absence of preeclampsia, growth restriction, and diabetes.

METHODS

The Danish Medical Birth Registry, established in 1968 and computerized since 1973, contains medical data on all live and still births in Denmark.(12,13) Notification of births is mandatory and data are collected on a standardized form completed by the attending midwife. Since 1977, information on all hospitalizations has been recorded in the National Hospital Discharge Register using the International Classification of Diseases (ICD).(14) We selected all singleton births delivered in 1973 through 1983 (n=664,068) and linked them to maternal records of hospitalizations or deaths via a unique personal identifier issued to every Danish citizen. Children who were adopted (n=6,672) or who could not be matched to their mothers (n=12) were excluded. A total of 453,337 women gave birth to 657,384 children during this study period. We additionally excluded women with missing information on gestional age (n=17,361), those who delivered preterm according to an indicator code but for whom there was no specific gestational age (n=1,283), those with a hospitalization for cardiovascular disease (n=1300) or diabetes mellitus (n=1221) before the first birth in our study period, those dying during delivery (n=3), and those with missing information on maternal education (n=4404). Women who were exlcuded had a preterm birth rate similar to those included in the study (5.8% vs. 6.2%, respectively). The final study population was 427,765 women.

Gestational age was based on the last menstrual period and was recorded in completed weeks. Preterm births in our study were those delivered before 37 weeks of gestation. All other births (≥37 weeks) were used as the referent. We categorized severity of preterm birth as <=32, 33–34 weeks, and 35–36 weeks because gestational age in the early period of the registry was categorized in these groups.

The 8th (1977–1993) and 10th ICD (1994–2006) revisions were used to code hospitalizations and mortalities during the time period of follow up. All cases of cardiovascular disease (ICD8 390–459, ICD10 I00–I99) were classified as due to ischemic heart disease (ICD8 410–414, ICD10 I20–I25.5), stroke (ICD8 430–438, ICD10 I60–I69.8), hypertension (ICD8 401–404, ICD 10 I10–I13.9), atherosclerosis (ICD8 440, ICD10 I70–I70.9), or thrombosis (ICD8 444, 452, 453; ICD10 I74, I81, I82). We also identified types I and II diabetes mellitus which were pooled in one group since these could not be distinguished in the early years (ICD8 250, ICD10 E10–E14). Women could be counted in more than one diagnostic group, but for the composite

CVD endpoint women were evaluated according to the first diagnostic event which from 1994 also included outpatient visits.

Covariates included maternal age at first birth in the study period, education and parity. Maternal education was derived from the Statistics Denmark and was only available beginning in 1978. We therefore applied education reported in 1978 to births that occurred between 1973–1977 and then the actual education for each birth year from 1978–1983. We did not have complete data on prior births in the early years of the cohort, and therefore a proxy measure of parity was defined as the number of births between 1973 and 1983. Small for gestational age (SGA) infants were identified as those weighing <10th percentile for gestational age and sex based on the distribution within our study cohort. Women with pregnancies complicated by preeclampsia (ICD8 637, ICD10 O14–O15) or gestational diabetes (ICD8 634.74, ICD10 O24) were identfied in the National Hospital Discharge Registry.

ANALYSIS

Data were analyzed using Cox proportional hazard models that included all births occurring during the study period and used mother's age at the time of delivery as the time axis. Women with any PTBs in this period were compared to those with only term births. For these analyses, women entered follow up at their first birth between 1973 and 1983 and were classified as "exposed" versus "unexposed" according to whether the birth was preterm or term. If a woman with a term birth later had a preterm birth she was moved to the exposed cohort at that time. All women were followed until the CVD event of interest, death, emigration or the end of 2006. We verified that the assumption for proportional hazards was not seriously violated using log-log plots. When the proportional assumption holds these plots should be approximately parallel, (15) which they were. All models were adjusted for maternal age at first birth, parity and maternal education.

Additional analysis was conducted for women with at least two births during the study period. First, we evaluated the relationship between PTB recurrence and risk of CVD by comparing women with only term births to women with either one PTB or two or more PTBs. For women with one PTB, follow-up started at this birth, while women with two or more PTBs entered follow-up at the second PTB. Secondly, CVD risk among women with all term births was compared with the risk among women with a single PTB. Women with a single PTB were divided into 2 exposure groups depending on whether this PTB was the first birth or a subsequent birth. Hazard ratios were considered different if the confidence intervals did not overlap.

Information about smoking was not available in the registries in this time period. However, the association between smoking and preterm birth has been well studied,(16) as has that between smoking and cardiovascular disease.(17) We therefore estimated the potential magnitude of the effect of unmeasured confounding due to smoking through sensitivity analysis. Briefly, this approach is based on estimates of the association between smoking and preterm birth as well as smoking and CVD derived from the source population.(18) We utilized a range of estimates from Northern European countries that should be comparable to our source population.

RESULTS

A total of 26,588 women (6.2%) had at least one recorded preterm birth during the study period (Table 1). Women with prior PTBs had more children compared to women with term births, they were more likely to have basic education levels, or to have had pregnancies complicated by preeclampsia. Over an average follow up time of 28 years, there were 42,939 hospitalized

CVD events in this cohort, and women with previous PTBs had higher rates of all CVD conditions evaluated (Tables 2 and 3). They also had higher rates of diabetes and were more likely to have died due to a CVD related cause compared to women who had given birth to term infants.

Women with at least one preterm birth had 30–40% excess CVD risk (HR 1.36, 95% CI 1.31, 1.41) adjusted for covariates (Table 2). Risk was attenuated but still elevated after excluding women with a history of preeclampsia or growth restriction, and the association was stronger for CVD mortality even after excluding preeclampsia (HR 1.98, 95% CI 1.73, 2.26). Exclusion of women with gestational diabetes or who developed diabetes after the first birth further attenuated these estimates, but only marginally.

Risk was similarly elevated among women with early, moderate, and late PTB. For example, the there was about a two-fold increased risk for CVD mortality associated with late PTBs delivered 35–36 weeks gestation and those delivered <=32 weeks (HR 1.87 [95% CI 1.59, 2.14] vs. HR 2.10 [95% CI 1.47, 3.00], respectively).

Among multiparous women, recurrent preterm births (regardless of gestational age of delivery) were associated with modestly higher risk for CVD compared to risk associated with only one preterm birth (HR 1.44, 95% CI 1.25, 1.65 vs. HR 1.24, 95% CI 1.17, 1.31). Among multiparous women with only one PTB, risk for CVD events was more elevated among those with preterm births that followed a first term birth than among those with a first PTB (HR 1.44, 95% CI 1.33, 1.55 vs. 1.16, 95% CI 1.06, 1.23).

There was evidence of excess risk for all types of CVD associated with a history of preterm birth, independent of preeclampsia or SGA (Table 3). Risk appeared to be particularly high for atherosclerosis (HR 4.11, 95% CI 3.28, 5.14), thrombosis (2.23, 95% CI 1.34, 3.74), and stroke (HR 1.67, 95% CI 1.48, 1.88). In addition, women with a prior preterm birth were 1.61-times more likely to be hospitalized with diabetes during follow up (95% CI 1.50, 1.73). Women with early PTBs that occurred before 32 weeks gestation appeared to have particularly elevated risk for thrombotic events. Among multiparous women, those with recurrent preterm births had significantly higher rates of ischemic cardiovascular events (HR 1.78, 95% CI 1.40, 2.27) and atherosclerosis (HR 8.70, 95% CI 4.37, 17.29) compared to women with only one preterm birth. In multiparous women with only one preterm birth, having a preterm birth after a first term birth was associated with higher risk for ischemic events than if the first birth was preterm.

Sensitivity analysis was conducted to estimate if confounding by smoking could explain our results. We estimated a range of risk ratios for the association between smoking and preterm birth from 1.3 which was the pooled result from a meta-analysis to 2.0 which was the highest single estimate in the meta analysis. (16) We also estimated a range of risk ratios for the association between smoking and cardiovascular disease [1.5 to 3.0]. (17) When we estimated that smokers had rates of preterm birth twice as high as non-smokers, that smokers had CVD rates 3 times higher than non-smokers, and that 30% of the population smoked, our hazard ratio of CVD mortality among women with at least one preterm birth was attenuated from 1.98 to 1.56 (21%). These results suggest that within a range of plausible assumptions about the correlation between smoking and preterm birth or CVD, it is unlikely that the associations we present between preterm birth and later life maternal CVD are entirely explained by confounding by smoking.

Discussion

Recurrent preterm births were associated with higher maternal risk of ischemic events and part of this association may be due to common causal factors for both outcomes. All types of CVD events occured with higher risk among women with a history of preterm birth independently

of preeclampsia, growth restriction, or diabetes. Early and moderate preterm births were both associated with excess maternal risk for CVD in our cohort. It is unlikely these results are entirely due to smoking confounding, but we expect our estimates to be somewhat inflated by this unmeasured confounder.

Our results are largely consistent with prior studies that have reported PTB to be associated with a 1.9 to 3.0-fold increased risk for maternal CVD mortality.(4,19,20) Our results, however, expand this early work by a longer follow up than in previous studies. Our associations are lower than found in previous studies perhaps because the genetic contribution to CVD mortality rates may be greater at younger ages.(21) Our data indicate, however, that even up to three decades post partum, prior PTBs may mark women at elevated risk for CVD. Prior studies related a first or randomly selected birth to maternal CVD risk. This approach does not account for the possibility that the relationship between pregnancy complications such as PTB and CVD risk should understood by taking a woman's total reproductive events into consideration.

Our results indicated that women with a prior PTB were at risk for all types of CVD and this lack of specificity may indicate confounding by lifestyle factors that we could not adjust for. On the other hand, genetic factors that affect the lipid profile or clotting tendencies may produce a variety of different phenotypes. In particular, recurrent PTBs were associated with higher risk of ischemic events and atherosclerosis in our data. These results are remarkably consistent with studies reporting dyslipidemia and inflammation during pregnancies that end up being delivered preterm.(22,23) Lipid metabolizing polymorphisms that explain a large portion of the variation in cholesterol concentrations may also be associated with PTB risk.(24) The fact that early PTBs (those delivered <=32 weeks gestation) were not substantially more strongly related to maternal CVD risk than moderate or later PTBs (those delivered 33–34 or 35–36 weeks) indicates that some of the very early PTBs may have a different etiology that does not share a common genetic cause with CVD.

We decided to use a maximum of 10 years of birth history in the exposure classification knowing that the decision to continue or stop reproduction will correlate with experience of reproductive complications and health in general. It was unexpected that we found a higher hazard ratio for CVD in women who delivered preterm later in their reproductive life than for the first birth. It is possible that the etiology of first vs. later PTBs may be more multifactorial, and that some causes are not associated with an excess risk of CVD. Our results are difficult to compare to others because most often primiparity is evaluated as all first births, even when there is only one birth, which will overestimate the importance of first births. (25) This was also true in our data. When we used the entire cohort including the 251,979 women with only one birth, a first birth that was preterm was associated with a 1.39 HR for CVD (95% CI 1.33, 1.46); subsequent preterm births had a HR of 1.29 (95% CI 1.17, 1.41). When we restricted the cohort to women with at least two births we found a HR of 1.16 for first PTBs, and a HR of 1.44 for subsequent PTBs.

Our data did not allow for evaluation of spontaneous vs. medically induced preterm birth in relation to future maternal CVD risk. Our results were only modestly attenuated, however, when limited to women with no history of preeclampsia or SGA which are the dominant indications for medically induced PTBs. Our results provide support for the possibility that some preexisting maternal factors may lead to placental insufficiency and PTB. Indeed, a third of spontaneous preterm births are associated with placental ischemia or insufficiency.(26,27)

Interpreting our results should take several limitations into consideration. While we adjusted our analysis for education, we may have inadequately accounted for the social gradient that is known to exist both among PTB and CVD. However, there is evidence that maternal education is the socioeconomic factor most strongly related to PTB risk,(28) as well as CVD risk among

women.(29) It is also possible that time stable environmental factors such as diet, body mass index, and family history of CVD may explain the associations we see. These data were not available in the registries during the time period of this study. A validation study of gestational age reporting for births in the Danish Medical Birth Registry registry from 1982–1987 indicated 87% concordance within one week between the registry compared to the medical record data.(13) This study also indicated that when discordant, the registry gestational age was typically recorded one week longer than the medical record.(13) Cases of late preterm birth may therefore be under-reported in our cohort.

Our results indicate that multiparous women with recurrent PTBs are at higher risk for ischemic disease compared to those with one or no PTBs. Early, moderate, and late preterm births were all associated with excess maternal risk for CVD. Preterm birth may mark women at increased risk for CVD, but more research is needed to determine mechanisms linking these conditions. Women with PTB may benefit from early screening and reduction of cardiovascular risk factors.

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Table 1

Maternal characteristics and cardiovascular disease morbidity according to preterm birth history (Danish National Birth and Hospitalization Registries, 1973–2006)

	All term births N=401,177	At least one PTB (<37 weeks) N=25,688	
Mean of maternal age at first birth	25.7	25.2	
Education			P<0.001
Basic	176,743(44.1)	13,573(51.1)	
Intermediate	154,248(38.5)	9,361(35.2)	
High	70,186(17.5)	3,654(13.7)	
Births from 1973–1983			P<0.001
One	240,181(59.9)	12,568(47.3)	
Two	141,154(35.2)	11,082(41.7)	
3 or more	19,842(5.0)	2,938(11.1)	
Preeclampsia*	12,785(3.2)	1,331(5.0)	P<0.001
Small for gestational age†	36,860(9.2)	3,481(13.1)	P<0.001
Gestational diabetes	588(0.2)	51(0.2)	P=0.064

*At least one birth complicated by preeclampsia between 1973 and 1983

†At least one birth delivered <10th percentile between 1973 and 1983

Table 2

Prevalence and adjusted hazard ratios (HR) for cardiovascular disease morbidity and mortality according to preterm birth

	CVD events					CVD mortality
	CVD prevalence (N, %)	Crude HR (95% CI)	Adjusted* HR (95% CI)	Excluding preeclampsia or SGA Adjusted HR† (95% CI)	Excluding preeclampsia or SGA or diabetes (95%CI)	Excluding preeclampsia or SGA Adjusted HR † (95% CI)
All term births	39,485 (9.7)	1.00	1.00	1.00	1.00	1.00
At least 1 preterm birth	3,454 (13.0)	1.33(1.28, 1.37)	1.36(1.31, 1.41)	1.21(1.14, 1.29)	1.18 (1.10, 1.25)	1.98 (1.73, 2.26)
Severity of preterm birth						
35 to 36 weeks	2,122 (12.8)	1.31 (1.26, 1.37)	1.34 (1.28, 1.40)	1.33 (1.27, 1.40)	1.26 (1.20, 1.33)	1.87 (1.59, 2.14)
33 to 34 weeks	889 (13.4)	1.34 (1.25, 1.43)	1.37 (1.28, 1.46)	1.32 (1.22, 1.42)	1.26 (1.16, 1.37)	2.10 (1.73, 2.78)
<=32 weeks	443 (12.0)	1.36 (1.24, 1.49)	1.41 (1.29, 1.55)	1.36 (1.22, 1.52)	1.36 (1.21, 1.53)	2.10 (1.47, 3.00)
Recurrent preterm birth‡						
All term births	14,634 (8.8)	1.0	1.0	1.0	1.0	1.0
One	1,434 (10.2)	1.27 (1.21, 1.34)	1.24 (1.17, 1.31)	1.19 (1.12, 1.27)	1.16 (1.09, 1.25)	1.70 (1.33, 2.16)
Two or more	208 (13.5)	1.51 (1.32, 1.73)	1.44 (1.25, 1.65)	1.37 (1.16, 1.60)	1.26 (1.05, 1.51)	2.12 (1.22, 3.68)
Timing of preterm birth§						
First birth	739 (10.5)	1.16 (1.06, 1.23)	1.12 (1.04, 1.21)	1.07 (0.98, 1.17)	1.04 (0.95, 1.14)	1.66 (1.21, 2.27)
Subsequent birth	689 (12.7)	1.44 (1.33, 1.55)	1.39 (1.29, 1.50)	1.36 (1.24, 1.49)	1.34 (1.21, 1.48)	1.74 (1.22, 2.47)

*Adjusted for maternal age at first birth, parity, education

†Women with preeclampsia or SGA births excluded, adjusted for maternal age at first birth, parity, education.

‡Limited to women with 2 or more births in the study period (n=182,146)

§Limited to women with 2 or more births in the study period, and not more than 1 PTB (n=178,893)

Table 3

Prevalence and adjusted* hazard ratios (HR, 95% CI) for cardiovascular conditions according to preterm birth, excluding women with preeclampsia or SGA

	Ischemic	Stroke	Hypertension	Atherosclerosis	Thrombosis	Diabetes
Term births, (n,%)	13,283 (3.3)	3,185 (0.8)	25,563 (6.4)	482 (0.1)	145 (0.04)	10, 064 (2.5)
Any PTBs (n, %)	1,272 (4.8)	351 (1.3)	2,164 (8.1)	124 (0.5)	23 (0.09)	1,106 (4.2)
			Hazard Ratios			
Any preterm birth	1.42 (1.34, 1.52)	1.67 (1.48, 1.89)	1.27 (1.21, 1.34)	4.11 (3.28, 5.14)	2.23 (1.34, 3.74)	1.61 (1.50, 1.73)
Severity of preterm birth						
35 to 36 weeks	1.41 (1.30, 1.53)	1.73 (1.49, 2.01)	1.28 (1.21, 1.37)	3.94 (2.99, 5.19)	1.93 (0.98, 3.81)	1.71 (1.58, 1.87)
33 to 34 weeks	1.49 (1.32, 1.68)	1.42 (1.10, 1.84)	1.22 (1.11, 1.35)	4.18 (2.79, 6.28)	2.04 (0.75, 5.55)	1.41 (1.22, 1.63)
<=32 weeks	1.38 (1.15, 1.66)	1.92 (1.38, 2.67)	1.29 (1.12, 1.49)	4.90 (2.81, 8.54)	4.14 (1.52, 11.31)	1.52 (1.25, 1.85)
Recurrent preterm birth†						
One	1.22 (1.09, 1.36)	1.77 (1.44, 2.17)	1.17 (1.08, 1.27)	2.72 (1.70, 4.35)	2.78 (1.29, 6.01)	1.33 (1.18, 1.50)
Two or more	1.78 (1.40, 2.27)	1.37 (0 .75, 2.49)	1.23 (1.00, 1.52)	8.70 (4.37, 17.29)	2.29 (0.31, 16.83)	1.50 (1.12, 2.00)
Timing of preterm birth‡						
First birth	1.03 (0.88, 1.20)	1.60 (1.22, 2.11)	1.11 (1.00, 1.24)	1.78 (0.87, 3.66)	3.12 (1.22, 7.87)	1.34 (1.14, 1.56)
Subsequent birth	1.48 (1.27, 1.72)	2.00 (1.50, 2.67)	1.24 (1.11, 1.40)	3.97 (2.21, 7.08)	2.33 (0.71, 7.61)	1.17 (0.97, 1.41)

*Adjusted for maternal age at first birth, parity, education, birth year. Women with pregnancies complicated by preeclampsia or SGA excluded

†Limited to women with 2 or more births in the study period (n=182,146)

‡Limited to women with 2 or more births in the study period, and not more than 1 PTB (n=178,893)