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Risk of preterm birth in relation to history of preterm birth: a population-based registry study of 213,335 women in Norway.

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SHORT TITLE: Recurrent preterm birth

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Abstract

Objective

To assess the relationship between preterm first birth and preterm second birth according to gestational age and to determine the role of placental disorder to recurrent preterm birth.

Design

Population-based registry study.

Setting

Medical Birth Registry of Norway and Statistics Norway.

Population

Women (N=213,335) who gave birth to their first and second singleton child during 1999–2014 (N=426,670 births).

Methods

Multivariate logistic regression analyses, adjusted for placental disorders, maternal, obstetric, and socioeconomic factors.

Main Outcome Measures

Extremely preterm ($<28^{+0}$ weeks), very preterm (28^{+0}–33^{+6} weeks), and late preterm (34^{+0}–36^{+6} weeks) second birth.

Results

Preterm birth (<37 weeks) rates were 5.6% for first births and 3.7% for second births. Extremely preterm second births (0.2%) occurred most frequent among women with an extremely preterm first birth (aOR 12.90; CI, 7.47–22.29). Very preterm second births (0.7%) occurred most frequent after an extremely preterm birth (aOR 12.98; CI 9.59–17.58). Late preterm second births (2.8%) occurred most frequent after a previous very preterm birth (aOR, 6.86; CI, 6.11–7.70). Placental disorders contributed with 30~40% of recurrent extremely and very preterm births and 10~20% of recurrent late preterm birth.

Conclusion

A previous preterm first birth was a major risk factor for a preterm second birth. The contribution of placental disorders was more pronounced for recurrent extremely and very preterm birth than for recurrent late preterm birth. Among women with any category of preterm first birth, more than one in six also had a preterm second birth (17.4%).

Tweetable abstract: 110 characters; Preterm first birth is a major risk factor for subsequent preterm birth, regardless maternal, obstetric, and fetal risk factors.

Abbreviations:

aOR: Adjusted odds ratio

CI: 95% confidence interval

EEA: European Economic Association

GA: Gestational age

HELLP: Hemolysis, elevated liver enzymes, low platelets

MBRN: The Medical Birth Registry of Norway

OR: Odds ratio

SGA: Small for gestational age

SSB: Statistics Norway

WHO: World Health Organization

Introduction

Preterm birth, defined as birth before a gestational age of 37 weeks, is a major cause of neonatal mortality and morbidity worldwide (1). Risk of adverse health outcomes correlates inversely with gestational age at birth, and neonates who are born extremely preterm, before gestational week 28, are at a particularly high risk (2, 3).

The mechanisms underlying preterm birth are complex, with risk factors that include infection, cervical disease, uterine over-distention, stress, and placental disorders (4, 5). Previous preterm birth is considered a main risk factor for preterm birth in subsequent pregnancies, regardless of the etiology of the prior preterm birth (6-11). World Health Organization (WHO) categorize preterm birth based on gestational age at birth into extremely preterm (<28 weeks), very preterm (28-31 weeks) and moderate to late preterm (32-36 weeks).

Most commonly, placental disorders present as intrauterine growth restriction or a hypertensive disorder of pregnancy. Both are risk factors for preterm birth and often recur in consecutive pregnancies (12). Studies of preterm placentas have been suggestive of common pathways for placental disorders and preterm birth (13-16) while population-based studies have suggested shared mechanisms among preterm birth, preeclampsia, and intrauterine growth restriction (17, 18).

Associations between extremely preterm, very preterm, and late preterm first and second births, adjusted for maternal, fetal, and placental factors have not been explored in population-based studies. The aims of this study were firstly to assess associations between preterm first and second births—categorized as extremely, very, or late preterm—and secondly to explore the extent to which observed associations are mediated by placental disorder.

Materials and methods

Study population and design

For this population-based registry study, data were obtained from two national registers, the Medical Birth Register of Norway (MBRN) and Statistics Norway (SSB) for all births in Norway between 1999 and 2014. Notification to the MBRN for all births in Norway has been mandatory since 1967. Information is obtained from antenatal health cards that are filled in at check-ups and birth medical records from hospitals. All antenatal care in Norway is standardized and free of charge for residents. We collected data on maternal pre-pregnancy health, pregnancy, and birth

from the MBRN. SSB compiles official statistics about Norwegian residents, such as country of birth and education level.

The study population consists of births in Norway with gestational ages (GA) at >22 weeks and <44 weeks, between years 1999 and 2014. Only women who gave birth to their first and second child in the time period were included, resulting in the inclusion of 237,602 women. Women whose pregnancies involved multiple fetuses (N = 3,871) and whose infants were registered with a congenital anomaly (N = 20,396) at the first and/or second birth were excluded, resulting in a sample of 213,335 women and 426, 670 births. Pregnancy dating was based on routine ultrasound examinations between gestational week 17 and 20. If ultrasound dating was not available (2%), gestational age was estimated based on first day of the woman's last menstruation.

The targeted outcome variable, gestational age for the second birth, was categorized into three groups as follows: extremely preterm, before week 28^{+0}; very preterm, between week 28^{+0} and 33^{+6} and late preterm, between week 34^{+0} and 36^{+6}. The distinction between very preterm and late preterm was set at week 34^{+0} because it is a point after which health prognosis is notably better. Norwegian clinical guidelines recommend treatment with tocolytics and corticosteroids in births before week 34^{+0}.

The main exposure was preterm first birth, categorized into extremely preterm birth, very preterm birth and late preterm birth in the first birth, with term first birth as reference.

Previously known risk factors for preterm birth were identified from previous studies and included in the analyses.

Mothers with any of the following conditions were considered to have a placental disorder: preeclampsia (blood pressure >140/90 and proteinuria), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, eclampsia, and/or small for gestational age (SGA) newborn as a proxy for intrauterine growth restriction. A birthweight below the 5th percentile was the criterion for SGA to avoid over- or underestimating SGA incidence. The cohort was categorized according to the placental disorders: neither pregnancies (reference group); first pregnancy only; second pregnancy only; or both pregnancies.

Maternal country of birth was categorized into 10 regions based on World Bank definitions. Women born in Norway were the reference group. European countries were divided into European

Economic Association (EEA) (including Switzerland) and non-EEA groups. Due to there being few women from Transcaucasia and Central Asia, they were included in the non-EEA group (19).

Information on education from SSB served as a proxy for socioeconomic status. The eight levels of education in the 2011 International Standard Classification of Education were merged into four groups according to years of highest completed education. Women who had completed secondary education served as the reference group. Marital status was categorized into married/cohabitating with partner or not. Maternal age at the time of birth was divided into 5-year intervals, with separate categories for <20 years or >40 years. Women with a maternal age of 25–29 years served as the reference group.

Smoking during the first trimester was registered in the MBRN as never, sometimes, or daily. Missing values were coded as "no". Diabetes was categorized as type 1, type 2, or gestational. In vitro fertilization was categorized as a yes/no dichotomous variable.

Missing data

Information on smoking was missing for 16.8% of the cases, which we categorized as non-smokers like other studies conducted with MBRN data (12, 20). Information on education was missing for 2.2% (4,670/213,335) of the study population. This group was included in the analysis as a separate category. Missing data rates were <1% for all other variables.

Ethical approval and patient consent

This study is part of The PURPLE Study approved by the Regional Committee for Medical Research Ethics in South-East Norway in 2015 (2015/681) and was evaluated by the Institutional Personal Data Officer in Oslo University Hospital. It was conducted in accordance with Norwegian Health Research legislation. All data were anonymized by registry management staff. The Norwegian SIDS and Stillbirth Society provided financial support, grant number 554.04/14, to retrieve data files from the registries. There was no patient involvement, since this is a study based on data from a mandatory national health registry.

Statistical analysis

Continuous data were categorized as defined above. Multivariate regression analyses were used to explore the crude and adjusted ORs (ORs and aORs, respectively) with 95% confidence intervals (CIs). Analyses were conducted separately for the three above-defined preterm outcomes for the second birth (Fig. 1).

We developed two separate models with distinct aORs. In model 1, we adjusted for placental disorder only. In model 2, all selected relevant variables were included. We calculated percentage differences between the crude model and model 1 with the formula $\frac{OR - aOR}{OR - 1}$ to assess how well placental disorder explained outcome differences. Assumptions underlying multivariate logistic regression were found to be adequately met (all factors had variant inflation factors <5). IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY) was used to perform the statistical analyses.

Results

Study population

Maternal characteristics by gestational age group at birth are presented in Table 1. For first births, 5.6% of women (11,887/213,335) gave birth before gestational week 37. For second births, 3.7% of women (7,914/213,335) gave birth before gestational week 37. Women with an extremely preterm first birth had the highest rate of preterm second births at 23.7% (134/566) (Table 1).

Extremely preterm second birth (GA<28^{+0})

The extremely preterm second birth rate was 0.2% (349/213,335), with the highest rates occurring among women with extremely preterm first births (2.7%, 15/566) and among women with placental disorder in both births (1.0%, 43/4,396)(Table 1). Compared to women with term first births, we observed a 19-fold increase in odds for extremely preterm second birth among women with extremely preterm first births (OR, 19.28; 95% CI, 11.40–32.63), a 6-fold increase in odds for women with very preterm first births (OR, 6.23; CI, 4.07–9.54), and a 2-fold increase in odds for women with late preterm first births (OR, 2.21; CI, 1.49–3.28) (Table 2). Adjusting for placental disorder (model 1) reduced the extremely preterm second births ORs by 33.4% for women with extremely preterm first births, by 39.8% for women with very preterm first births and by 33.1% for women with late preterm first births. When other maternal and obstetric risk factors were accounted for (model 2), ORs were altered by less than 2 percentage points (calculations not

shown). Compared to women without a placental disorder, we observed a 5.7-fold increase in the odds of having an extremely preterm second birth (aOR, 5.72; CI, 4.03-8.12) among women with a placental disorder in both births (Table 3).

Very preterm second birth (GA 28^{+0}–33^{+6})

The very preterm second birth rate was 0.7% (1,562/213,335), with the highest rates occurring among women with an extremely preterm first birth (9.5%, 54/566) or a very preterm first birth (7.0%, 185/2,639)(Table 1). Compared to women with term first births, we observed a 20-fold increase in odds of a very preterm second birth among women with extremely preterm first births (OR, 19.87; CI, 11.91–26.48), a 14-fold increase in odds for women with very preterm first births (OR, 13.92; CI, 11.85–16.35), and a 5-fold increase in odds for women with late preterm first births (OR, 4.97; CI 4.30–5.74) (Table 2). Adjusting for placental disorder (model 1) reduced the very preterm second birth ORs by 31.8% for women with extremely preterm first births, by 37.4% for women with very preterm first births, and by 23.7% for women with late preterm first births. When other maternal and obstetric risk factors were accounted for (model 2), ORs were altered by less than 5 percentage points (calculations not shown). Compared to women without a placental disorder, we observed a 6.6-fold increase in the odds of having a very preterm second birth (aOR, 6.63; CI, 5.67–7.75) among women with a placental disorder in both births (Table 3).

Late preterm second birth (GA 34^{+0} – 36^{+6})

The late preterm second birth rate was 2.8% (6,003/213,335), with the highest rates occurring among women with type 1 diabetes (16.2%, 150/928) and in women with very preterm (15.5%, 410/2,639) and late preterm (12.2%, 1,058/8,682) first births (Table 1). Compared to women with term first births, we observed a 7-fold increase in odds of a late preterm second birth among women with extremely preterm first births (OR, 6.58; CI, 5.06–8.56), a 9-fold increase in odds for women with very preterm first births (OR, 8.88; CI, 7.95–9.91) and a 6-fold increase in odds for women with late preterm first births (OR, 6.28; CI 5.85–6.75)(Table 2). Adjusting for placental disorder (model 1) reduced the late preterm second birth ORs by 21.1% for women with extremely preterm first birth, by 22.1 % for women with very preterm first birth and by 10.8% for women with late preterm first birth. When other maternal and obstetric risk factors were accounted for (model 2), ORs were altered by less than 5 percentage points (calculations not shown). Compared to women who never experienced a placental disorder, we observed a 3.6-fold increase in odds of

a late preterm second birth (aOR, 3.58; CI, 3.22–3.98) among women with a placental disorder in both births (Table 3).

Risk of recurrence

ORs for preterm second births tended to decrease with increasing gestational age for the first birth, compared to term first births. After adjustment for all factors, a preterm first birth remained a significant risk factor for a preterm second birth, albeit with reduced ORs. Except for the risk of having a very preterm second birth following having experienced a very preterm first birth, the CIs obtained after all-factor adjustment overlapped with the CIs obtained prior to adjustment. The crude ORs and aORs obtained for preterm second births following an extremely preterm, very preterm, or late preterm first birth compared to a term first birth are illustrated in supplementary figure S1.

Discussion

Main findings

Women who experienced an extremely preterm first birth had the highest odds of having a preterm second birth. Placental disorders explained 30~40% of the increased odds for having an extremely or very preterm second birth and explained 10~22% of the increased odds for having a late preterm second birth.

Strengths and limitations

Strengths: The main strength of this study is the large sample analyzed owing to the use of data from the MBRN. The inclusion of a large sample enables rare outcomes to be investigated. To the best of our knowledge, this is the first study that has investigated recurrent preterm birth with a separate extremely preterm birth group for both first and second births. Because the MBRN is a population-based registry of pre–defined variables that includes all births in Norway, there was no selection bias in the sample population. Missing value rates were overall quite low. Cases with a missing education level datum were analyzed as a separate education category. Validation studies on the MBRN have confirmed the reliability of the registry and that its data are suitable for research (21-23).

Limitations: Because the MBRN and SSB are repositories for pre–defined variables, some potentially relevant variables are not accessible to researchers analyzing datasets from these

sources. Notably, we could not adjust for some risk factors that may recur in successive pregnancies, including urogenital infections and cervical insufficiency. Incorrect categorization of variables may occur in large–scale data registration. However, such errors would be expected to weaken associations.

Interpretations

Our estimation of the relative importance of placental disorders in recurrent preterm birth is novel. Placental disorders in first and second births explained up to 40% of recurrent extremely and very preterm births, and up to 22% of recurrent late preterm births. Previous studies have reported that 30–35% of preterm births can be attributed to maternal or fetal indications, as opposed to spontaneous preterm births, which in our study may reflect the role of placental disorder (4). The contribution of placental disorders was more pronounced for extremely and very preterm second births. In the ASPIRIN study (21), low-dose acetylsalicylic acid was found to reduce risk of preterm birth, compared to placebo, in nulliparous women with a singleton pregnancy in low- and middle-income countries. The effect was most pronounced for preterm births before 34 weeks. The incidence of preeclampsia and SGA was similar between the acetylsalicylic acid and placebo groups (24).

Our findings of associations between preterm first and second births are consistent with the notion of recurrent preterm birth. In a prior study with preterm first birth and smoking as the main exposure factors and only two preterm birth categories (<32 weeks and 32–36 weeks), Cnattingius et al. (25) obtained risk estimates comparable to ours, despite their use of different gestation age categories. However, because they did not adjust for complications, their results did not take recurrent complications into account as possible confounders or differentiate between possible causal pathways of preterm birth (25). Meanwhile, employing the same categories as Cnattingius et al., Yang et al. (26) found that women were at increased risk of delivering before 32 weeks or at 32–36 weeks if they delivered their first baby before the 39th gestational week, compared to women whose first birth occurred later. Although Yang et al. adjusted their ORs for pregnancy complications and reported risk estimates comparable to ours, their study did not include an extremely preterm birth category.

Among women with any category of preterm birth at their first birth, more than one in six had a preterm second birth [17.4% (2066/11,887)]. Almost 1 in 4 women who experienced an extremely or very preterm first birth had a preterm second birth [23.5% (752/3205)]. Of the women who experienced a late preterm first birth, 1 in 7 had a preterm second birth [15.1% (1314/8682)]. By contrast, preterm second births were rare [1 in 34; 2.9% (5848/201448)] among women with a term first birth. Our study confirms the importance of following the guidelines recommending specialized antenatal care to women with a history of a preterm birth. Targeted and individualized care should be offered according to the etiology of her previous preterm birth, distinguishing between placental disorder, cervical insufficiency and infections. Women with a history of a preterm birth without placental disorder should be offered routine cervical measurement and progesterone treatment when a short cervix is observed.

The preventive effects of low dose acetylsalicylic acid on the risk of preterm preeclampsia is confirmed, and treatment is globally recommended for women in high risk of preeclampsia(27). Additionally, several studies have suggested that placental disorders may have common pathways leading to preterm birth with different clinical manifestations, such as placental malperfusion and chronic inflammation (13-15). Our findings are consistent with the hypothesis that preterm birth, preeclampsia, and SGA may share etiology. First-pregnancy SGA has been shown to be significantly associated with second-pregnancy preeclampsia (17). Furthermore, with term first births as a reference group, Rasmussen et al. found that women who had a preterm first birth without preeclampsia were at a 4- to 7-fold increased risk of having a second pregnancy with preterm preeclampsia, and that women who had a preterm first birth without preeclampsia were at a 2- to 3-fold increased risk of developing term preeclampsia in a second pregnancy (18). Despite these findings, prevention with acetylsalicylic acid is neither added to the national guidelines in Norway, nor to the NICE guidelines for women with SGA or preterm birth without hypertensive disorder (28).

Whether women with a previous preterm SGA birth should be included in the recommendation of preventive low dose acetylsalicylic acid remains unclear, potential benefit of acetylsalicylic acid for delay or prevention of preterm labor should be further investigated (24, 29). An ongoing study investigating acetylsalicylic acid and the prevention of preterm birth may enlighten the effect of acetylsalicylic acid among women with a previous preterm birth without placental disorders(16).

Conclusion

A history of preterm first birth was a major risk factor for subsequent preterm birth, even after adjusting for placental disorders in the first and second birth. The risk of preterm birth was particularly high after an extremely or very preterm gestational age at first birth. The role of placental disorders was more pronounced for extremely and very preterm birth. It is important to customize antenatal care for pregnant women with a history of preterm birth.

Disclosure of interest

The authors report no conflict of interest.

Contribution to authorship

TT, ÅV, SR, LS, GM and KL contributed to the planning and design of the study, interpretation of data and have critically revised the manuscript. TT drafted the manuscript and performed the analyses.

Details of ethics approval

This study is part of The PURPLE Study approved by the Regional Committee for Medical Research Ethics in South East Norway in 2015 (2015/681) and was evaluated by the Institutional Personal Data Officer in Oslo University Hospital. It was conducted in accordance with Norwegian Health Research legislation. All data were anonymized by registry management staff.

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Table 1 Prevalence of factors associated with extremely, very and late preterm birth for a woman's second birth, (N = 213,335).

Factors	Outcome second birth			
	Extremely preterm birth $<28^{+0}$ weeks	Very preterm birth 28^{+0}–33^{+6} weeks	Late preterm birth 34^{+0}–36^{+6} weeks	Term birth $\geq37^{+0}$ weeks
	0.2% (N=349)	0.7% (N=1,562)	2.8% (N=6,003)	96.3% (N=205,421)
First birth:				
Extremely preterm (N=566, 0.3%)	2.7% (15)	9.5% (54)	11.5% (65)	76.3% (432)
Very preterm (N=2,639, 1.2%)	0.9% (23)	7.0% (185)	15.5% (410)	76.6% (2,021)
Late preterm (N=8,682, 4.1%)	0.3% (27)	2.6% (229)	12.2% (1,058)	84.9% (7,368)
Term (N=201,448, 94.4%)	0.1% (284)	0.5% (1,094)	2.2% (4,470)	97.1% (195,600)
Placental disorder in				
Neither birth (N=82,241, 85.4%)	0.1% (218)	0.5% (936)	2.4% (4331)	97.0% (176,756)
First birth only (N=19,935, 9.3%)	0.1% (24)	0.9% (171)	3.6% (726)	95.4% (19,014)
Second birth only (N=6,763, 3.2%)	0.9% (64)	3.1% (210)	6.9% (446)	89.1% (6,023)
Both births (N=4,396, 2.1%)	1.0% (43)	5.6% (245)	10.9% (480)	82.5% (3,628)
Second birth:				
Type 1 diabetes	0.1% (1)	4.2% (39)	16.2% (150)	79.5% (738)
Type 2 diabetes	0.2% (1)	2.5% (11)	7.5% (33)	89.7% (393)
Gestational diabetes	0.1% (3)	1.0% (33)	5.7% (186)	93.2% (3,025)
In vitro fertilization	0.3% (10)	1.8% (64)	4.4% (155)	93.5% (3,299)
Smoking in start of second				

pregnancy				
Never	0.2% (323)	0.7% (1380)	2.8% (5,353)	96.4% (187,259)
Sometimes	0.2% (4)	1.1% (28)	2.8% (72)	95.9% (2,462)
Daily	0.1% (22)	0.9% (154)	3.5% (578)	95.4% (15,700)
Age grouped in 5 years in second birth				
<20	0.3% (2)	1.2% (8)	6.9% (47)	91.6% (620)
20–24	0.2% (41)	0.9% (212)	3.3% (782)	95.7% (23,014)
25–29	0.2% (110)	0.6% (469)	2.7% (1,920)	96.5% (69,785)
30–34	0.1% (123)	0.7% (556)	2.7% (2,212)	96.5% (79,500)
35–39	0.2% (63)	0.9% (280)	3.0% (904)	95.8% (28,710)
40+	0.3% (10)	0.9% (37)	3.5% (138)	95.3% (3,792)

Table 2 Risk of preterm birth in second births according to preterm first birth category, before (crude ORs) and after adjusting for risk factors in first and second births.

	Extremely preterm birth < 28 gestational weeks in second birth (N=213,335)			
First birth category	Crude analysis	Multivariate regression model 1*	Difference from OR to aOR1	Multivariate regression model 2**
	OR (95% CI)	aOR1 (95% CI)	(%)	aOR2 (95% CI)
Term	Reference	Reference		Reference
Extremely preterm	19.28 (11.40-32.63)	13.18 (7.65-22.71)	33.37	12.90 (7.47-22.29)
Very preterm	6.23 (4.07-9.54)	4.15 (2.65-6.49)	39.77	4.17 (2.66-6.51)
Late preterm	2.21 (1.49-3.28)	1.81 (1.21-2.70)	33.06	1.83 (1.23-2.72)
	Very preterm birth 28^{+0}-33^{+6} gestational weeks in second birth (N=212,986)			
Term	Reference	Reference		Reference
Extremely preterm	19.87 (14.91-26.48)	13.87 (10.26-18.74)	31.80	12.98 (9.59-17.58)
Very preterm	13.92 (11.85-16.35)	9.09 (7.65-10.81)	37.38	8.81 (7.41-10.47)
Late preterm	4.97 (4.30-5.74)	4.03 (3.47-4.67)	23.68	3.85 (3.32-4.47)

	Late preterm birth 34^{+0}-36^{+6} gestational weeks in second birth (N=211,424)			
Term	Reference	Reference		Reference
Extremely preterm	6.58 (5.06-8.56)	5.40 (4.13-7.06)	21.14	5.13 (3.92-6.71)
Very preterm	8.88 (7.95-9.91)	7.14 (6.37.8.01)	22.08	6.86 (6.11-7.70)
Late preterm	6.28 (5.85-6.75)	5.71 (5.32-6.15)	10.80	5.47 (5.08-5.88)

*Model 1, adjusted for placental disorder (preeclampsia, eclampsia, HELLP or SGA)

**Model 2, adjusted for all factors including placental disorder in the first and second birth as well as the following factors for the second birth; diabetes (type 1, type 2 or gestational) in vitro fertilization, smoking, maternal age, marital status, education and maternal country of birth. Difference between crude OR and aOR1 in % is calculated by the formula:

$$(OR - aOR1)/(OR - 1)$$

Table 3 Risk of preterm second birth according to placental disorder in the first or second birth, before (crude ORs) and after adjusting for gestational category of first birth (aORs).
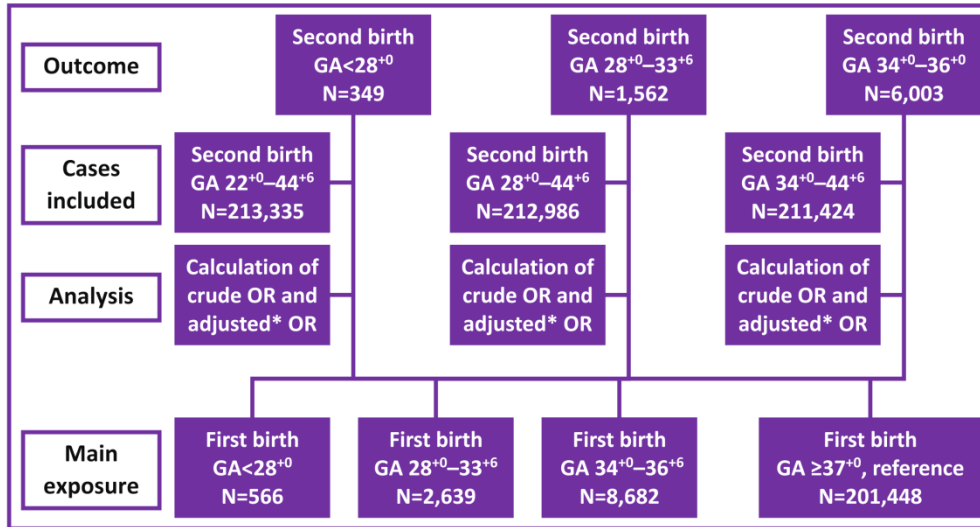
	Outcome second Birth					
Birth(s) with placental disorder	Extremely preterm birth <28^{+0} weeks		Very preterm birth 28^{+0}-33^{+6} weeks		Late preterm birth 34^{+0}-36^{+6} weeks	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Neither	Reference	Reference	Reference	Reference	Reference	Reference
First	1.01 (0.66-1.53)	0.87 (0.57-1.32)	1.68 (1.42-1.97)	1.27 (1.07-1.50)	1.56 (1.44-1.69)	1.23 (1.12-1.33)
Second	7.98 (6.03-10.55)	7.46 (5.64-9.90)	6.26 (5.38-7.29)	5.63 (4.83-6.57)	3.16 (2.86-3.49)	2.88 (2.60-3.19)
Both	8.25 (5.94-11.46)	5.72 (4.03-8.12)	11.54 (9.99-13.33)	6.63 (5.67-7.75)	5.40 (4.89-5.97)	3.58 (3.22-3.98)

Figure Caption List

Figure 1 Flowchart illustrating case inclusion for the regression analysis. The three outcomes were analyzed in separate regression anlysis. Multivariate regression analysis were conducted to calculate aORs, *adjusting for placental disorder in the first and second births and adjustingfor second birth-associated diabetes, in vitro fertilization, smoking, maternal age at birth, education, marital status, and maternal country of birth. GA=gestational age at birth. OR=odds ratio.

Supplementary figure S1 Risk of extremely, very, and late preterm second birth after an extremely (top), very (middle), or late (bottom) preterm first birth. Factors adjusted for include placental disorder in association with the first and second births as well as the following factors for the second birth: diabetes (type 1, type 2, and gestational), in vitro fertilization, smoking, maternal age at birth, marital status, education, and maternal country of birth.

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