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Term complications and subsequent risk of preterm birth: registry based study

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ABSTRACT

OBJECTIVE

To explore conditions and outcomes of a first delivery at term that might predict later preterm birth.

DESIGN

Population based, prospective register based study.

SETTING

Medical Birth Registry of Norway, 1999-2015.

PARTICIPANTS

302 192 women giving birth (live or stillbirth) to a second singleton child between 1999 and 2015.

MAIN OUTCOME MEASURES

Main outcome was the relative risk of preterm delivery (<37 gestational weeks) in the birth after a term first birth with pregnancy complications: pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age.

RESULTS

Women with any of the five complications at term showed a substantially increased risk of preterm delivery in the next pregnancy. The absolute risks for preterm delivery in a second pregnancy were 3.1% with none of the five term complications (8202/265 043), 6.1% after term pre-eclampsia (688/11 225), 7.3% after term placental abruption (41/562), 13.1% after term stillbirth (72/551), 10.0% after term neonatal death (22/219), and 6.7% after term small for gestational age (463/6939). The unadjusted relative risk for preterm birth after term pre-eclampsia was 2.0 (95% confidence interval 1.8 to 2.1), after term placental abruption was 2.3 (1.7 to 3.1), after term stillbirth was 4.2 (3.4 to 5.2), after term neonatal death was 3.2 (2.2 to 4.8), and after term small for gestational age was 2.2 (2.0 to 2.4). On average, the risk of preterm birth was increased 2.0-fold (1.9-fold to 2.1-fold) with one term complication in the first pregnancy, and 3.5-fold (2.9-fold to 4.2-fold) with two or more complications. The associations

persisted after excluding recurrence of the specific complication in the second pregnancy. These links between term complications and preterm delivery were also seen in the reverse direction: preterm birth in the first pregnancy predicted complications in second pregnancies delivered at term.

CONCLUSIONS

Pre-eclampsia, placental abruption, stillbirth, neonatal death, or small for gestational age experienced in a first term pregnancy are associated with a substantially increased risk of subsequent preterm delivery. Term complications seem to share important underlying causes with preterm delivery that persist from pregnancy to pregnancy, perhaps related to a mother's predisposition to disorders of placental function.

Introduction

Women with a pregnancy at term are generally considered to be at reduced risk for subsequent preterm birth, whereas a previous preterm birth is a major predictor of a future one.^{1 2} The strong risk of recurrent preterm birth suggests persistent causal factors in the mother or her environment. These factors could act through disorders of placental function, which are often found in preterm birth and can also contribute to other complications such as pre-eclampsia and placental abruption in both term and preterm pregnancies.³

Preterm birth—especially before 34 weeks—is more than the simple onset of labour. Underlying conditions almost certainly play a role.³ These conditions might act on the fetus and mother for weeks or months before delivery. This idea is supported by the observation that fetuses born preterm are smaller than those of the same gestational age who continue in utero.^{4 5} The term “great obstetrical syndromes” is intended to call attention to the possibility of shared pathways linking pregnancy conditions and outcomes such as pre-eclampsia, placental abruption, poor fetal growth, and fetal death.⁶⁻⁸ Some authors have suggested that these various conditions and outcomes could all be considered as manifestations of dysfunctional placental function (ischaemic placental disease), rather than distinct entities.⁹⁻¹¹ The associations among these conditions have been identified mainly when they occur in preterm births.¹¹⁻¹⁵

The possible relation between obstetrical complications or poor infant outcomes at term and later preterm birth has been less closely studied. Clinical guidelines for identifying pregnancies at risk of preterm birth do not mention previous complications in a term first pregnancy as a risk factor.¹⁶⁻¹⁹ We explore the possibility that underlying pathologic mechanisms

WHAT IS ALREADY KNOWN ON THIS TOPIC

Preterm delivery is an important predictor of future preterm delivery
Generally, women who deliver at term have low risk of preterm delivery in later pregnancies

WHAT THIS STUDY ADDS

A subset of women who deliver at term with specific complications are at substantially increased risk of subsequent preterm delivery
The link between term complications including pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age infants, and preterm delivery implies shared underlying causal factors
These findings can help identify women at increased risk of preterm delivery despite having had a previous term birth

might link conditions occurring in term pregnancies with later preterm birth.

We used the population based registries of Norway to explore whether pregnancy complications or poor outcomes at term (pre-eclampsia, placental abruption, stillbirth and neonatal death, and poor fetal growth) might increase the risk of preterm birth in a subsequent pregnancy.

Methods

Data sources

We obtained the main data from the population based Medical Birth Registry of Norway. Since 1967, the registry has collected data on all births after 16 weeks of gestation.²⁰ Data collected includes demographic, medical and reproductive history, lifestyle, pre-pregnancy and prenatal information transferred from the antenatal chart, complications during pregnancy and delivery, and fetal and infant outcomes. The birth registry notification form was revised in 1998 to include information on smoking, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, and ultrasound based gestational age. We restricted analysis to a woman's first and second deliveries (live births and stillbirths), which were linked using the maternal identification number. Information on maternal education were obtained from Statistics Norway.

Study cohort and demographic variables

The main study cohort consisted of 302 192 women giving birth (live birth or stillbirth) to a second singleton child between 1999 and 2015. We focused on this most recent period because it reflects current clinical practice. We also conducted secondary analyses of births from the complete available registry period (1967-2015).

Women with information missing on gestational age (3.0%) or birth weight (0.2%), or with gestational age outside the range of 20-46 weeks (0.5%) were excluded. To eliminate unlikely gestational age and birthweight combinations, we further excluded women with babies who weighed more than 5 standard deviations above the mean for gestational week of birth (0.1%).²¹ The final eligible study population was 302 192 women. The primary analysis focused on women with a term first birth (n=284 225).

Outcomes and exposures

Our main outcome was preterm birth in the second delivery, defined as a liveborn or stillborn infant delivered at 20 to 36 gestational weeks. Gestational age was defined as completed weeks and is based on the date of the last menstrual period. Exceptions were those with missing information on last menstrual period or for which the last menstrual period differed from the ultrasound result by more than 10 days, in which case we used the ultrasound result, or for pregnancies conceived by in vitro fertilisation for which we used the date of embryo transfer plus 14 days.

We identified five complications or poor outcomes of term pregnancy for analysis: pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age. For the sake of simplicity, we refer to these collectively as "complications." The causes of these complications are complex and include placental dysfunction.^{3 6 8 9 22} As with preterm birth, these complications all tend to recur in subsequent pregnancies.²³⁻²⁶ We included neonatal deaths (in the first 28 days of life) because infants who die shortly after birth are likely to include those exposed to placental dysfunction. To exclude most constitutionally small infants, we used a strict centile for small for gestational age (parity specific birthweight below the 2.5th centile at each term gestational week, grouping births at weeks 44 and later).

Before 1999, pre-eclampsia, eclampsia, and placental abruption had been recorded in the medical birth registry as free text. From 1999, check boxes for these outcomes were added to the registry forms, which improved data quality. The pre-eclampsia outcome includes pregnancies with pre-eclampsia, HELLP syndrome, or eclampsia, as well as chronic hypertension with superimposed pre-eclampsia. A validation study of pre-eclampsia diagnosis as recorded in the birth registry (1999-2010), found a satisfactory positive predictive value (84%) and high specificity (99%) but low sensitivity (43%)—that is, the registry misclassifies a substantial number of cases (mostly mild) as non-cases.²⁷ All cases of eclampsia since 1999 are verified by hospitals.

Owing to registry coding routines, 2015 data for pre-eclampsia, placental abruption, and initiation of delivery (spontaneous, indicated, caesarean section) were incomplete in the dataset available for analysis. Analyses are therefore restricted to 1999-2014 for those three variables.

Statistical analysis

Primary analysis

We used log binomial regression to calculate relative risks with 95% confidence intervals for the association between term complications in first pregnancies and risk of preterm birth in second pregnancies. Separate models were used for each term complication. The reference for each model was first pregnancies at term with none of the five complications. Our focus is on prediction, in the same way that preterm delivery in the first pregnancy is an important predictor of later preterm birth. For this reason, we present unadjusted relative risks as the main finding, without adjustment for possible shared causal factors that might contribute to predictive power. In additional analysis, we adjusted for known demographic and lifestyle factors that might contribute to the observed associations.

Co-occurrence of complications and recurrence of complications

These term complications might co-occur in a given pregnancy. We therefore ran an additional model estimating the associations between having any one

complication, or any two or more complications, and the subsequent risk of preterm birth. Despite population level data being available for more than a decade, numbers were too small to consider unique combinations of complications. We therefore modelled the variables no complication, any one complication, and any two or more complications in a single model.

A complication of term pregnancy might contribute to a future preterm birth if the same complication recurred before term in the next pregnancy. To remove the influence of such recurrences, we reanalysed our data after excluding second pregnancies with the same complication as the first.

Role of clinical intervention

A previous complication at term might also increase preterm birth by prompting clinicians to deliver babies shortly before term to avoid recurrence of the same term outcome. To the extent this occurs, we would expect an excess of preterm births to occur in the later preterm weeks (weeks 34-36). We therefore assessed the risk of delivery across the full range of gestational weeks, using all pregnancies in utero at the beginning of each week interval as the denominator (a fetuses at risk approach). Specifically, the risk of birth in a given gestational week interval (20-24, 25-27, 28-30, 31-33, 34-36, 37-38, 39-40, and 41-42 weeks) was expressed as births occurring in the given interval divided by all fetuses in utero at the beginning of that interval.

Clinical intervention resulting in preterm birth in the second pregnancy might also be suggested if estimates differed between spontaneous and induced preterm births. We examined the associations within mutually exclusive strata of preterm birth that capture the initiation of labour: spontaneous or iatrogenic (including induced labour and caesarean section). Caesarean section in this context captures only deliveries where the procedure was performed before the spontaneous or medically induced onset of labour.

Secondary analysis

We conducted a series of secondary analyses to identify possible explanatory factors and vulnerable subpopulations.

Adjustment for known shared risk factors

Known demographic or behavioural risk factors might contribute to the associations. These risk factors included maternal age, smoking, education, country of birth; year of delivery; and prepregnancy body mass index (BMI). We adjusted for known risk factors at the time of the first pregnancy to avoid introducing bias from factors that might have changed as a result of a poor outcome in the first pregnancy. Information on smoking and BMI was available for the more recent subset of data (smoking in births occurring in 1999-2015 and BMI in births occurring in 2006-15). Smoking behaviour at the end of pregnancy was dichotomised into non-smoking (reference) and any smoking (occasional and daily smoking). Adjustment

for smoking excluded 48 914 women (21%) with missing data.

Weight and height have been registered through an electronic birth notification system that the birth registry has gradually adopted since 2006, and which was not complete until 2014. The proportion of women with registered height and weight increased from 0.1% in 2006 to 72% in 2014.²⁸ For our analysis, we divided prepregnancy BMI into three categories: 15-24.9 (reference), 25-29.9, and 30 or more. Owing to the gradual uptake of BMI registration, 70% (n=83 574) of women with first pregnancies in 2006-15 were missing information on prepregnancy BMI in the first pregnancy and were excluded from the analyses adjusting for BMI.

Year of first birth was treated as an indicator variable, with 1974 (the earliest first delivery in our analytical subset) as the reference. Maternal education level was divided into less than 11 years and 11 years or more (reference). In Norway, 11 years of education is equivalent to high school or secondary school. Maternal country of birth was categorised as Nordic or non-Nordic.

“Reverse” analysis

An observed association between term complications in a first pregnancy and subsequent preterm birth could be due to shared causal factors. A less likely possibility is that such associations could be caused by physiological damage to the maternal reproductive system from the earlier complication. If this were true, we would not expect associations to hold in the reverse direction—preterm birth in the first pregnancy should not increase the risk of term complications in the next pregnancy. We therefore assessed preterm birth in the first pregnancy as a risk factor for term complications in the second pregnancy, excluding women with the specific condition in the first pregnancy. We first considered preterm birth in all weeks as a single group and then dichotomised into early preterm (20-33 weeks) and late preterm (34-36 weeks). Outcomes in this “reverse” analysis were the same five complications (term pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age), now in second pregnancies. The denominator for neonatal mortality in second pregnancies was restricted to live births. All analyses used first pregnancies ending in term delivery as the reference group. The reference further excluded women with the complication of interest in the second pregnancy.

Changes over time and change in partner and interpregnancy interval

To assess the possible impact of changes in clinical practice over time, we repeated the primary analysis for each of three periods (second births in 1967-82, 1983-98, and 1999-2015) and compared the strength of the associations over time.

To address a possible contribution of paternal factors, we conducted separate analyses stratified by whether women had the same partner or different

partners for their two pregnancies. In additional analysis we adjusted for interpregnancy interval as an indicator variable categorised using centile cut points (10th, 25th, 50th, 75th, and 90th centile) of the months between first birth and second conception.

Restricting to a narrow definition of term births in first pregnancy

Finally, we repeated the main analysis restricting to first term births at weeks 39-41. This excluded early term births (which may share features with preterm births) and post-term births. The supplementary tables provide further descriptions of these secondary analyses together with results. Analyses were conducted in STATA version 15.0 (College Station, TX).

Patient and public involvement

Patients, families, or the public were not involved in the design, choice of outcome measures, or interpretation of results in the current study.

Results

In total, 302 192 women had a second birth in 1999-2015 (fig 1). Table 1 provides a description of this sample. The overall risk of preterm birth in the first pregnancy was 5.9% (17 967/302 192). Among women with term births in their first pregnancy, 4.2% (11 225/266 380) had pre-eclampsia, 0.2%

(562/266 380) had placental abruption, 0.2% (551/284 225) had stillbirth, 0.1% had a neonatal death (219/284 225), and 2.4% (6939/284 220) had a small for gestational age infant (table 1).

The risk of recurrence of preterm birth in the second pregnancy was 18.1% (3257/17 967), with a relative risk of 5.5 (95% confidence interval 5.3 to 5.7) compared with a term first birth. Although lower than the recurrence risk of preterm birth, each of the five complications of term pregnancy was associated with a substantially increased risk of preterm birth in the subsequent pregnancy (table 2, fig 2). The absolute risks for preterm birth in the second pregnancy were 3.1% with none of the five complications (8202/265 043), 6.1% after pre-eclampsia (688/11 225), 7.3% after placental abruption (41/562), 13.1% after stillbirth (72/551), 10.0% after neonatal death (22/219), and 6.7% after small for gestational age (463/6939). The unadjusted relative risk of preterm birth after pre-eclampsia was 2.0 (95% confidence interval 1.8 to 2.1), after placental abruption was 2.3 (1.7 to 3.1), after stillbirth was 4.2 (3.4 to 5.2), after neonatal death was 3.2 (2.2 to 4.8), and after small for gestational age was 2.2 (2.0 to 2.4) (table 2).

Compared with having none of the five complications in the first pregnancy, having any one of them was associated with a doubling in risk of a subsequent preterm birth (relative risk 2.0, 95% confidence

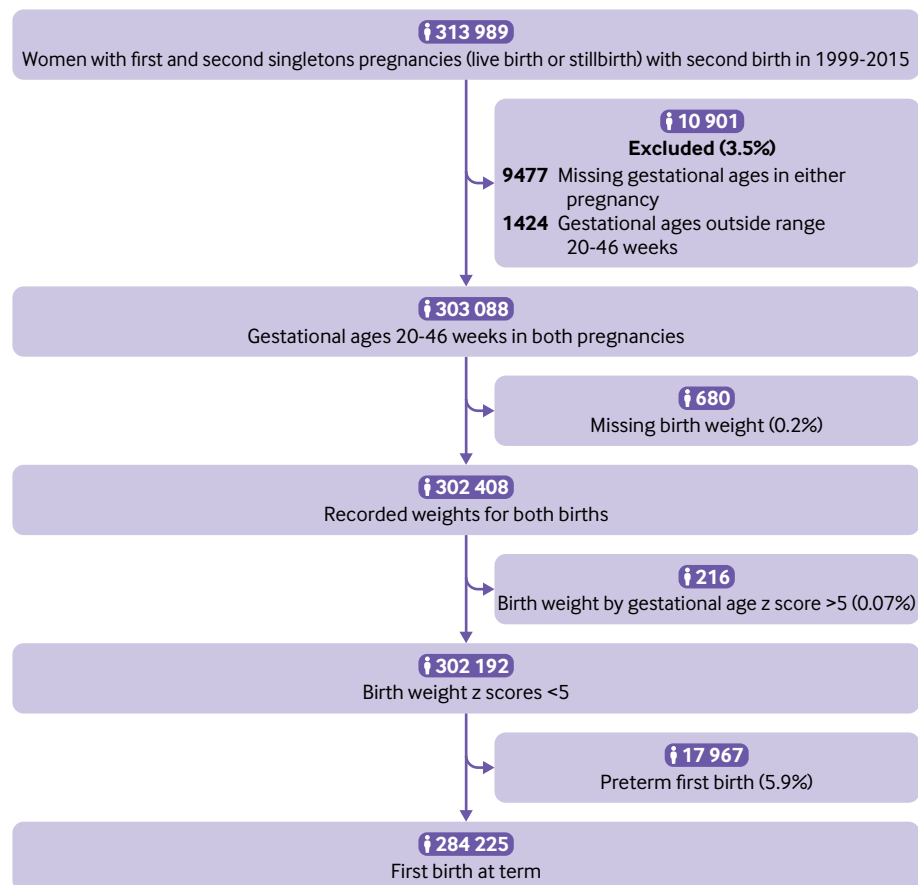


Fig 1 | Flowchart of study population

Table 1 | Characteristics of 302 192 women with two successive singleton pregnancies, Norway 1999-2015

Characteristics	No (%)
Total No	302 192 (100)
Maternal age at first birth (years):	
<20	17 951 (6)
20-24	83 810 (28)
25-29	122 788 (41)
30-34	64 394 (21)
≥35	13 249 (4)
Maternal education (years):	
<11	41 551 (14)
≥11	254 743 (84)
Unknown	5898 (2)
Mother born in Nordic country*	258 868 (86)
Maternal smoking†:	
No	170 426 (72)
Yes	16 458 (7)
Not registered	48 914 (21)
Maternal prepregnancy body mass index‡:	
15-24.9	25 293 (21)
25.29.9	7,287 (6)
≥30	3,633 (3)
Change in partner§	33 574 (11)
Outcome in 1st pregnancy:	
Preterm	17 967 (5.9)
Term	284 225 (94.1)
Outcome among women with term 1st pregnancy (No/No at risk (%)):	
Pre-eclampsia¶	11 225/266 380 (4.2)
Placental abruption¶	562/266 380 (0.2)
Stillbirth	551/284 225 (0.2)
Neonatal death	219/284 225 (0.1)
Small for gestational age (2.5th centile)**	6939/284 220 (2.4)

*Include Norway, Denmark, Finland, Iceland, and Sweden. Information was missing for 4070 (1%) women.

†For supplemental analysis including smoking at end of first pregnancy as a covariate, women with smoking not registered (n=48 914/235 798 (21%)) were excluded from analysis. As smoking was first recorded from 1999, these analyses include only women whose first births were from 1999 (n=235 798).

‡For sensitivity analysis on prepregnancy, body mass index data are only available incrementally from maternity units from 2006 to 2015. In this period, data were missing for 83 574/119 787 (70%) women.

§296 659 women had an identified partner in both pregnancies.

¶For analysis, the period is restricted to 1999-2014 (n=266 380), as reflected by the percentage.

**To avoid the possibility of data entry issues, term births with birth weight fewer than three digits (≤999 g) were excluded from the small for gestational age analysis (n=5).

interval 1.9 to 2.1) (absolute risk 6.2%), whereas the relative risk with two or more complications was 3.5 (2.9 to 4.2) (absolute risk 10.9%).

When recurrences of a specific complication in the second birth were excluded, the relative risks of preterm birth were largely unchanged. The exception was for risk after pre-eclampsia, which decreased from 2.0 to 1.4 (1.3 to 1.6) (table 2).

Adjusting for known shared risk factors

The associations were slightly attenuated after adjusting for maternal age, education, and year of birth except for risk after pre-eclampsia and stillbirth in the first pregnancy, which remained unchanged (fig 2). After further adjustment for smoking (restricted to both births occurring during 1999-2015) and maternal country of birth the findings were similar to unadjusted results during the same period. Results were also similar after adding pre-pregnancy BMI from the first pregnancy to the adjustment variables and restricting the dataset to those women with recorded BMI (supplementary eTable 1).

Role of clinical intervention

The relative risk of a preterm birth in a second pregnancy after complications in a first pregnancy at term was increased in nearly every preterm interval, with no evidence of a concentration of risk among the late preterm or early term weeks (fig 3, and supplementary eTable 2 and eTables 3a-3b). On the contrary, the relative risks of delivery after a term complication were highest early in the next pregnancy, in weeks 28-30.

Medical intervention in the second pregnancy does not appear to account for the observed associations. All modes of delivery initiation were associated with increased risks for preterm birth after term complications, with the highest risks generally observed for spontaneous preterm birth (supplementary eTable 4).

Secondary analyses

Reverse association

The associations between term complications and subsequent preterm birth suggest shared underlying causes. If so, the associations would be expected to hold in the other direction as well: preterm birth should increase the risk of complications in a subsequent term pregnancy. This was confirmed (table 3). Women whose first pregnancy ended in preterm birth had a generally increased risk of term complications in their second pregnancy, with the strongest associations after early preterm birth (20-33 weeks).

Periods of second birth

In general, the strength of the associations increased over time. Every relative risk was higher in the most recent period compared with earlier periods—some substantially increased (supplementary eTable 5).

Change in partner and interpregnancy interval

A change in partner means a change in half of the genetic contribution to the placenta and fetus, plus possible changes in residence or other aspects of the mother's environment, plus a generally longer interval between pregnancies. Eleven per cent of mothers changed partners between their first and second births. While the estimates are less precise owing to smaller numbers, results were similar for mothers with new partners. Adjusting for interpregnancy interval did not change the results (supplementary eTable 6).

Restricting to a narrow definition of term births in first pregnancy

When first term births were restricted to those in weeks 39-41 four of the relative risks were slightly attenuated and the fifth was strengthened (risk of preterm birth after term neonatal death; supplementary eTable 7).

Discussion

In this large, population based registry study, women with complications or poor outcomes in a first birth at term were at substantially increased risk of preterm

Table 2 | Relative risk of preterm birth (PTB)* in second pregnancy by term complications in first pregnancy with and without exclusion of recurrent complications, Norway 1999-2015

First pregnancy (at term)	PTB in second pregnancy		PTB in second pregnancy (recurrences excluded)†	
	No with PTB/No at risk (%)	Relative risk (95% CI)	No with PTB/No at risk (%)	Relative risk (95% CI)
No complications‡	8202/265 043 (3.1)	Reference	—	—
Pre-eclampsia§	688/11 225 (6.1)	2.0 (1.8 to 2.1)	7069/244 496 (2.9) 404/9696 (4.2)	Reference 1.4 (1.3 to 1.6)
Placental abruption§	41/562 (7.3)	2.3 (1.7 to 3.1)	7463/247 527 (3.0) 35/547 (6.4)	Reference 2.1 (1.5 to 2.9)
Stillbirth	72/551 (13.1)	4.2 (3.4 to 5.2)	7712/264 247 (2.9) 69/548 (12.6)	Reference 4.3 (3.5 to 5.4)
Neonatal death	22/219 (10.0)	3.2 (2.2 to 4.8)	7547/263 945 (2.9) 22/218 (10.1)	Reference 3.5 (2.4 to 5.2)
SGA 2.5¶	463/6939 (6.7)	2.2 (2.0 to 2.4)	7994/259 629 (3.1) 426/5900 (7.2)	Reference 2.3 (2.1 to 2.6)

*Birth between 20 and 36 gestational weeks.

†Excludes both exposed and unexposed women with same complication in 2nd pregnancy. Therefore, number at risk in reference group changes slightly for each exposure.

‡For main analyses reference is term first pregnancies with none of the five complications. For analysis excluding recurrence of the same complication, reference further excludes women with the complication of interest in the second pregnancy.

§Reference category "No complications" for term pre-eclampsia and placental abruption is (number with PTB in 2nd pregnancy/number at risk) 7750/248 214 (3.1%) because the analytical period is restricted to 1999-2014 for these analyses.

¶Small for gestational age (SGA) 2.5th centile by each term gestational week (weeks 44-46 grouped). To avoid the possibility of data entry issues, term births with infants with birth weight less than 1000 g were excluded (n=5) from analyses on term SGA, and preterm infants in second pregnancy with birth weight ≤100 g were excluded (n=8).

birth in a subsequent pregnancy. Term complications included pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age. Relative risks for preterm birth were twofold to fourfold higher after these term complications. The presence of one term complication was associated with a twofold higher risk of subsequent preterm birth, whereas two or more complications were associated with a 3.5-fold higher risk. For comparison, the recurrence of preterm birth in this population was fivefold.

The largest increase in relative risk of preterm birth was seen for births in the very preterm period (weeks 28-30) (fig 3 and eTable 2). Similarly, the reverse analysis showed that early preterm birth (20-33 weeks) in the first pregnancy was most strongly associated with an increased risk of term complications in a subsequent pregnancy. These unadjusted results (table 2) support a hypothesis of shared pathways linking term complications and preterm birth. The consistent associations across a wide range of term complications suggest the presence of maternal specific factors that

predispose them to these outcomes. Our adjustments for known demographic and lifestyle factors had little influence on these associations, pointing towards more fundamental shared conditions such as a maternal propensity to placental dysfunction. The likely presence of maternal specific factors is further supported by the persistence of the associations among women who change their partner between first and second pregnancies.

Our results from the most recent period (1999-2015) were consistently stronger than results from earlier periods. This might reflect changes over time in clinical practice. However, if medical interventions explained our observations of increased risk of preterm birth after term complications, we would expect to see a greater increased risk in gestational weeks 34-36. Instead, we found that risks were more strongly increased during earlier weeks of gestation. Furthermore, the observed increases in risk of preterm birth were seen with all modes of delivery; spontaneous as well as iatrogenic preterm birth.

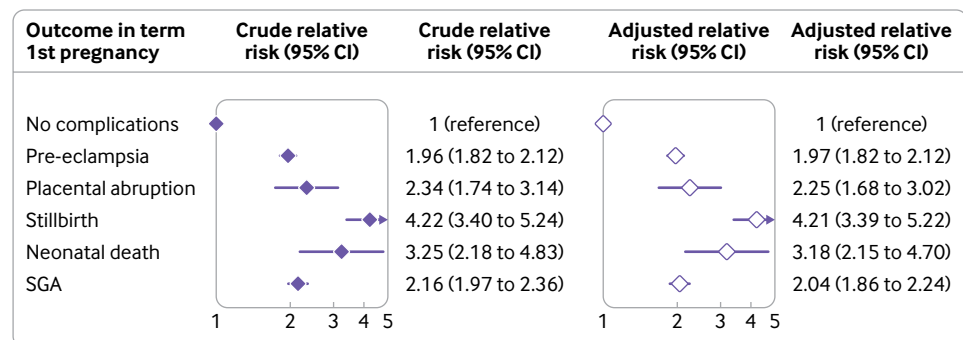


Fig 2 | Unadjusted (filled diamonds) and adjusted (open diamonds) relative risks for preterm birth in second pregnancy by complications in first pregnancy at term, Norway, 1999-2015. Reference is term birth in first pregnancy without any of the five complications. Analyses are adjusted for maternal age, year of birth for first child, and maternal education. Supplementary eTable 1 presents adjusted relative risks (95% confidence intervals) with further adjustments. SGA=small for gestational age

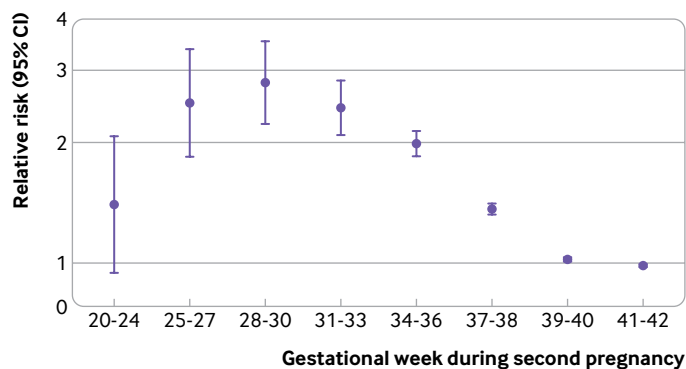


Fig 3 | Relative risks (95% confidence intervals) for birth in specific gestational weeks in second pregnancy for women with any term complications in first pregnancy, Norway 1999-2015. Exposure is any term complication (one or more of five complications). Reference is term birth in first pregnancy without any of the five complications. Because pre-eclampsia and placental abruption are included in the “Any complication” category, analysis is restricted to 1999-2014. Denominators are all fetuses in utero at the beginning of the specific week interval. With 100% of births occurring in the final interval (≥ 43 weeks), no estimates were calculated for these last gestational weeks. Filled circles represent unadjusted relative risks for birth in specific gestational weeks in the second pregnancy

Improvements in data recording could have contributed to stronger associations over time. For example, the association between pre-eclampsia in a term first pregnancy and preterm birth in the second pregnancy increased from 1.3 (95% confidence interval 1.2 to 1.5) in 1967-82 to 2.0 (1.8 to 2.1) in 1999-2014, when registration of pre-eclampsia was improved. Overall improvements in the Medical Birth Registry of Norway from 1998 might have reduced misclassification and strengthened some of the other associations. Also, reductions in other causal factors might help to expose the underlying associations reported here. For example, smoking has become much less common, and the rates of stillbirth and neonatal mortality have steadily declined.

The exact nature of the shared factors remains unclear. The possibilities of shared pathways linking these outcomes has been called to attention by the concepts of “great obstetrical syndromes”⁶⁻⁸ or

“ischaemic placental disease.”⁹ A mother’s risk of future cardiovascular disease might also relate to these shared pathways linking the five complications and preterm birth.²⁹

Comparison with other studies

Various sensitivity analyses produced no meaningful differences in the results. Given this robustness, it might seem surprising that these observations did not emerge earlier. A few suggestions of such associations are found throughout the literature, specifically for pre-eclampsia and stillbirths. For the other outcomes we could find no comparable literature.

Pre-eclampsia is the only complication for which we have found similar findings to ours in the literature—although even here, the studies are few. Most studies investigating pre-eclampsia and subsequent preterm birth have not focused on pre-eclampsia among term births.^{14 30} A study that did (a Swedish study from 1992 to 2006) did not find an association between pre-eclampsia in a first pregnancy at term and later spontaneous preterm birth.¹⁵ However, the researchers’ different criteria for the exposure and reference groups make it difficult to compare their study with our study. We found that the associations strengthened over time (supplementary eTable 5) and the relative risk for preterm birth was still increased when restricting to a second spontaneous preterm birth (supplementary eTable 4). One study considered the reverse association with pre-eclampsia. Rasmussen et al reported that preterm birth in a first pregnancy was associated with an increased risk of term pre-eclampsia in the second pregnancy.³¹ Another Norwegian study assessed the reverse association of stillbirth in a pregnancy at term after a previous preterm birth, again with results similar to ours.³²

We have found no studies that looked at other complications at term and risk of later preterm birth. For example, a recent systematic review produced a pooled odds ratio of 2.8 (95% confidence interval 2.3 to 3.5) for preterm birth after stillbirth, but the analysis did not consider term stillbirths separately from preterm stillbirths.³³

Table 3 | Relative risk of term complications in second births after preterm birth in first pregnancy among women without specific complications in first pregnancy (both among term and preterm), Norway 1999-2015

First pregnancy	Second pregnancy (No (%) with complication/No (%) at risk)									
	Term pre-eclampsia		Term placental abruption		Term stillbirth		Term neonatal death*		Term SGA 2.5‡	
	Pre-eclampsia†	Relative risk (95% CI)	Placental abruption†	Relative risk (95% CI)	Stillbirth	Relative risk (95% CI)	Neonatal death	Relative risk (95% CI)	SGA 2.5	Relative risk (95% CI)
Term	3149/246 926 (1.3)	Reference	446/256 942 (0.2)	Reference	341/274 327 (0.1)	Reference	149/273 789 (0.05)	Reference	5467/268 324 (2.0)	Reference
All preterm	349/11 353 (3.1)	2.4 (2.2 to 2.7)	45/13 416 (0.3)	1.9 (1.4 to 2.6)	17/13 942 (0.1)	0.98 (0.6 to 1.6)	(0.07)§	1.3 (0.7 to 2.6)	551/14 336 (3.8)	1.9 (1.7 to 2.1)
20-33 weeks	99/2893 (3.4)	2.7 (2.2 to 3.3)	19/3599 (0.5)	3.0 (1.9 to 4.8)	(0.2)§	1.6 (0.8 to 3.5)	(0.2)§	4.0 (1.9 to 8.5)	206/3961 (5.2)	2.6 (2.2 to 2.9)
34-36 weeks	250/8460 (3.0)	2.3 (2.0 to 2.6)	26/9817 (0.3)	1.5 (1.03 to 2.3)	(0.1)§	0.8 (0.4 to 1.4)	(0.03)§	0.5 (0.2 to 1.7)	345/10 375 (3.3)	1.6 (1.5 to 1.8)

SGA 2.5=small for gestational age 2.5th centile.

*Study period restricted to 1999-2014 (n=258 279).

†Pregnancies ending in stillbirth (n=358) are excluded from the at risk group for the outcome of neonatal death.

‡To avoid data entry issues in the calculation of SGA centiles, four women with term pregnancies with birth weights <100 g were excluded in term SGA analyses, and eight women with preterm pregnancies and birth weights ≤ 100 g were excluded from the preterm SGA analyses.

§Cell counts ≤ 10 are suppressed to protect potentially identifiable rare outcomes.

Strengths and limitations of this study

Outcomes and exposures for this analysis rely on data from the Medical Birth Registry of Norway, with inevitable misclassification. In particular, more women are estimated to have pre-eclampsia than are recorded in the birth registry.²⁷ To the extent that women in our comparison group have unrecorded complications, our main results might be biased towards the null.

Strengths of the study include population based birth data, linking each mother with all her pregnancies. Prospectively recorded events minimise recall bias. The large dataset makes it possible to study relatively rare outcomes with precision. By restricting our analysis to first and second births, we limited the influence of selection, since 80% of women in Norway continue to a second pregnancy. At the same time, our restriction to this relatively unselected group of women makes it more difficult to extrapolate to third or later pregnancies.

Our findings are based on women in a country with universal free and accessible healthcare. The relatively homogeneous Norwegian population and its strong public support systems might limit the generalisability of these findings. Notably, although the preterm birth rate is around 6% in Norway, the corresponding rate is close to 9% in the rest of Europe and close to 10% in the United States.³⁴ In a more heterogeneous population with greater income and health disparities the shared factors resulting in poor outcomes across pregnancies would presumably include a wider array of structural and social causes, with less opportunity to observe underlying biological propensities.

Conclusions

Serious complications in pregnancy at term imply an increased risk not only of recurrence of the same outcome but also of preterm birth in a subsequent pregnancy. These findings might inform antenatal clinical care by helping to identify women at increased risk of preterm delivery. Further exploration of the causal factors underlying these shared risks might provide insight into fundamental biological mechanisms that link a broad range of pregnancy complications.

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Contributors: LGK, AJW, RS, and QEH conceived and designed the study. RS obtained access to data. LGK conducted the data analysis and drafted the initial version of the manuscript. AJW, RS, TØ, and QEH provided important insight during the data analysis. All authors contributed in the interpretation of the data and critically revised the manuscript. All authors had full access to tables and figures in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. LGK is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICME uniform disclosure form at www.icmje.org/doi_disclosure.pdf and declare: LGK reports grants from the US-Norway Fulbright Foundation for Educational Exchange, during the conduct of the study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the regional ethics committee in Norway (2015/1728), with an exemption from written informed consent.

Data sharing: No additional data available.

The lead author (LGK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: A summary of the results will be sent to the Norwegian newsletter *Fødselsnytt* published by the Norwegian Institute of Public Health, which is distributed to maternity wards and hospitals and children's ward throughout Norway.

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Web appendix: Supplemental material