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## Preterm birth

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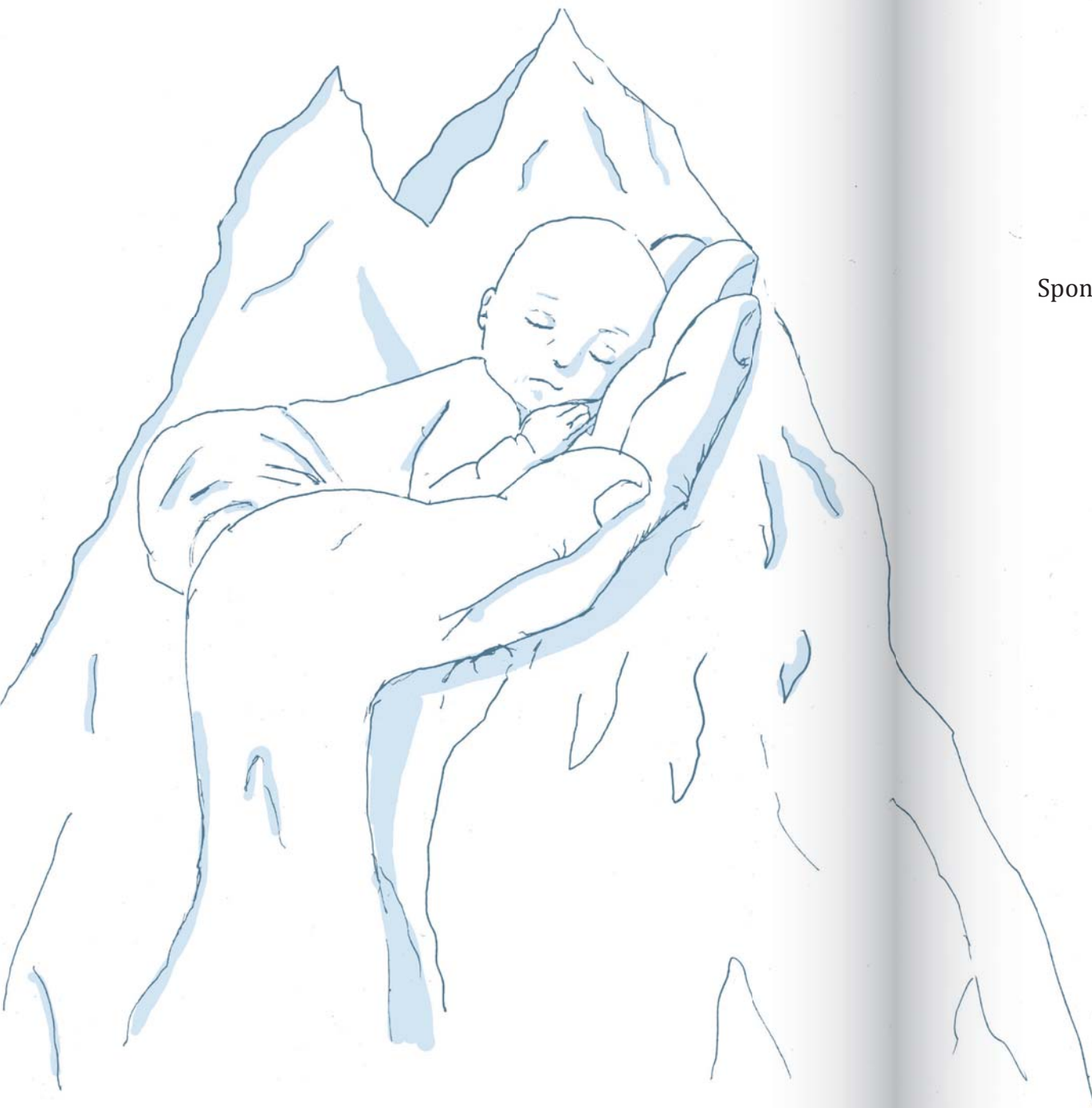
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### Spontaneous and iatrogenic preterm birth rates among unselected women in three consecutive pregnancies

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## ABSTRACT

**Objective:** To assess the risk of spontaneous PTB (sPTB) and iatrogenic PTB (iPTB) in women with three consecutive singleton pregnancies and the impact of the outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy on the (recurrent) PTB risk in the 3<sup>rd</sup> pregnancy.

**Study design:** A nationwide retrospective cohort study using the population based longitudinal linked dataset of the Netherlands. We included all nulliparous women with three consecutive singleton pregnancies ending between 22 and 44 weeks of gestation between 1999 and 2009. We excluded congenital abnormalities and stillbirths. We compared the incidence of sPTB and iPTB in the three pregnancies (<37, <34 and <30 weeks). Logistic regression analysis was performed to predict PTB in the 3<sup>rd</sup> pregnancy, adjusting for maternal age, fetal gender, socio-economic status, hypertension, interpregnancy interval, artificial reproductive technology, and small for gestational age. Analyses were also performed stratified by prior PTB subtype, gestational age and combined outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy.

**Results:** We studied 52,978 women. PTB occurred in 7.0%, 3.7% and 3.4% in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy, respectively. The outcome of the 2<sup>nd</sup> pregnancy is more predictive for PTB in the 3<sup>rd</sup> pregnancy than the outcome of the 1<sup>st</sup> pregnancy (sPTB aOR 7.3 (95% CI 6.3-8.4) and iPTB aOR 5.9 (95% CI 4.5-7.9) in 2<sup>nd</sup> pregnancy vs. sPTB aOR 3.0 (95% CI 2.6-3.4) and iPTB aOR 2.7 (95% CI 2.1-3.4) in the 1<sup>st</sup> pregnancy). In the prediction of sPTB in the 3<sup>rd</sup> pregnancy, sPTB in the 2<sup>nd</sup> pregnancy is most predictive (aOR 8.2, 95% CI 7.1-9.6) and for prediction iPTB in the 3<sup>rd</sup> pregnancy, iPTB in the 2<sup>nd</sup> pregnancy is most predictive (aOR 12.1, 95% CI 8.5-17.2).

**Conclusion:** We studied a population with three subsequent singleton deliveries within 10 years. The incidence of PTB decreased with 50% from the 1<sup>st</sup> to the 2<sup>nd</sup> pregnancy, to then stay relative stable in the 3<sup>rd</sup> pregnancy. Compared to PTB in the 1<sup>st</sup> pregnancy, PTB in the 2<sup>nd</sup> pregnancy is more predictive for the occurrence of PTB in the 3<sup>rd</sup> pregnancy.

## INTRODUCTION

Preterm birth (PTB) is the leading cause of neonatal morbidity and mortality both in well resourced and in low resourced countries. In 2010 over 10% of all children worldwide were born preterm.<sup>1</sup> PTB is defined as any birth before 37 completed weeks of gestation, but often a subdivision to express the severity of PTB is used (i.e. severe PTB <30 weeks, moderate PTB 30-34 weeks and mild PTB 34-37 weeks). This subdivision is important since increasing gestational age (GA) at birth is associated with decreasing mortality, morbidity and intensity of neonatal care, and hence decreasing costs.

PTB can be subdivided in spontaneous and iatrogenic PTB. Spontaneous PTB (sPTB) is associated with an increased risk of sPTB in a subsequent pregnancy, with increasing risk with the number of prior PTBs, earlier GA at prior delivery, and with higher risk of subsequent PTB if the immediately preceding birth was preterm.<sup>2</sup> Iatrogenic PTB (iPTB) is performed for maternal or fetal reasons, for example pre-eclampsia or intra-uterine growth restriction, respectively.

Emerging data suggests that sPTB and iPTB at least partially share a pathophysiological mechanism involving placental dysfunction or inflammation of the placenta or membranes.<sup>3-7</sup> Improper remodelling of the uterine spiral arteries in early pregnancy and subsequent decidual changes may lead to reduced placental perfusion. This can cause PTB as well as subsequent dysfunction of the maternal vascular endothelium, leading to pre-eclampsia and subsequent iatrogenic PTB. However, our understanding of recurrent sPTB risk has mainly focused on sPTB and has not taken iPTB into consideration, and vice versa.

Here, we study the incidence of spontaneous and iatrogenic PTB rates in unselected women with three subsequent singleton pregnancies both on population and individual level. We also study the risk of (recurrent) PTB in the third pregnancy in relation to GA at delivery and type of PTB in previous pregnancies.

## MATERIAL AND METHODS

For this nationwide retrospective cohort study we used data from the Perinatal Registry in the Netherlands (PRN). The PRN consists of nationwide population-based data that contain information on pregnancies, deliveries  $\geq 22$  weeks of gestation and a birth weight of  $\geq 500$  g, and readmissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2), and the neonatology

registry (LNR) of hospital admissions of newborns.<sup>8</sup> Longitudinal linkage of these databases has been described previously.<sup>9-11</sup> The PRN registry covers about 96% of all deliveries in the Netherlands. As all data were registered anonymous, separate ethical approval was not needed for this study under Dutch law. The PRN gave permission for this study (approval number 11.44).

We studied data of all women with three consecutive singleton pregnancies who gave birth between January 1, 1999, and December 31, 2009. We included women who delivered between 22-44 weeks of GA and excluded women who had any pregnancy complicated by stillbirth or congenital anomalies, leaving women with three consecutive singleton pregnancies with a live birth.

Calculation of GA was based on the women's last menstrual period and ultrasound dating. PTB was defined as delivery before 37 weeks of gestation. We made a subdivision for severity of PTB into three groups with severe PTB defined as a birth before 30 weeks of gestation, moderate PTB as a birth between 30-34 weeks and mild PTB as a birth between 34-37 weeks of gestation.

Furthermore we divided PTB in spontaneous and iatrogenic PTB, leading to a total of six subgroups. Spontaneous PTB was defined as PTB starting with a spontaneous rupture of the membranes or spontaneous contractions. Iatrogenic PTB was defined as an elective Caesarian section or induction of labour.

The overall incidences of PTB separated in the 6 subcategories are given for the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy on a population level.

Subsequently, a logistic regression analysis was performed to assess the association between pregnancy outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy and the risk of (recurrent) PTB <37 weeks in the 3<sup>rd</sup> pregnancy, both for overall PTB and separated for iatrogenic and spontaneous PTB. We defined the outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy as spontaneous or iatrogenic PTB and by the severity of PTB (i.e. <30, 30-34 and 34-37 weeks of gestation). In a multivariate analysis we adjusted for maternal age, fetal gender, artificial reproductive technology (ART), low social-economic-status (SES), hypertension, interpregnancy interval and small for gestational age (SGA).

Similar analyses were performed to assess the (recurrent) overall PTB risk <37 weeks in the 3<sup>rd</sup> pregnancy, in which the previous pregnancy outcomes were separated by GA per week for spontaneous and iatrogenic PTB in the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy. Also, the (recurrent) PTB risk in the 3<sup>rd</sup> pregnancy, based on the combined outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy (i.e. iPTB in 1<sup>st</sup> and at term in 2<sup>nd</sup>, sPTB in 1<sup>st</sup> and at term in 2<sup>nd</sup> etc) was assessed.

Finally, in a supplementary analysis, the incidence of PTB 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy on an individual level are given, conditional on the outcome of the previous pregnancies, i.e. we divided the outcome of the first pregnancy in the six subgroups and per subgroup the incidence of PTB in the second pregnancy is given divided in the six subgroups and for those subgroups again the incidence of PTB in the third pregnancy is given per subgroup. Statistical analysis was performed in SAS, version 9.3 (SAS Institute, Cary, NC, USA).

## RESULTS

After the longitudinal linkage procedure, we identified 61,664 women who had three deliveries between 1999-2009. We excluded women with multiple pregnancies (n = 1,907), women who delivered at a gestational age before 22.0 weeks or beyond 44.0 weeks onwards (n=25), women who suffered antenatal deaths (n= 2,007), or fetal congenital anomalies (n=4,747), leaving 52,978 women with three sequential singleton deliveries between 22 and 44 weeks of gestation for further analysis.

### *Baseline characteristics*

The baseline characteristics of our cohort (n=52,978) are shown in Table 1. The baseline characteristics are shown for the total cohort and separated by outcome of the 3<sup>rd</sup> pregnancy, i.e. separated in a term birth, iPTB or sPTB in the 3<sup>rd</sup> pregnancy. Furthermore the characteristics, when applicable, are also shown for each pregnancy, i.e. mean age at delivery in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy.

**Table 1:** Baseline characteristics of the total cohort (n = 52,978) and separated by the outcome of the third pregnancy

Characteristics	In which pregnancy	Total cohort		Separated by outcome of third pregnancy	
		Total Cohort (n = 52,978)	No PTB (n = 51,193)	iPTB (n = 448)	sPTB (n = 1,337)
Mean maternal age at delivery (yrs.±SD)	1 <sup>st</sup>	27.5 ± 4.0	27.5 ± 4.0	27.3 ± 4.3	26.4 ± 4.5
	2 <sup>nd</sup>	29.7 ± 3.9	29.7 ± 3.9	29.6 ± 4.2	28.7 ± 4.4
	3 <sup>rd</sup>	32.4 ± 3.9	32.5 ± 3.9	32.5 ± 4.2	31.4 ± 4.6
Non-white European ethnicity n (%)	3 <sup>rd</sup>	7,342 (13.9%)	6,998 (13.7%)	76 (17.0%)	268 (20.0%)
	1 <sup>st</sup>	11,787 (22.3%)	11,294 (22.0%)	123 (27.5%)	338 (29.0%)
	2 <sup>nd</sup>	11,203 (21.2%)	10,762 (21.0%)	117 (26.1%)	379 (28.4%)
	3 <sup>rd</sup>	10,721 (20.3%)	10,298 (20.1%)	112 (25.0%)	366 (27.3%)
Conception by ART n (%)	1 <sup>st</sup>	1,307 (2.5%)	1,259 (2.5%)	17 (3.8%)	37 (2.8%)
	2 <sup>nd</sup>	693 (1.3%)	658 (1.3%)	10 (2.2%)	26 (1.9%)
	3 <sup>rd</sup>	283 (0.5%)	263 (0.5%)	7 (1.6%)	13 (1.0%)
Male Fetus n (%)	1 <sup>st</sup>	27,528 (52.2%)	26,692 (52.1%)	253 (56.5%)	698 (52.2%)
	2 <sup>nd</sup>	27,362 (51.9%)	26,509 (51.8%)	253 (56.5%)	717 (53.6%)
	3 <sup>rd</sup>	26,845 (50.9%)	25,955 (50.7%)	234 (52.2%)	771 (57.7%)
Mean GA at delivery (w+d ± SD)	1 <sup>st</sup>	39 + 2 ± 2.2	39+2 ±2.2	37+5 ± 3.6	37+4 ± 3.5
	2 <sup>nd</sup>	39 + 3 ± 1.8	39+3 ± 1.7	37+6 ± 3.1	37+3 ± 3.3
	3 <sup>rd</sup>	39 + 3 ± 1.6	39+4 ± 1.2	33+5 ± 3.2	34+3 ± 2.7
Birth weight (g, ±SD)	1 <sup>st</sup>	3385 ± 600	3400 ± 588	3012 ± 848	2957 ±768
	2 <sup>nd</sup>	3585 ± 555	3602 ± 540	3162 ± 788	3073 ±723
	3 <sup>rd</sup>	3626 ± 544	3667 ± 491	2252 ± 793	2530 ± 636
Hypertensive disorder n (%)	1 <sup>st</sup>	6,102 (11.6%)	5,828 (11.4%)	122 (27.2%)	178 (13.3%)
	2 <sup>nd</sup>	2,798 (5.3%)	2,629 (5.1%)	92 (20.5%)	93 (7.0%)
	3 <sup>rd</sup>	2,621 (5.0%)	2,379 (4.7%)	141 (31.5%)	103 (7.7%)
Mean pregnancy interval (months ± SD)	1 → 2	17.4 ± 11.3	17.4 ± 11.3	18.8 ± 12.9	19.4 ± 13.2
	2 → 3	23.8 ± 14.9	23.7 ± 14.8	26.4 ± 17.5	24.2 ± 16.8

PTB = preterm birth, iPTB = iatrogenic preterm birth, sPTB = spontaneous preterm birth, SES = socio-economic status, ART = artificial reproductive technology, GA = gestational age.

### Incidence of PTB

Table 2 shows the incidence of PTB in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy, split for spontaneous or iatrogenic PTB and severity of PTB (<30, 30-34 and 34-37 weeks of GA). Amongst the cohort of 52,978 women, 3,714 (7.0%) suffered PTB <37 weeks in the 1<sup>st</sup> pregnancy, 1,949 (3.7%) in the 2<sup>nd</sup> and 1,785 (3.4%) in the 3<sup>rd</sup> pregnancy. Among the 7.0% of women who delivered preterm in their 1<sup>st</sup> pregnancy, 5.5% suffered sPTB, and 1.5% iPTB.

Spontaneous PTB occurred in 3.0% and iPTB in 0.6% of the 2<sup>nd</sup> pregnancies and in the 3<sup>rd</sup> in 2.5% and 0.8%, respectively. The incidence of sPTB decreased with nearly 50% from the 1<sup>st</sup> to the 2<sup>nd</sup> pregnancy, independent of the severity, to then stay relative stable in the 3<sup>rd</sup> pregnancy compared to the 2<sup>nd</sup> pregnancy (Table 2). The incidence of iPTB also decreased by 50% or more from the 1<sup>st</sup> to the 2<sup>nd</sup> pregnancy, to then stay relative stable, expect from a slight increase from 0.4% in the 2<sup>nd</sup> to 0.6% in the 3<sup>rd</sup> for iPTB between 34-37weeks (Table 2). There were 193 (0.4%) women suffered a PTB in their 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy and 1,123 (2.1%) women who suffered PTB after a term birth in both the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy.

**Table 2:** The incidence of spontaneous and iatrogenic preterm birth in the first, second and third pregnancy by severity of preterm birth.

	GA (weeks)	First pregnancy		Second pregnancy		Third pregnancy	
		n	%	n	%	n	%
Spontaneous PTB	<30	327	0.6%	182	0.3%	77	0.1%
	30-33.6	416	0.8%	208	0.4%	199	0.3%
	34-36.6	2,183	4.1%	1,218	2.3%	1,061	2.0%
	<b>&lt;37</b>	<b>2,926</b>	<b>5.5%</b>	<b>1,608</b>	<b>3.0%</b>	<b>1,337</b>	<b>2.5%</b>
Iatrogenic PTB	<30	169	0.3%	72	0.1%	50	0.1%
	30-33.6	222	0.4%	83	0.2%	84	0.2%
	34-36.6	397	0.7%	186	0.4%	314	0.6%
	<b>&lt;37</b>	<b>788</b>	<b>1.5%</b>	<b>341</b>	<b>0.6%</b>	<b>448</b>	<b>0.8%</b>
Total PTB	<b>&lt;37</b>	<b>3,714</b>	<b>7.0%</b>	<b>1,949</b>	<b>3.7%</b>	<b>1,785</b>	<b>3.4%</b>
No PTB	≥37	49,264	93.0%	51,029	96.3%	51,193	96.6%
Total	All	52,978	100%	52,978	100%	52,978	100%

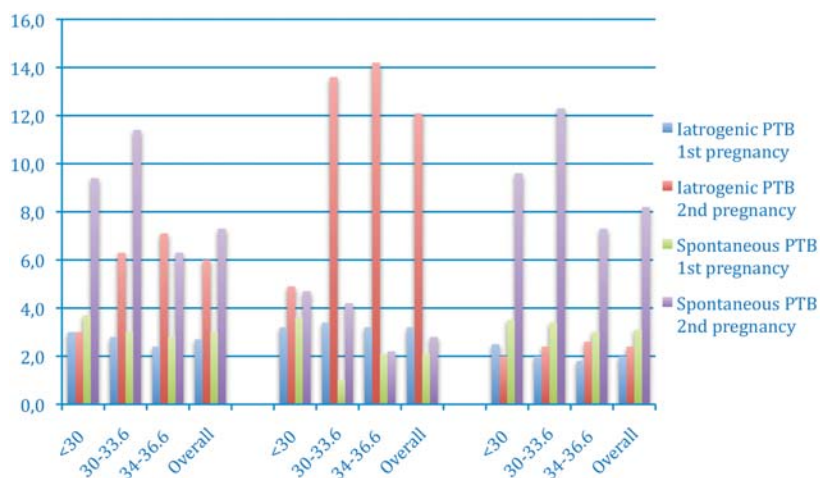
PTB= preterm birth, GA = gestational age.

### Predictors for (Recurrent) PTB in the 3<sup>rd</sup> pregnancy

The results of the logistic regression analysis of (recurrent) PTB <37 weeks in the 3<sup>rd</sup> pregnancy, overall and separated by type of PTB (i.e. spontaneous or iatrogenic PTB) are shown in Figure 1 and supplementary File 1. The aORs varied from 2.7

(95% CI 2.1-3.5) for iPTB in the 1<sup>st</sup> pregnancy to 7.3 (95%CI 6.3-8.4) for sPTB in the 2<sup>nd</sup> pregnancy. The outcome of the 2<sup>nd</sup> pregnancy was more predictive for (recurrent) overall PTB in the 3<sup>rd</sup> pregnancy than the outcome of the 1<sup>st</sup> pregnancy (sPTB aOR7.3 (95%CI 6.3-8.4) and iPTB aOR 5.9 (95% CI 4.5-7.9) in 2<sup>nd</sup> pregnancy vs. sPTB aOR 3.0 (95% CI 2.6-3.4) and iPTB aOR 2.7 (95% CI 2.1-3.4) in the 1<sup>st</sup> pregnancy). A similar pattern is seen for the several subgroups of severity of PTB with an exception of PTB <30 weeks where sPTB in the 2<sup>nd</sup> pregnancy is most predictive, followed by sPTB in the 1<sup>st</sup> pregnancy (aOR3.7), however due to smaller numbers sometimes with overlapping 95% CIs.

The best predictor for iPTB in the 3<sup>rd</sup> pregnancy was iPTB in the 2<sup>nd</sup> pregnancy (aOR 12.1, 95% CI 8.5-17.2). The best predictor for sPTB in the 3<sup>rd</sup> pregnancy was sPTB in the 2<sup>nd</sup> pregnancy (aOR 8.3, 95% CI 7.1-9.6).

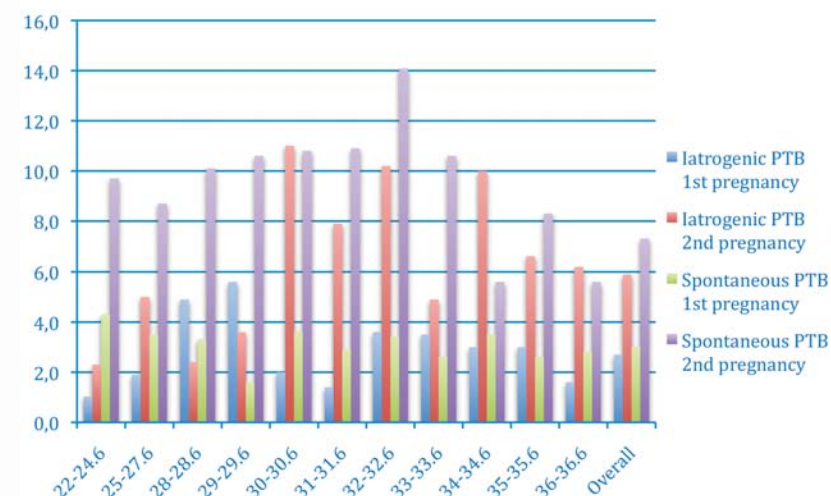


**Figure 1:** Logistic regression analysis of preterm birth <37 weeks in the third pregnancy overall (left) and separated by iatrogenic (middle) and spontaneous preterm birth (right) and separated by gestational age at birth and type of preterm birth in first and second pregnancy. PTB = preterm birth

#### Predictors for (Recurrent) PTB in the 3<sup>rd</sup> pregnancy by GA

The results of the logistic regression analysis of (recurrent) PTB <37 weeks in the 3<sup>rd</sup> pregnancy as predicted by duration of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy are shown in figure 2. When divided by GA per week, sPTB and iPTB in the 2<sup>nd</sup> pregnancy are most predictive for the (recurrent) risk of PTB in the 3<sup>rd</sup> pregnancy, with an

exception from 28-30 weeks where iPTB in the 1<sup>st</sup> pregnancy seems the second best predictor and 22-25 weeks where sPTB in the 1<sup>st</sup> pregnancy is the second best predictor after sPTB in the 2<sup>nd</sup> pregnancy.



**Figure 2:** Logistic regression analysis of preterm birth <37 weeks in the 3<sup>rd</sup> pregnancy, separated by gestational age at birth and type of preterm birth in the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy. PTB = preterm birth

#### Combined outcome of 1st and 2nd pregnancy recurrent PTB risk in the 3<sup>rd</sup> pregnancy

The results of a logistic regression analysis of PTB <37 weeks in the 3<sup>rd</sup> pregnancy separated by the combination of outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy are shown in Table 3. The risk of (recurrent) PTB by combined outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy ranges from a term birth in the 2<sup>nd</sup> pregnancy, preceded by either iPTB or sPTB (aOR3.1) to sPTB in the 1<sup>st</sup> pregnancy followed by iPTB in the 2<sup>nd</sup> pregnancy (aOR24.2).

In accordance with our previous results, the outcome of the 2<sup>nd</sup> pregnancy is more predictive for (recurrent) PTB in the 3<sup>rd</sup> pregnancy than the 1<sup>st</sup> pregnancy with the lowest aORs for iPTB or sPTB in the 1<sup>st</sup> pregnancy followed by a term birth in the 2<sup>nd</sup> pregnancy (aOR3.1 (95% CI 2.4-4.1) and aOR3.1, (95% CI 2.6-3.6) respectively). In ascending order in the prediction of recurrent PTB in the 3<sup>rd</sup> pregnancy on combined outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy, these two are followed by a term birth in the 1<sup>st</sup> pregnancy and either iPTB (aOR5.8, 95% CI 4.1-8.2) or sPTB (aOR8.0,

95% CI 6.7-9.5) in the 2<sup>nd</sup> pregnancy. Then followed by iPTB in the 1<sup>st</sup> pregnancy with either a sPTB (aOR10.5, 95% CI 5.2-21.0) or iPTB (aOR13.9, 95% CI 7.1-27.3) in the 2<sup>nd</sup> pregnancy. And the highest recurrent PTB risk in the 3<sup>rd</sup> pregnancy after sPTB in the 1<sup>st</sup> pregnancy followed by either sPTB (aOR20.3, 95% CI 16.5-25.0) or iPTB (aOR24.2, 95% CI 12.9-45.3) in the 2<sup>nd</sup> pregnancy. These figures point at a higher impact of sPTB compared to iPTB. However with a history of PTB in the 1<sup>st</sup> pregnancy (either sPTB or iPTB), recurrent iPTB in the 2<sup>nd</sup> pregnancy has more impact on the recurrent risk of PTB in the 3<sup>rd</sup> pregnancy than sPTB.

**Table 3:** Logistic regression analysis of preterm birth <37 weeks in the third pregnancy separated by the combination of outcome of the first and second pregnancy.

First pregnancy	Second pregnancy	aOR (95%CI)	N (%)
Iatrogenic PTB	At term	3.1 (2.4-4.1)	65 (9.3%)
Spontaneous PTB	At term	3.1 (2.6-3.6)	171 (7.0%)
At term	Iatrogenic PTB	5.8 (4.1-8.2)	42 (16.2%)
At term	Spontaneous PTB	8.0 (6.7-9.5)	191 (17.2%)
Iatrogenic PTB	Spontaneous PTB	10.5 (5.2-21.0)	11 (23.9%)
Iatrogenic PTB	Iatrogenic PTB	13.9 (7.1-27.3)	15 (38.5%)
Spontaneous PTB	Spontaneous PTB	20.3 (16.5-25.0)	150 (33.2%)
Spontaneous PTB	Iatrogenic PTB	24.2 (12.9-45.3)	17 (39.5%)
At term	At term	REF	1,123 (2.3%)

PTB= preterm birth, aOR = adjusted odds ratio, CI= confidence interval.

\* Adjusted for: SGA in first and second pregnancy, ART in first and second pregnancy, fetal gender in first and second pregnancy, maternal age, low SES, hypertension in first and second pregnancy and interpregnancy interval.

#### Recurrent PTB on individual level

Supplementary file 3 shows the outcome of the 3<sup>rd</sup> pregnancy, conditional on the outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy on an individual level. Of the 327 women with sPTB <30weeks in the 1<sup>st</sup> pregnancy, 71% delivered at term in the 2<sup>nd</sup> pregnancy, compared to 75% and 86% of the women with sPTB 30-34 and 34-37 weeks in their 1<sup>st</sup> pregnancy, respectively. Overall there was a trend of a higher recurrent sPTB risk after more severe sPTB. Furthermore, the main type of recurrent PTB is sPTB after sPTB.

Of the women delivering their baby preterm after an iPTB in the 1<sup>st</sup> pregnancy, 85-90% delivered their baby at term in the 2<sup>nd</sup> pregnancy, independent of the severity of iPTB in the 1<sup>st</sup> pregnancy.

Overall the table shows a lower recurrent risk of iPTB (4-6%) compared to sPTB (12-27%), however after iPTB in both the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy, this risk multiplies by 5-10 (30-44%). After a term birth in the 1<sup>st</sup> pregnancy, 2.8% of the women delivered preterm in the 2<sup>nd</sup> pregnancy, of which 81% was a sPTB (1,110) vs. 19% iPTB (259). Of the 1,110 women suffering sPTB the majority (76.3%) was between 34-37 weeks.

Overall there is a pattern that the type of PTB in the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy is the main type of PTB in the 3<sup>rd</sup> pregnancy, i.e. sPTB in the 1<sup>st</sup>, if recurrent, is more often again sPTB in the 2<sup>nd</sup> and 3<sup>rd</sup>, then iPTB and vice versa.

## COMMENTS

### Main findings

In this large cohort study reporting on women in three consecutive pregnancies, PTB occurred in 7.0%, 3.7% and 3.4% in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy, respectively. The outcome of the 2<sup>nd</sup> pregnancy is more predictive for (recurrent) PTB in the 3<sup>rd</sup> pregnancy than the outcome of the 1<sup>st</sup> pregnancy (sPTB aOR7.3 (95% CI 6.3-8.4) and iPTB aOR 5.9 (95% CI 4.5-7.9) in 2<sup>nd</sup> pregnancy vs. sPTB aOR 3.0 (95% CI 2.6-3.4) and iPTB aOR 2.7 (95% CI 2.1-3.4) in the 1<sup>st</sup> pregnancy). In the prediction of sPTB in the 3<sup>rd</sup> pregnancy, sPTB in the 2<sup>nd</sup> pregnancy is most predictive (aOR8.2, 95% CI 7.1-9.6) and for prediction iPTB in the 3<sup>rd</sup> pregnancy, iPTB in the 2<sup>nd</sup> pregnancy is most predictive (aOR12.1, 95% CI 8.5-17.2). The risk of (recurrent) PTB by combined outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy ranges from a term birth in the 2<sup>nd</sup> pregnancy, preceded by either iatrogenic or sPTB (aOR3.1) to sPTB in the 1<sup>st</sup> pregnancy followed by iatrogenic PTB in the 2<sup>nd</sup> pregnancy (aOR24.2).

### Strength and limitations

A strength of our study is that it is based on a large population-based national data system in the Netherlands. The 4% missing birth data are due to nonreporting general practitioners and midwives. Pregnancies with PTB are unlikely to have been missed because of nonreporting midwives and general practitioners, since PTB is an indication for referral to an obstetrician and delivery in obstetric care. We used a probabilistic linkage method to link the first and subsequent pregnancy. Nonlinkage was possible due to missing values of linkage variables and the small number of linkage variables. Zip code of the mother was one linkage variable, but in the event of women moving address over time, or if the date of the last child was not recorded in the national registry, most woman could be linked based on the

two other linkage variables. A more common reason for nonlinkage was women having their first birth before 1999 or their third birth after 2009. Since in this case the reason for nonlinkage was not related to the primary outcome measures, it is not likely that nonlinked pregnancies would have influenced our results to a significant degree.

Another strength of our analysis is that we studied women with three consecutive pregnancies, not only from a population perspective, but also on an individual level. This gave us the opportunity to compare the impact of the outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy on (recurrent) PTB in the 3<sup>rd</sup> pregnancy. Finally we separated our findings for sPTB and (recurrent) iPTB instead of focussing on either one. This separation, together with several severities of PTB in three pregnancies provided new insights in the (recurrent) risk of PTB and the option for more tailor made counselling for patients.

Our study also has limitations. Since our study is based on data of the PRN, only data provided in the system could be taken in account. For example, deliveries <22 weeks are not registered. Therefore a miscarriage or immature delivery <22 weeks in between two pregnancies with a delivery >22 weeks cannot be taken in account. As we did not have information on the identity of male partners, we could not control for a different identity of the partner in subsequent pregnancies. Also, preventive treatments were not registered. Since women with a previous preterm birth < 35 weeks and women with two previous preterm births <37 weeks have an indication for obstetric care in their subsequent pregnancy, these women are more likely to have received interventions like progesterone, cerclage or pessary, as well as screening for short cervical length or infections. We think however that those treatments at most partially explain the large differences in incidence that we observed.

In addition, we only included women with three consecutive pregnancies, which is only 15% of the population in the longitudinal dataset with two consecutive pregnancies. These women might differ in sociodemographic and medical characteristics from women with two births.

### Interpretation

It is well described that a history of PTB increases the risk of (recurrent) PTB. Most studies focus on the recurrent risk from the 1<sup>st</sup> to the 2<sup>nd</sup> pregnancy and do not take 3 pregnancies in account. However, the NICHD Consecutive Pregnancies Study studied three consecutive pregnancies and found a higher recurrent PTB risk after PTB in the most recent pregnancy (i.e., the 2<sup>nd</sup> pregnancy) than PTB in the 1<sup>st</sup> pregnancy, similar to our results.<sup>7</sup>

Studies on PTB tend to focus on either sPTB or iPTB, while we studied both types of PTB and evaluated the impact of each and the increased risk of each type of PTB on subsequent births. The previously mentioned NICHD Consecutive Pregnancies Study also studied recurrent PTB by subtype, however only from the 1<sup>st</sup> to the 2<sup>nd</sup> pregnancy and not from the 2<sup>nd</sup> to the 3<sup>rd</sup>. They found that women who had an iPTB in the 1<sup>st</sup> pregnancy were not only at higher risk of recurrent iPTB in their subsequent pregnancy but also carry an increased risk of sPTB. Ananth et al.<sup>8</sup> also studied recurrent PTB stratified by type of PTB from the 1<sup>st</sup> to the 2<sup>nd</sup> pregnancy and found similar results after iPTB, but also an increased risk of both sPTB and iPTB after sPTB in the 1<sup>st</sup> pregnancy (aOR 1.7, 95% CI 1.5-1.9), where in the study of the NICHD this did not reach statistical significant difference (aRR 1.6, 95% CI 0.98-2.7). We found an increase risk of PTB in the 3<sup>rd</sup> pregnancy after both sPTB and iPTB in the 1<sup>st</sup> or 2<sup>nd</sup> pregnancy varying from aOR 2.7 (95% CI 2.1-3.5) to 7.3 (95% CI 6.3-8.4). When separated for iPTB in the 3<sup>rd</sup> pregnancy this increased risk persisted, ranging from aOR 2.1 (95% CI 1.6-2.9) for sPTB in the 1<sup>st</sup> pregnancy to 12.1 (95% CI 8.5-17.2) for iPTB in the 2<sup>nd</sup> pregnancy. A similar pattern is seen when stratified for sPTB in the 3<sup>rd</sup> pregnancy, however ranging from 2.0 (95% CI 1.5-2.9) for iPTB in the 1<sup>st</sup> pregnancy to 8.2 (95% CI 7.1-9.6) for sPTB in the 2<sup>nd</sup> pregnancy. The NICHD also studied the risk of PTB in the 3<sup>rd</sup> pregnancy on combined outcome of the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy, however not separated by subtype of PTB. They found an increased risk of PTB ranging from aRR3.5 (95% CI 2.9-4.3) for PTB in 1<sup>st</sup> and term birth in 2<sup>nd</sup> pregnancy, to 10.6 (95% CI 9.0-12.3) for PTB both in the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy. In our analysis we found similar figures for PTB in the 3<sup>rd</sup> pregnancy after PTB in the 1<sup>st</sup> pregnancy followed by a term birth in the 2<sup>nd</sup> pregnancy (aOR3.1, 95% CI 2.4-4.1). The risk of PTB in both the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy varied from iPTB followed by sPTB (aOR10.5, 95% CI5.2-21.0) to sPTB followed by iPTB (aOR24.2, 95% CI 12.9-45.3).

The fact that in 2<sup>nd</sup> and high order pregnancies the prevalence of both sPTB and iPTB was so much lower has also consequences for our thinking about the mechanisms of both sPTB as well as hypertensive pregnancy complications. While this phenomenon is well known for preeclampsia, it is rather new for sPTB. If we would understand the mechanisms leading to PTB that are different in the 1<sup>st</sup> and in the subsequent pregnancies, this could guide preventive treatments. Also, the fact that in a single woman the 2<sup>nd</sup> pregnancy is much more predictive for PTB in the 3<sup>rd</sup> pregnancy implicates that the mechanism leading to PTB was different in the 2<sup>nd</sup> as compared to the 1<sup>st</sup> pregnancy. Immunological causes are more likely to have played a role in PTB in the 1<sup>st</sup> pregnancy as compared to subsequent



pregnancies. This could potentially have consequences for the effectiveness of treatments in different categories of high risk women.

Since we studied the (recurrent) risk of PTB in the 3<sup>rd</sup> pregnancy, separated by severity and type of PTB of previous pregnancy outcomes, our results can be used for counseling patients with a history of PTB who are contemplating a 2<sup>nd</sup> or 3<sup>rd</sup> pregnancy. Preterm delivery remains the leading cause of neonatal morbidity and mortality in the Western world, which means that our data could be used for tailored made counseling for mothers who have had prior PTB and consider another pregnancy.

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## SUPPLEMENTARY FILES

**Supplementary file I:** Logistic regression analysis of preterm birth <37 weeks in the third pregnancy overall and separated by iatrogenic and spontaneous preterm birth and separated by gestational age at birth and type of preterm birth in first and second pregnancy.

Third pregnancy							
Predictors:	GA (weeks)	PTB <37 weeks aOR*	95% CI	iPTB < 37 weeks aOR*	95% CI	sPTB < 37 weeks aOR*	95% CI
1st pregnancy	<30	3.0	1.9-4.9	3.2	1.5-6.7	2.5	1.4-4.7
iatrogenic PTB	30-33.6	2.8	1.8-4.3	3.4	1.8-6.3	2.0	1.1-3.7
	34-36.6	2.4	1.7-3.5	3.2	1.9-5.4	1.8	1.1-2.9
	<b>Overall</b>	<b>2.7</b>	<b>2.1-3.5</b>	<b>3.2</b>	<b>2.2-4.7</b>	<b>2.0</b>	<b>1.5-2.9</b>
1st pregnancy	<30	3.7	2.6-5.1	3.6	1.9-6.7	3.5	2.4-5.0
spontaneous PTB	30-33.6	3.0	2.2-4.1	1.0	0.4-2.9	3.4	2.5-4.7
	34-36.6	2.8	2.4-3.3	2.1	1.5-3.0	3.0	2.5-3.6
	<b>Overall</b>	<b>3.0</b>	<b>2.6-3.4</b>	<b>2.1</b>	<b>1.6-2.9</b>	<b>3.1</b>	<b>2.7-3.6</b>
1st pregnancy	≥37	Ref	Ref	Ref	Ref	Ref	Ref
2nd pregnancy	<30	3.0	1.4-6.4	4.9	1.6-14.6	2.0	0.7-5.6
iatrogenic PTB	30-33.6	6.3	3.7-10.7	13.6	7.1-25.7	2.4	1.0-5.6
	34-36.6	7.1	5.0-10.2	14.2	9.2-22.1	2.6	1.5-4.5
	<b>Overall</b>	<b>6.0</b>	<b>4.5-7.9</b>	<b>12.1</b>	<b>8.5-17.2</b>	<b>2.4</b>	<b>1.6-3.7</b>
2nd pregnancy	<30	9.4	6.6-13.3	4.7	2.1-10.4	9.6	6.6-14.0
spontaneous PTB	30-33.6	11.4	8.3-15.6	4.2	2.0-8.9	12.3	8.8-17.1
	34-36.6	6.3	5.4-7.4	2.2	1.4-3.4	7.3	6.2-8.7
	<b>Overall</b>	<b>7.3</b>	<b>6.3-8.4</b>	<b>2.8</b>	<b>1.9-3.9</b>	<b>8.2</b>	<b>7.1-9.6</b>
2nd pregnancy	≥37	Ref	Ref	Ref	Ref	Ref	Ref

PTB= preterm birth, iPTB = iatrogenic preterm birth, sPTB = spontaneous preterm birth, GA = gestational age, aOR = adjusted odds ratio, CI= confidence interval.

\* Adjusted for: SGA in first and second pregnancy, ART in first and second pregnancy, fetal gender in first and second pregnancy, maternal age, low SES, hypertension in first and second pregnancy and interpregnancy interval.

**Supplementary file II:** Logistic regression analysis of preterm birth <37 weeks in the third pregnancy, separated by gestational age at birth and type of preterm birth in the first and second pregnancy

Predictors:	GA (weeks)	First pregnancy (aOR*)	Second pregnancy (aOR*)
Iatrogenic PTB	22-24.6	1.0	2.3
	25-27.6	1.9	5.0
	28-28.6	4.9	2.4
	29-29.6	5.6	3.6
	30-30.6	2.0	11.0
	31-31.6	1.4	7.9
	32-32.6	3.6	10.2
	33-33.6	3.5	4.9
	34-34.6	3.0	10.0
	35-35.6	3.0	6.6
	36-36.6	1.6	6.2
	<b>Overall</b>	<b>2.7</b>	<b>5.9</b>
	Spontaneous PTB	22-24.6	4.3
25-27.6		3.5	8.7
28-28.6		3.3	10.1
29-29.6		1.6	10.6
30-30.6		3.6	10.8
31-31.6		2.9	10.9
32-32.6		3.4	14.1
33-33.6		2.6	10.6
34-34.6		3.5	5.6
35-35.6		2.6	8.3
36-36.6		2.8	5.6
<b>Overall</b>		<b>3.0</b>	<b>7.3</b>
At term		REF	1.0

PTB= preterm birth, GA = gestational age, aOR = adjusted odds ratio.

\* Adjusted for: SGA in first and second pregnancy, ART in first and second pregnancy, fetal gender in first and second pregnancy, maternal age, low SES, hypertension in first and second pregnancy and interpregnancy interval

**Supplementary file III:** Incidence of spontaneous and iatrogenic preterm birth by severity of preterm birth in the third pregnancy, conditional on the outcome of the first and second pregnancy on an individual level.

First pregnancy	Second pregnancy						Third pregnancy								
	n	Outcome	GA	n	Spontaneous			Iatrogenic			PTB Total	No PTB Total			
					<30	30-34	34-37	<30	30-34	34-37					
Spontaneous PTB <30weeks	327	Spontaneous	<30	23	1	1	7	9	0	1	2	3	12	11	
			30-33.6	20	2	1	4	7	0	0	2	2	9	11	
			34-36.6	44	0	0	12	12	0	0	1	1	13	31	
			<37	87	3	2	23	28	0	1	5	6	34	53	
			iatrogenic		1	1	0	1	0	0	0	0	1	0	
			30-33.6	3	0	1	0	1	0	0	0	0	1	2	
			34-36.6	3	0	0	1	1	0	0	0	0	1	2	
			<37	7	1	1	1	3	0	0	0	0	3	4	
			No PTB	233	1	2	11	14	0	1	5	6	20	213	
			Spontaneous PTB	416	<30	7	1	1	3	0	0	1	1	4	3
30-34weeks	327	Spontaneous	30-33.6	18	0	2	7	9	0	0	0	0	9	9	
			34-36.6	73	2	3	12	17	0	0	1	1	18	55	
			<37	98	3	6	20	29	0	0	2	2	31	67	
			iatrogenic		1	0	0	0	0	0	0	0	0	1	
			30-33.6	0	0	0	0	0	0	0	0	0	0	0	
			34-36.6	2	0	0	0	0	0	0	0	0	0	2	
			<37	3	0	0	0	0	0	0	0	0	0	3	
			No PTB	315	1	3	19	23	0	1	1	2	25	290	
			Spontaneous PTB	2,183	<30	12	1	0	3	4	0	0	0	4	8
			34-37weeks	327	Spontaneous	30-33.6	36	1	3	8	12	1	1	3	5
34-36.6	219	1				15	44	60	0	2	2	4	64	155	
<37	267	3				18	55	76	1	3	5	9	85	182	
iatrogenic		3				0	0	1	1	0	0	1	2	1	
30-33.6	11	0				0	0	0	0	2	1	3	3	8	
34-36.6	19	0				0	1	1	0	1	7	8	9	10	
<37	33	0				0	2	2	0	3	9	12	14	19	
No PTB	1,883	5				17	83	105	2	4	15	21	126	1,757	

**Supplementary file III:** Continued.

First pregnancy	Second pregnancy						Third pregnancy								
	n	Outcome	GA	n	Spontaneous			Iatrogenic			PTB Total	No PTB Total			
					<30	30-34	34-37	<30	30-34	34-37					
Iatrogenic PTB <30weeks	169	Spontaneous	<30	1	0	0	0	0	0	0	0	0	0	1	
			30-33.6	4	0	0	2	2	0	0	0	2	2		
			34-36.6	11	0	0	2	2	0	0	0	2	9		
			<37	16	0	0	4	4	0	0	0	4	12		
			iatrogenic		2	0	0	0	0	0	0	0	2		
			30-33.6	3	0	0	0	0	0	2	2	2	1		
			34-36.6	5	0	0	0	0	0	1	1	1	4		
			<37	10	0	0	0	0	0	3	3	3	7		
			No PTB	143	1	2	6	9	1	1	5	7	16	127	
			Iatrogenic PTB	222	<30	1	0	0	0	0	0	0	0	0	1
30-34weeks	169	Spontaneous	30-33.6	0	0	0	0	0	0	0	0	0	0		
			34-36.6	7	0	0	0	0	0	0	0	0	7		
			<37	8	0	0	0	0	0	0	0	0	8		
			iatrogenic		0	0	0	0	0	0	0	0	0		
			30-33.6	4	0	0	0	0	0	1	1	2	2		
			34-36.6	8	0	0	1	1	0	1	1	2	3		
			<37	13	0	0	1	1	0	2	2	4	5		
			No PTB	201	0	3	8	11	3	0	7	10	21	180	
			Iatrogenic PTB	397	<30	1	0	0	0	0	0	0	0	0	1
			34-37weeks	169	Spontaneous	30-33.6	4	0	1	2	3	0	0	0	3
34-36.6	17	0				0	3	3	0	0	1	4	13		
<37	22	0				1	5	6	0	0	1	7	15		
iatrogenic		2				0	0	0	0	0	0	0	2		
30-33.6	3	0				0	0	0	0	0	1	1	2		
34-36.6	11	0				0	0	0	1	2	3	6	5		
<37	16	0				0	0	0	1	2	4	7	9		
No PTB	359	1				1	13	15	2	2	9	13	28	331	

## Supplementary file III: Continued.

First pregnancy Outcome	Second pregnancy		Third pregnancy				PTB		No PTB ≥37					
	n	Outcome	GA	n	<30	30-34	34-37	Total		Total				
No PTB >37 weeks	49,264	Spontaneous	<30	137	7	7	13	27	2	1	0	3	30	107
			30-33.6	126	3	9	13	25	0	1	0	1	26	100
			34-36.6	847	3	17	98	118	2	2	13	17	135	712
			<37	1,110	13	33	124	170	4	4	13	21	191	919
		iatrogenic	<30	62	0	0	2	2	1	0	2	3	5	57
			30-33.6	59	0	1	4	5	0	2	3	5	10	49
			34-36.6	138	0	2	9	11	0	6	10	16	27	111
			<37	259	0	3	15	18	1	8	15	24	42	217
		No PTB	≥37	47,895	45	107	671	823	35	52	213	300	1,123	46,772
Total	52,978				77	199	1,061	1,337	50	84	314	448	1,785	51,190

PTB= preterm birth, GA = gestational age.