Preterm birth

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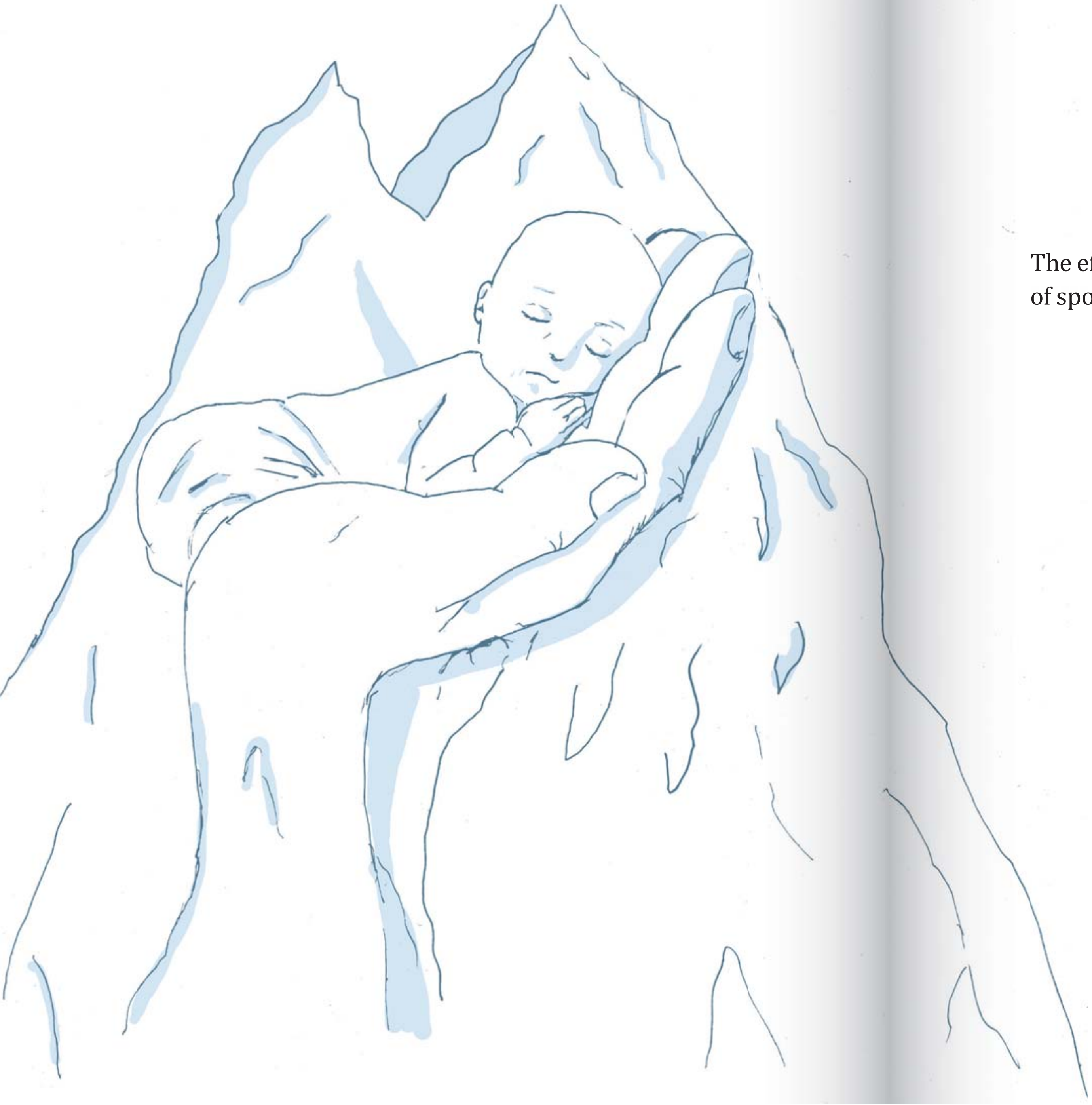

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The effect of interpregnancy interval on the recurrence rate of spontaneous preterm birth: a retrospective cohort study

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ABSTRACT

Objective: We assessed, in women with previous spontaneous preterm birth, what the effect was of interpregnancy interval on the preterm birth rate.
Design: Retrospective cohort study.
Setting: A nationwide longitudinal dataset of the National Perinatal Registry The Netherlands.
Population: Women with three sequential singleton pregnancies between 1999-2009 and a spontaneous preterm birth <37 weeks in the first pregnancy.
Methods: We evaluated the impact of interpregnancy interval on the course of the next pregnancies. Antenatal death and/or congenital abnormalities were excluded. Conventional and conditional logistic regression analysis were applied. We adjusted for maternal age, ethnicity, socioeconomic status, artificial reproductive techniques and year of birth.
Main outcome measures: Outcomes studied were preterm birth <37 weeks, <32 weeks, low birth weight <2500 grams and small for gestational age <10th percentile.
Results: Among 2,361 women with preterm birth in the first pregnancy logistic regression analysis indicated a significant effect of a short interpregnancy interval (0-5 months) on recurrent preterm birth <37 weeks (OR 2.22, 95% CI 1.62-3.05), <32 weeks (OR 2.90, 95% CI 1.43-5.87), and low birth weight (OR 2.69, 95% CI 1.79-4.03). In addition, a long interval (≥ 60 months) had a significant effect on preterm birth <37 weeks (OR 2.19, 95% CI 1.29-3.74). Conditional logistic regression analysis confirmed the effect of a short interval on the recurrence of preterm birth rate <37 weeks and low birth weight.
Conclusion: In women with a previous spontaneous preterm birth, a short interpregnancy interval has a strong impact on the risk of preterm birth before 37 weeks and low birth weight in the next pregnancy, irrespective of the type of analysis performed.

INTRODUCTION

Preterm birth, defined as birth before 37 weeks of gestation, is the most common cause of perinatal mortality and neonatal morbidity in developed countries,[1] mostly due to respiratory immaturity, intracranial hemorrhages and infections. These conditions can result in long term neurodevelopmental sequelae such as intellectual impairment, cerebral palsy, chronic lung disease, deafness and blindness.[2] The incidence of preterm birth in The Netherlands is 7.7% of all pregnancies and 1.3% occurs before 32 weeks. The rate of spontaneous preterm birth in singleton pregnancies is 5.4%.[3]
Risk factors for spontaneous preterm birth are various and include black ethnicity, low maternal body-mass index and low socioeconomic status. It is also known that preterm birth is associated with an increased risk of preterm birth in a subsequent pregnancy.[4,5] In addition, previous studies indicate that either a short or a long interval between pregnancies is associated with adverse perinatal outcomes, including preterm birth, low birth weight and small for gestational age. This suggests that there is an optimal interval between pregnancies and that spacing pregnancies appropriately could help to prevent these adverse perinatal outcomes.[6-8] The World Health Organization recommends a minimum interpregnancy interval of two years based on the available information and evidence.[9]
However, whether this association is confounded by other risk factors, including various aspects of socioeconomic status, ethnicity, demographics and lifestyle, is unclear.[7] Several authors propose that the relation between interpregnancy interval and perinatal outcome is entirely due to these confounders, i.e. other (maternal) factors which are correlated with interpregnancy interval and the perinatal outcome in subsequent pregnancy.[10,11] Recently, Ball et al. re-evaluated the link between interpregnancy interval and adverse birth outcome. They stated that previous analyses based on between mother comparison may have inadequately adjusted for such unknown confounders. Ball et al. subsequently analyzed the interpregnancy interval using a matched model, in which each mother was used as her own control for risk factors, in order to adjust completely for persistent maternal factors. While conventional logistic regression analysis in their data showed strong relations between a short interpregnancy interval and adverse outcome in a subsequent pregnancy, only small effects of a short interpregnancy interval on the total preterm birth rate <37 weeks, small for gestational age and low birth weight remained when they used conditional logistic regression. Based on these results the authors concluded that the impact of short interpregnancy interval and adverse outcome of the subsequent pregnancy is minimal.[11]

It is of high importance to determine whether there is an independent association between extreme interpregnancy intervals and adverse neonatal outcome. This information could reasonably be provided to counsel women about birth spacing, particularly in those women with a previous preterm birth, which makes this issue relevant to public health and clinical practice. The aim of the present study was to evaluate the effect of the time to conception of the next pregnancy on the preterm birth rate in the subsequent pregnancy in women who suffered spontaneous preterm birth. We explored this issue by using both conventional and conditional logistic regression analyses, as suggested recently by Ball et al., in a cohort of women who have had three births.

METHODS

Dataset

This study was based on data from The Perinatal Registry Netherlands (PRN). The PRN consists of population based data that contain information on all pregnancies of ≥22 weeks gestation deliveries, and readmissions until 28 days after birth in the Netherlands. The PRN database is obtained by a validated linkage of 3 different registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of new-born infants.[12, 13] The coverage of the PRN registry is approximately 96% of all deliveries in The Netherlands.

Longitudinal linkage

A probabilistic linkage procedure was performed in which records of children born between January 1, 1999 and December 31, 2009 of the same mother were linked. All children born from their mothers' second with the first (391,026) and the third with the second pregnancies (61,664) in the PRN registry were linked. The linkage was based on the variables day, month and year of the birth date of mother of the day, month and year of the birth date of a (previous) child, and the postal code of mother (4 digits). The record linkage was performed with a "two-stage" procedure. In the first stage, the dataset with first born children was linked to the dataset containing the second born children. The method to link these two records is described in more detail by Schaaf et al.[14,15] A temporary dataset was made from all record pairs with a posterior probability >0.80 of belonging to the same mother. In the second stage of the procedure, the temporary dataset was linked to the dataset containing the third born children. To determine whether a mother with two children also gave birth to a third child, we compared the linkage variables of her second child to the linkage variables of the children in the dataset containing the third born children. We performed the same linkage procedure as in the first stage. All combinations of mothers with two children and a third born child with a probability >0.80 were used to create the dataset which was used for the analysis. The final linked longitudinal cohort with complete data on first, second and third deliveries of the same mother consisted of 61,664 women and 184,992 (3 x 61,664) deliveries.

Ethical approval

The data in the perinatal registry are anonymous, and therefore, ethical approval was not needed. The Dutch Perinatal Registry gave their approval for the use of their data for this study (approval no. 14.11).

Inclusion and exclusion criteria

From this longitudinal database, we selected women with three sequential singleton pregnancies. Women whose first, second and/or third pregnancy was complicated by congenital abnormalities, antepartum fetal mortality, birth after 44 weeks or a primary caesarean section were excluded. Next we selected only women with a spontaneous preterm birth before 37 weeks in the first pregnancy. Whether a delivery commences as spontaneous (i.e. with spontaneous rupture of the membranes or contractions), or as iatrogenic (i.e. primary Caesarean section or induction), is a required field within the PRN data set, which makes it possible to distinguish between spontaneous and non-spontaneous births. The final database thus contained data of women who had three pregnancies, a first, a second and a third, amongst whom the first pregnancy had ended spontaneously before 37 weeks. These inclusion and exclusion criteria are collected in the perinatal registry and are thereby identifiable from the database.

Outcome measures

Our primary outcome measure was preterm birth before 37 weeks in the second and third pregnancy. Additional outcomes studied were preterm birth before 32 weeks, birth weight less than 2500 grams and small for gestational age less than the 10^{th} percentile.

Interpregnancy interval was documented as the time interval between delivery of the first pregnancy and the conception of the subsequent pregnancy (delivery date minus gestational age at birth). Interpregnancy interval was divided in categorical variables, classed as 0-5 months, 6-11 months, 12-17 months, 18-23 months (ref), 24-59 months and 60 months or longer.

Statistics

Women with a spontaneous preterm birth before 37 weeks in the first pregnancy were selected. In this group, we compared the recurrence rate of preterm birth before 37 and 32 weeks, the incidence of low birth weight (less than 2500 grams) and small for gestational age (less than the 10^{th} percentile) in the second and third pregnancy between women with different interpregnancy intervals. These intervals were subdivided into six categories based on widely used intervals in literature. To estimate the effect of the different interpregnancy intervals on the outcomes in the second and third pregnancy, univariate logistic regression modelling was used, and the results were expressed as odds ratios (OR) with 95% confidence interval (CI). We used multivariate logistic regression analysis to adjust for low maternal age (<25 years) and high maternal age (>35 years), non-White ethnicity, low socioeconomic status, artificial reproductive techniques and year of birth. The information about these factors is combined by using the variables of the first pregnancy for the interval between first and second pregnancy, and the variables of the second pregnancy for the interval between second and third pregnancy.

In addition, to correct for all possible maternal confounders, we used univariate and multivariate conditional logistic regression analysis to measure the effect of interpregnancy interval in the same group of women.[11] Using this analysis we were able to perform an individual analysis for each mother. We adjusted for the same risk factors in the same way as described above. The probabilistic longitudinal linkage procedure was performed with the R statistical software environment (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria), and the data were analyzed with the SAS statistical software package (version 9.3; SAS Institute Inc, Cary, NC).

RESULTS

There were 61,664 women identified as having three sequential deliveries between 1999 and 2009. Women who in their first, second or third pregnancy had a twin pregnancy (1,907 = 3.1%), gestational age of 44 weeks or more (25 = 0.04%), antepartum fetal mortality (240 = 0.4%) or congenital abnormalities (1,284 = 2.1%) were excluded. After selecting women with a spontaneous preterm birth before 37 weeks in the first pregnancy and excluding women with a negative pregnancy interval (37 = 0.06%), 2,361 women with complete follow-up data remained (see Figure 1). Baseline characteristics of our cohort are presented in Table 1 (second births) and Table 2 (third births). The prevalence of adverse outcomes in the women with spontaneous preterm birth in first pregnancy were higher in the second than in the third pregnancy.

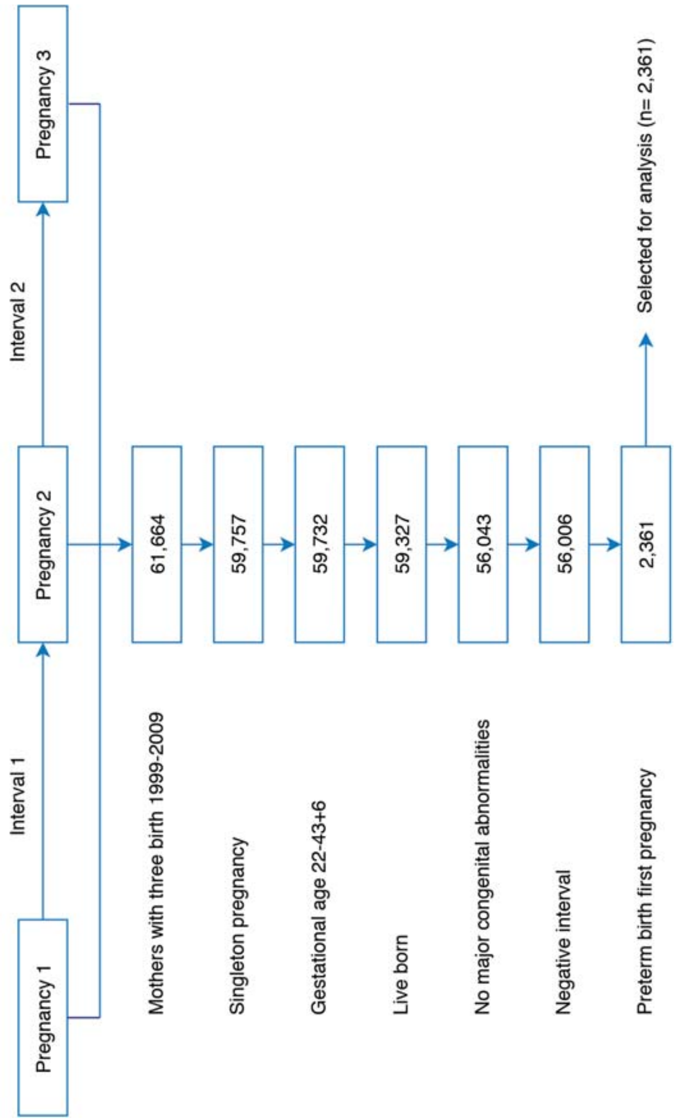

Figure 1: The selection of records used in this study

Table 1: Characteristics of second births

Characteristics	PTB <37 weeks (%)	PTB <32 weeks (%)	LBW (%)	SGA (%)	Total
Total	419 (17.8)	62 (2.6)	237 (10.0)	215 (9.1)	2,361
Interpregnancy interval (months)					
0-5	79 (26.4)	16 (5.4)	53 (17.7)	33 (11.0)	299
6-12	105 (17.1)	14 (2.3)	59 (9.6)	54 (8.8)	614
12-17	74 (13.2)	8 (1.4)	32 (5.7)	49 (8.7)	562
18-23 (ref)	54 (15.3)	8 (2.3)	28 (7.9)	27 (7.6)	354
24-59	98 (19.4)	16 (3.2)	61 (12.1)	46 (9.1)	505
≥60	9 (33.3)	0 (0.0)	4 (14.8)	6 (22.2)	27
Maternal age (years)					
<25	115 (22.1)	18 (3.5)	76 (14.6)	63 (12.1)	521
20-35 (ref)	298 (16.6)	42 (2.3)	154 (8.6)	147 (8.2)	1,800
>35	6 (15.0)	2 (5.0)	7 (17.5)	5 (12.5)	40
Ethnic origin					
White (ref)	359 (17.3)	53 (2.6)	200 (9.6)	173 (8.3)	2,077
Non-White	60 (21.1)	9 (3.2)	37 (13.0)	42 (14.8)	284
Socio-economic status					
High/middle (ref)	311 (17.3)	41 (2.3)	169 (9.4)	147 (8.2)	1,802
Low	108 (19.3)	21 (3.8)	68 (2.9)	68 (12.2)	559
Year of birth					
1999	67 (16.4)	9 (2.2)	43 (10.5)	33 (8.1)	408
2000	73 (16.5)	10 (2.3)	49 (11.1)	41 (9.3)	443
2001	77 (19.2)	14 (3.5)	35 (8.7)	29 (7.2)	401
2002	61 (17.4)	7 (2.0)	29 (8.3)	33 (9.4)	350
2003 (ref)	59 (19.1)	6 (1.9)	26 (8.4)	36 (11.7)	309
2004	38 (15.8)	8 (3.3)	28 (11.7)	22 (9.2)	240
2005	31 (19.6)	5 (3.2)	18 (11.4)	18 (11.4)	158
2006	10 (22.7)	3 (6.8)	6 (13.6)	2 (4.6)	44
2007	3 (37.5)	0 (0.0)	3 (37.5)	1 (12.5)	8
ART					
No (ref)	320 (17.6)	47 (2.6)	183 (10.0)	164 (9.0)	1,822
Yes	99 (18.4)	15 (2.8)	54 (10.0)	51 (9.5)	539

PTB = Preterm birth; LBW = low birth weight; SGA = small for gestational age; ART = artificial reproductive techniques

Table 2: Characteristics of third births

Characteristics	PTB <37 weeks (%)	PTB <32 weeks (%)	LBW (%)	SGA (%)	Total
Total	274 (11.6%)	34 (1.4)	160 (6.8)	194 (8.2)	2,361
Interpregnancy interval (months)					
0-5	26 (19.6)	6 (4.5)	15 (11.3)	12 (9.0)	133
6-11	52 (13.0)	7 (1.8)	26 (6.5)	41 (10.2)	401
12-17	37 (8.2)	2 (0.4)	25 (5.5)	31 (6.9)	452
18-23 (ref)	36 (8.7)	5 (1.2)	16 (3.9)	27 (6.5)	415
24-59	109 (12.2)	13 (1.5)	72 (8.1)	78 (8.7)	894
≥60	14 (21.2)	1 (1.5)	6 (9.1)	5 (7.6)	66
Maternal age (years)					
<25	46 (17.6)	6 (2.3)	35 (13.4)	33 (12.6)	262
20-35 (ref)	214 (10.9)	24 (1.2)	110 (5.6)	150 (7.6)	1,968
>35	14 (10.7)	4 (3.1)	15 (11.5)	11 (8.4)	131
Ethnic origin					
White (ref)	216 (10.5)	27 (1.3)	122 (5.9)	158 (7.7)	2,056
Non-White	58 (19.0)	7 (2.3)	38 (12.5)	36 (11.8)	305
Socio-economic status					
High/middle(ref)	198 (10.9)	24 (1.3)	116 (6.4)	142 (7.8)	1,823
Low	76 (14.1)	10 (1.9)	44 (8.2)	52 (9.7)	538
Year of birth					
1999	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2
2000	13 (12.3)	4 (3.8)	8 (7.6)	9 (8.5)	106
2001	29 (11.2)	1 (0.4)	10 (3.9)	20 (7.8)	258
2002	33 (9.7)	2 (0.6)	18 (5.3)	30 (8.8)	342
2003 (ref)	42 (9.7)	6 (1.4)	25 (5.8)	29 (6.7)	431
2004	42 (11.8)	8 (2.3)	23 (6.5)	28 (7.9)	356
2005	41 (12.5)	6 (1.8)	32 (9.7)	32 (9.7)	329
2006	41 (12.9)	3 (0.9)	26 (8.2)	30 (9.4)	318
2007	25 (13.9)	4 (2.2)	15 (8.3)	13 (7.2)	180
2008	8 (20.5)	0 (0.0)	3 (7.7)	3 (7.7)	39
ART					
No (ref)	203 (11.3)	22 (1.2)	118 (6.6)	147 (8.2)	1,799
Yes	71 (12.6)	12 (2.1)	42 (7.5)	47 (8.4)	562

PTB = Preterm birth; LBW = low birth weight; SGA = small for gestational age; ART = artificial reproductive techniques

Conventional logistic regression analysis

Using the interval of 18-23 months as the reference, logistic regression analysis showed a strong effect of a short interpregnancy interval (0-5 months) on the rate of preterm birth before 37 weeks (OR 2.2, 95% CI 1.6-3.1), rate of very preterm birth before 32 weeks (OR 2.9, 95% CI 1.4-5.9), and low birth weight (OR 2.7, 95% CI 1.8-4.0) after adjusting for confounders. There was an insignificant effect on small for gestational age (OR 1.4, 95% CI 0.9-2.1). In addition, a long interval (≥ 60 months) showed a significant effect on preterm birth before 37 weeks (OR 2.2, 95% CI 1.3-3.7), with no significant effect on the incidence of preterm birth before 32 weeks (OR 0.6; 95% CI 0.1-4.7), low birth weight (OR 1.8; 95% CI 0.9-3.8) and small for gestational age (OR 1.5; 95% CI 0.7-2.9) [Table 3].

Table 3: Relation between interpregnancy interval (in months) and adverse neonatal outcomes.

Interpregnancy interval (months)	Logistic regression analysis		Conditional regression analysis	
	Unadjusted OR	Adjusted OR	Unadjusted OR	Adjusted OR
PTB <37 weeks				
0-5	2.42 (1.78-3.31)	2.22 (1.62-3.05)	1.86 (1.05-3.28)	1.90 (1.03-3.50)
6-11	1.38 (1.05-1.82)	1.35 (1.02-1.78)	1.03 (0.65-1.64)	1.14 (0.69-1.88)
12-17	0.93 (0.69-1.25)	0.93 (0.69-1.25)	0.90 (0.55-1.45)	0.89 (0.53-1.49)
18-23 (ref)	1.0	1.0	1.0	1.0
24-59	1.31 (1.01-1.71)	1.29 (0.98-1.68)	0.71 (0.46-1.10)	0.74 (0.45-1.20)
≥60	2.48 (1.47-4.17)	2.19 (1.29-3.74)	1.50 (0.61-3.72)	1.17 (0.41-3.31)
PTB <32 weeks				
0-5	3.12 (1.56-6.26)	2.90 (1.43-5.87)	1.00 (0.33-3.01)	2.75 (0.64-11.77)
6-11	1.23 (0.61-2.47)	1.22 (0.61-2.46)	0.69 (0.23-2.09)	1.55 (0.39-6.24)
12-17	0.58 (0.25-1.33)	0.57 (0.25-1.31)	0.62 (0.19-2.11)	0.74 (0.17-3.19)
18-23 (ref)	1.0	1.0	1.0	1.0
24-59	1.23 (0.64-2.38)	1.21 (0.62-2.36)	0.88 (0.30-2.52)	1.23 (0.34-4.48)
≥60	0.63 (0.08-4.89)	0.60 (0.08-4.72)	0.39 (0.03-5.29)	0.67 (0.03-17.67)
LBW <2500 gram				
0-5	3.08 (2.06-4.59)	2.69 (1.79-4.03)	1.97 (1.02-3.84)	2.58 (1.24-5.36)
6-11	1.51 (1.03-2.20)	1.44 (0.98-2.10)	1.28 (0.70-2.33)	1.38 (0.72-2.68)
12-17	0.98 (0.66-1.47)	0.96 (0.64-1.45)	1.32 (0.67-2.56)	1.60 (0.78-3.30)
18-23 (ref)	1.0	1.0	1.0	1.0
24-59	1.73 (1.22-2.25)	1.72 (1.20-2.46)	1.23 (0.69-2.20)	1.48 (0.78-2.81)
≥60	1.99 (0.96-4.09)	1.83 (0.87-3.84)	0.75 (0.27-2.09)	0.79 (0.24-2.64)
SGA <p10				
0-5	1.54 (1.02-2.33)	1.39 (0.92-2.12)	0.91 (0.47-1.78)	0.96 (0.47-1.95)
6-11	1.37 (0.97-1.94)	1.33 (0.94-1.89)	1.47 (0.86-2.52)	1.53 (0.86-2.72)
12-17	1.13 (0.79-1.62)	1.14 (0.80-1.63)	0.97 (0.54-1.72)	0.98 (0.53-1.79)
18-23 (ref)	1.0	1.0	1.0	1.0
24-59	1.29 (0.92-1.80)	1.20 (0.86-1.68)	1.05 (0.61-1.79)	0.95 (0.54-1.69)
≥60	1.78 (0.89-3.53)	1.45 (0.72-2.93)	0.59 (0.19-1.85)	0.41 (0.12-1.43)

PTB = preterm birth; LBW = low birth weight; SGA <p10 = small for gestational age, less than the 10^{th} percentile

Conditional logistic regression analysis

When conditional logistic regression analysis was used, the significant effect of a short interpregnancy interval (0-5 months) on the preterm birth rate before 37 weeks (OR 1.9; 95% CI 1.03-3.5) and low birth weight (OR 2.6; 95% CI 1.2-5.4) persisted after adjusting for confounders. However, no significant effect on preterm birth before 32 weeks (OR 2.8; 95% CI 0.6-11.8) and small for gestational age (OR 0.96; 95% CI 0.5-2.0) was seen. Large interpregnancy intervals showed no significant effect on any of the outcomes [Table 3].

DISCUSSION

Main findings

We assessed the effect of interpregnancy interval on adverse neonatal outcomes in the subsequent second and third pregnancy of a subgroup of women with three sequential deliveries, after spontaneous preterm birth before 37 weeks in the first pregnancy. After controlling for confounders, we found that a short interpregnancy interval is associated with a higher risk of preterm birth before 37 weeks, very preterm birth before 32 weeks, and low birth weight. However, after controlling for possible confounders using conditional logistic regression analysis, no effect on preterm birth before 32 weeks was seen, whereas the effect of a short interpregnancy interval on both preterm birth before 37 weeks and low birth weight persisted. This effect was, however, less prominent compared to the results of the conventional method of analysis. For the large intervals, conventional logistic regression analysis revealed an association with preterm birth before 37 weeks, however this did not persist after applying the conditional method of analysis.

Strengths and Limitations

There are several potential strengths and limitations in our study. In order to perform a conditional analysis, we based our outcomes of second and third births on mothers delivering their first three singleton births as live infants at the start of labor. We could not include women with more or less than two consecutive pregnancies after the first (85% of the population in the longitudinal dataset had only two consecutive pregnancies), who might differ in socio-demographic and medical characteristics from women with three births. In addition, interpregnancy intervals were calculated only between pregnancies that ended at a gestational age of 22 or more weeks. Pregnancies ended before 22 weeks, including miscarriages before 16 weeks and

spontaneous immature births between 16 and 22 weeks, were not included in our database. This may distort the interpregnancy interval values in some cases.
To perform our analysis, a probabilistic linkage method to follow up mothers with three sequential births was used. A risk of using data from a record linkage procedure is the presence of non-linkage, which could be due to missing values for the linkage variables, or the presence of false matches, caused by the partially identifying nature of the linkage variables. Missing values mainly result from the fact that the first child was born before the start of the PRN registry in 1999, or after the period we included in our linkage procedure, i.e. 2009. The postal code of the mother was one of the linkage variables, thus, changes of home address over time will lead to non-linkage. However we found that the longitudinally linked dataset was comparable with the national pregnancy characteristics for our main outcomes so we do not think that non-linked pregnancies have influenced our results to a large degree. Furthermore, false matches in linked data could distort the dataset. However, we used a high probability to define a linking match and therefore we expect that the false matching rate in this cohort is rather low.
A major strength of our study is that we were able to use a conditional logistic regression approach to analyze the data, which allowed adjustment for possible unknown risk factors for adverse outcomes. In addition, we performed classic logistic regression analysis on the same population, thus mimicking the many previous studies of interpregnancy intervals and neonatal outcomes.

Interpretation

To our knowledge, this is the first study that has analyzed the effect of interpregnancy interval in this subgroup of woman with a previous spontaneous preterm birth on the recurrence rate of preterm birth and other adverse neonatal outcomes in a conditional model. Most previous studies assessed the effect of interpregnancy interval on a general population, while we selected women who were at high risk of preterm birth since they already delivered a spontaneous preterm infant. DeFranco et al. assessed the effect of a short interpregnancy interval on the recurrence rate of preterm birth and suggested that a short interpregnancy interval is a risk for the recurrence of preterm birth [16], which is confirmed in our study.
The conditional logistic regression analysis allowed us to analyze several interpregnancy intervals for the same mother, rather than comparing intervals between different mothers, and therefore controls better for possible unmeasured and unknown mother specific covariates. Ball and colleagues were the first to apply a within-mother method of analysis, in which mothers essentially act as their own controls, to examine the relationship between interpregnancy interval and adverse neonatal outcome including total preterm birth.[11] In their study they show that short intervals (less than 18 months) are not associated with adverse neonatal outcomes. However, an association between a long interpregnancy interval (more than 59 months) and a higher incidence of small for gestational age and low birth weight was evident, which supports earlier findings linking large interpregnancy intervals with poor neonatal outcomes.[17] Our results do not support this association when applying the conditional method of analysis. Although we could not confirm the relationship between a large interpregnancy interval and small for gestational age, a large interval may have an adverse effect on maternal health[18] and risk of antenatal deaths or early neonatal death.[19]
Furthermore, an association between short interpregnancy interval and an increased incidence of poor neonatal outcome has been supported by strong and consistent findings over many years and in a wide range of countries.[6, 7, 16, 17] Although our study confirms the relationship between a short interpregnancy interval and increased risk of preterm birth before 37 weeks and low birth weight, an effect on preterm birth before 32 weeks and small for gestational age was not supported by our conditional logistic regression analysis model. This might be due to the small number of women having a preterm birth before 32 weeks in their second and/or third pregnancy in our data set. We performed additional analyses in which we divided the interpregnancy interval in quartiles (25%, 50% and 75%) to create larger groups in each interval. Using the interval of the second quartile (25-50%) as the reference, these results showed a significant effect for preterm birth before 32 weeks after a short interval (<25%) when conditional logistic regression analysis was applied. This supports the theory of a small number of women in the shortest interpregnancy interval (0-5 months) used in our main analysis. Another explanation might be that preterm birth before 32 weeks depends on different risk factors compared to preterm birth before 37 weeks.
In comparison to our study, earlier studies may have inadequately adjusted for possible confounders as different interpregnancy intervals were compared between mothers, as proposed by Ball et al. However, in contrast to the latter study, we have shown persistent effects of a short interpregnancy interval on preterm birth before 37 weeks and low birth weight. Nevertheless, these effects were found in a subgroup of women with a previous spontaneous preterm birth before 37 weeks where Ball et al. studied all births in Australia during their study period.
The biological mechanisms linking interval between births and incidence of preterm labor are unknown, and are challenging to investigate while the causes and mechanisms leading to preterm labour remain elusive.[20] Since both sterile and infectious stimuli can activate the inflammation that leads to preterm labour

[20], and the quality of placental development and function may also contribute [21,22], the maternal immune response and physical structure and function of the uterus may be two contributing factors. It seems reasonable to assume that the biological functions of the uterus take some time to return to homeostasis after birth, and that conception before complete recovery from recent birth may interfere with optimal future placental development and capacity to sustain a following pregnancy. Additionally it might be speculated that since the maternal immune response is affected by previous pregnancies [22], particularly the adaptive immune compartment that generates T regulatory cells, immune tolerance may be compromised when conception occurs in the phase following recent parturition during which maternal immunity re-equilibrates.[23] Since an active maternal immune response is essential to protect from infection and gestational disorders stemming from placental incompetence [24] including preterm labor [25], appropriate recovery of endometrial immune activity following previous pregnancy may be necessary. In rodent model systems, the strength of suppressive capability in the regulatory T cell pool is regulated by exposures to paternal seminal fluid before and between pregnancies, as well as gestational antigens [24], and varies according to memory of any previous pregnancy [26], so coital activity between pregnancies could also be a factor. Preterm birth may alter the kinetics by which uterine structure and immune function return to normal status in the post-partum phase, but whether and how this occurs requires further investigation.

CONCLUSION

Both conventional and conditional analyses demonstrated an increased risk of preterm birth before 37 weeks and low birth weight after a short interpregnancy interval in in a subgroup of women with a previous spontaneous preterm birth before 37 weeks. This increased risk was found after controlling for known and possible unknown confounders. Despite the fact that the impact of interpregnancy interval in an unselected population has been called into question by Ball et al, we found, in a subgroup of women with a history of a spontaneous preterm birth before 37 weeks, a significant effect on pregnancy and neonatal outcomes when applying the controlled method suggested by Ball et al.

Our results may assist clinicians in the counseling of women with a history of spontaneous preterm delivery. We recommend these women to consider an interval of at least 12 months before conception of the next pregnancy. To investigate the impact of interpregnancy interval in a variety of populations, we encourage the use of conditional methods of analysis.

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