Risk factors and prognostic models for preterm birth

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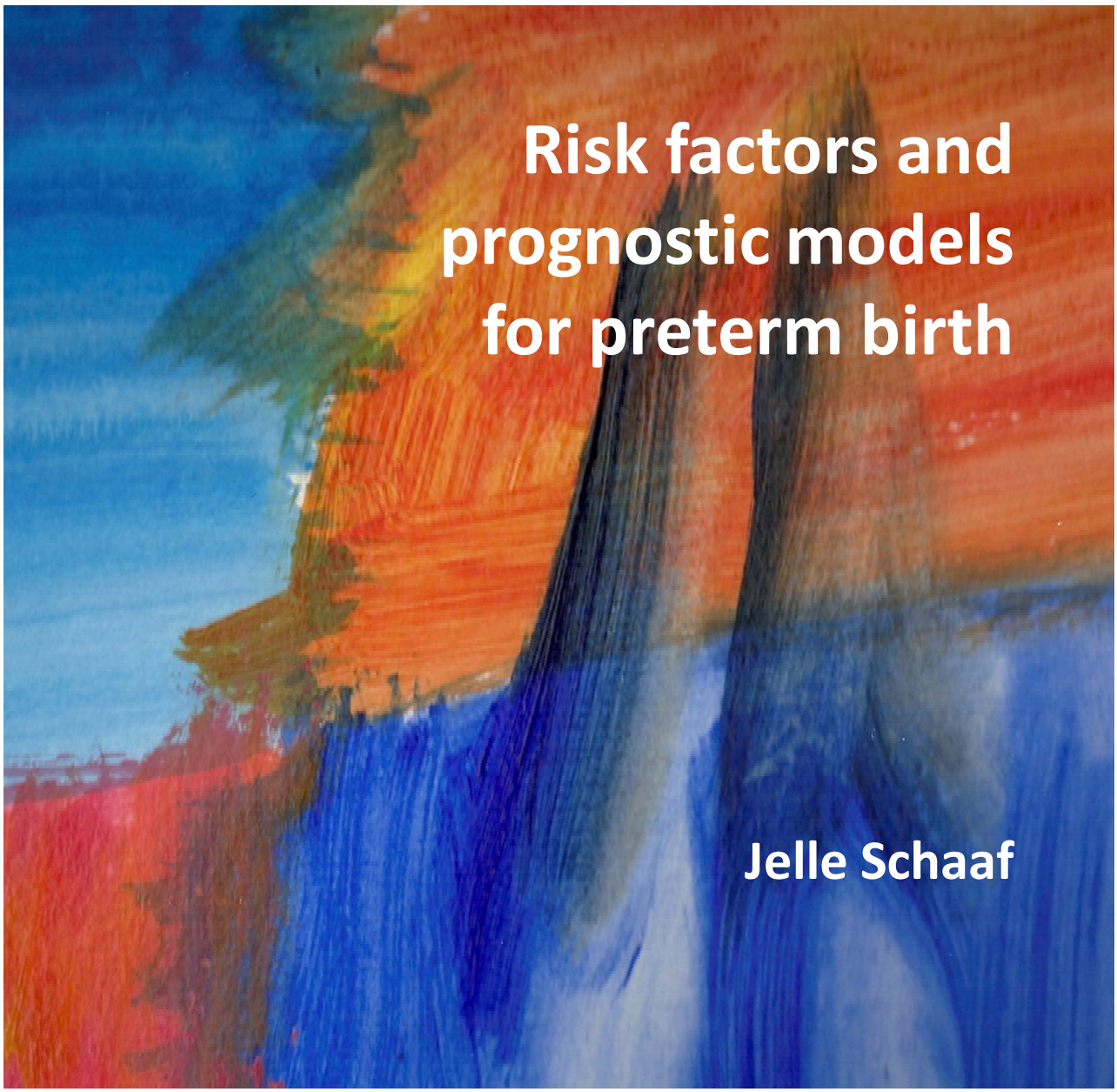
Risk factors and
prognostic models
for preterm birth
Jelle Schaaf

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Risk factors and prognostic models for preterm birth

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geboren te Tilburg

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CHAPTER 1

General introduction

In an uncomplicated pregnancy the optimal gestational age at the time of delivery is approximately 40 weeks. According to international guidelines we consider deliveries between 37 and 42 weeks as *term* births. If the birth takes place before 37 completed weeks of gestation we consider it to be *preterm.*[1] Preterm births are further categorized depending on the gestational age at the time of delivery (figure 1).

The WHO report *Born too soon* describes that worldwide, more than 10% of the babies born in 2010 were delivered preterm. The incidence of preterm birth varies between countries and ranges from 5-18%.[1,2] Studies on trends in the incidence of preterm birth showed that in many developed countries the incidence of preterm birth is increasing.[3,4] The estimated 15 million preterm births in 2010 were related to more than 1 million neonatal deaths.[2] Prematurity is the single most important cause of death in the first month of life and the second-leading cause of death in children less than 5 years old.[5]

The impact of preterm birth extends beyond the neonatal period and throughout the life cycle. Besides perinatal deaths, preterm birth also causes severe neonatal morbidity[6], mostly due to respiratory immaturity, intracranial haemorrhages and Infections.[7] These conditions can have long term consequences such as cerebral palsy, intellectual impairment, chronic lung disease, and hearing and vision loss.[6] All these adverse effects of preterm birth exact not only a high toll on individuals born preterm, but also on their families and the communities in which they live.[8]

Preterm birth can either be a result of medical intervention or can occur spontaneously.[1] In the case of severe maternal and/or fetal complications, such as preeclampsia or intra uterine growth restriction, obstetricians can decide to deliver the baby through induction of labour or elective caesarean section.

Figure 1. Overview of definitions for preterm birth.

In daily practice, these are difficult decisions as the caregiver has to balance the possible harmful effect of preterm birth versus the possible harmful effect of lengthening a complicated pregnancy.[9] In the majority of cases, however, preterm birth occurs spontaneously with or without prelabour rupture of membranes (PROM).[9]

A lot of scientific effort has been put in the unravelment of the pathogenesis of preterm birth. Multiple risk factors have been identified, and preterm birth appears to be a multifactorial and heterogeneous adverse outcome of pregnancy.[10] The risk factors pertain to basis demographic characteristics, medical or obstetrical history, and specific characteristics of the current pregnancy. The most important risk factors are summarized in figure 2. The figure shows the complexity of the problem; the separate risk factors not only play a role in the pathogenesis of preterm birth, they are also strongly interrelated (indicated with the arrows).

Despite the identification of these risk factors, their prognostic interaction is not well understood. As a result it is often difficult to assign risk of preterm birth to individual women. This hinders caregivers from selecting women at higher risk of preterm birth for early referral to secondary care and selecting women for trials on preventive measures such as the admission of progesterone during pregnancy.

Prognostic models are promoted as helpful tools to support clinicians: by producing an individual's risk score they can be applied in selecting patients for clinical trials, clinical decision making and counselling patients.[11,12] In literature, few clinical scoring systems have been presented for assigning risk of preterm birth to individual women, but none of them was accurate enough to be applied in daily practice.[13] Most of the risk assessment tools were based on small datasets or did not present predictions in a quantitative manner.

The complexity of the pathogenesis of preterm birth, the related difficulties in early risk assessment and the small amount of effective preventive measures makes preterm birth one of the major challenges in clinical obstetric practice and scientific research.[2] On the side of the neonatologists the improved care of premature infants during the last decades has led to significant better outcomes on the short- and the long term.[14] However, on the side of the obstetric caregivers still lies a big challenge to reduce the number of preterm births and in that way improve perinatal care.

Outline of this thesis

For the majority of our studies in this thesis we were allowed to use the data of the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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.[15,16] The coverage of the PRN registry is about 96% of all deliveries in the Netherlands.

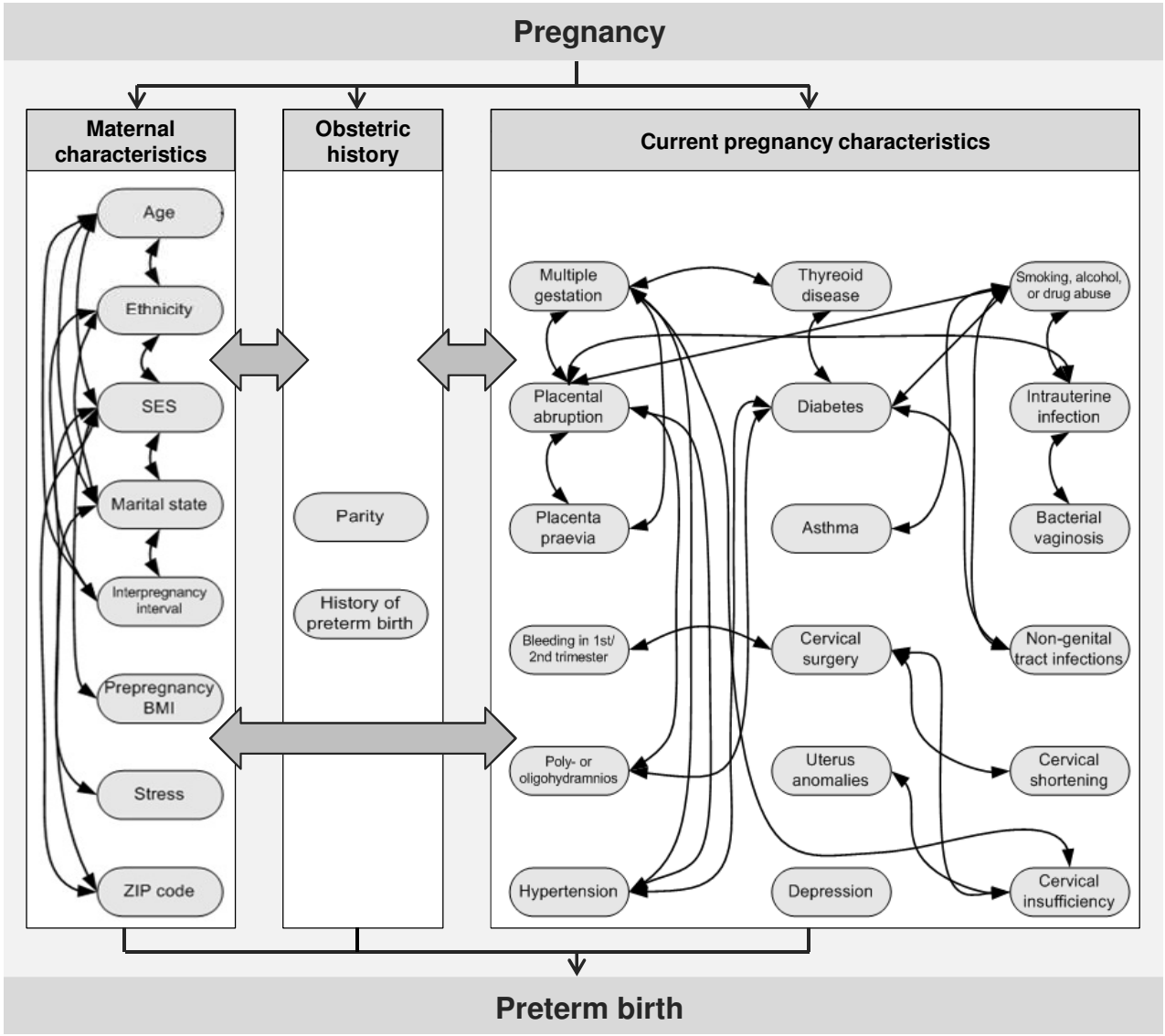

Figure 2. Risk factors for preterm birth and their interrelationship.

Part 1. Trends and risk factors

Chapter 2 investigates temporal trends in the incidence of preterm birth in The Netherlands and compares the Dutch figures to those of other developed countries. In the next chapters we further explore some important risk factors for preterm birth. **Chapter 3** is a systematic review and meta-analysis of literature on ethnic or racial disparities in the risk of preterm birth. It summarizes all relevant studies which of which the majority was performed in the United States. **Chapter 4** explores ethnic disparities in the risk of preterm birth in The Netherlands and thus focuses more on the European ethnic composition of society. Furthermore we investigate ethnic disparities in the risk of preterm birth related adverse neonatal outcome.

As shown in figure 2, preterm birth is associated with an increased risk of preterm birth in the subsequent pregnancy. This increased risk is well established and reconfirmed in several studies.[17,18] However, these studies only focused on the risk of singleton preterm birth after a previous singleton birth. Little is known whether the recurrence risk also holds for twin pregnancies following a preceding singleton preterm birth or the other way around. **Chapter 5** investigates the recurrence risk of preterm birth in subsequent singleton pregnancy following previous preterm twin delivery. The exact opposite is under investigation in the next chapter. **Chapter 6** presents the recurrence risk of preterm birth in subsequent twin pregnancy following previous preterm singleton delivery.

Part 2. Prognostic models

In the second part of this thesis we aim to improve the individual risk assessment for preterm birth and for adverse neonatal outcome after preterm birth. **Chapter 7** describes the development and internal validation of a prognostic model for predicting spontaneous preterm birth. The intended model should be useful for a risk assessment around 20 weeks of gestation. **Chapter 8** presents the development of a prognostic model for predicting neonatal mortality after very preterm birth. In neonatology, similar prognostic models are already used for clinical decision making and counselling. However, these models are based on variables which can only be known after birth (e.g. birth weight or Apgar score).[19] We aim to develop a model which is solely based on variables that are known before birth, which enables an earlier risk assessment in these complicated pregnancies.

Part 3. Impact of preterm birth

Chapter 9 provides an insight in the psychological consequences of preterm birth for the parents. For this we analyse data of a cohort of women who suffered from early onset pre-eclampsia, a severe pregnancy-related hypertensive disorder leading to (medically indicated) preterm birth. We investigate the rates of subsequent pregnancies in women with a history of preterm birth due to early-onset pre-eclampsia and interview women without the wish of a subsequent pregnancy to determine the reasons not to attempt a subsequent pregnancy.

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CHAPTER 2

Trends in preterm birth: singleton and multiple pregnancies The Netherlands 2000 through 2007

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Abstract

Objective *Several studies have reported increasing trends in preterm birth in developed countries, mainly attributable to an increase in medically indicated preterm births. Our aim was to describe trends in preterm birth among singleton and multiple pregnancies in the Netherlands.*

Design *Prospective cohort study.*

Setting *Nationwide study.*

Population *We studied 1,451,246 pregnant women, from 2000 to 2007.*

Methods *We assessed trends in preterm birth. We subdivided preterm birth in spontaneous preterm birth after premature prelabour rupture of membranes (pPROM), medically indicated preterm birth, and spontaneous preterm birth without pPROM. We performed analyses separately for singletons and multiples.*

Main outcome measures *Primary outcome was preterm birth defined as birth before 37 weeks of gestation, with very preterm birth (<32 weeks of gestation) being a secondary outcome.*

Results *Risk of preterm birth was 7.7% and risk of very preterm birth was 1.3%. In singleton pregnancies, the preterm birth risk significantly decreased from 6.4 to 6.0% ($p<0.0001$), mainly due to a decrease in spontaneous preterm births without pPROM (3.6 to 3.1%, $p<0.0001$). In multiple pregnancies, the preterm birth risk increased significantly (47.3% to 47.7%, $p=0.047$), mostly due to the subtype of medically indicated preterm birth which increased from 15.0 to 17.9% ($p<0.0001$).*

Conclusion *In The Netherlands, the preterm birth risk in singleton pregnancies significantly decreased over the years. The trend of increasing preterm birth risk reported in other countries was only observed in (medically indicated) preterm birth in multiple pregnancies.*

Preterm birth, defined as birth before 37 completed weeks of gestation, is strongly related to perinatal morbidity and mortality.[1-3] In the developed countries, it accounts for 75% of perinatal mortality and more than half of the long-term neurocognitive, ophthalmologic and respiratory morbidity.[2] Preterm birth is a multifactorial and heterogeneous outcome of pregnancy.[3-5] It might result from a series of disorders, but in a considerable amount of cases the cause is unknown.[1,6-9] Furthermore, preterm birth can be medically indicated when maternal and/or fetal conditions enforce induction of labour or primary caesarean section. Such might be the case in women suffering from hypertensive disorder or pregnancies complicated by intra uterine growth restriction (IUGR).[10]

Many developed countries have reported an increase in the risk of preterm birth during the last two decades.[10-14] A recent study in the United States, where the overall incidence of preterm birth was high (13%), showed that the increase in risk of preterm birth was mainly caused by an increase in medically indicated deliveries, whereas spontaneous preterm birth risk showed a decrease.[3,15] Scottish data showed an overall increase in preterm birth risk that was caused by both an increase in medically indicated and spontaneous deliveries. In the latter study the risk of medically indicated preterm deliveries showed the largest increase. Recent research showed that the level of proactive treatment leading to medically indicated preterm birth has great variations between several European countries due to varying socio-cultural and organisational factors and thus varying doctor's behaviour.[16] The contributions of the subtypes of preterm births to all preterm births appeared to vary by ethnic group and gestational age.[1]

More recent data were provided by the European Peristat project, which monitors perinatal health in Europe. In the years 1998/99 as well as in 2004 several countries and regions contributed data for analysis. In the report on 2004, incidence of preterm birth ranged between 5.4% in Lithuania and 11.4% in Austria. The report showed the incidence of preterm birth in The Netherlands (7.4%) was about average compared to the rest of Europe. The two Peristat reports showed that the incidence of preterm birth increased in the majority of the contributing countries and regions.[17,18] However, the Peristat data were insufficient for the analysis of possible trends in preterm birth risk. Furthermore, the European Peristat project showed that perinatal mortality in The Netherlands is relatively high when compared to other European countries.[19] The pathways leading to this relatively high perinatal mortality risk in the Netherlands are not clear and under investigation.[20,21]

The aim of this study is to describe in detail recent trends in preterm birth in The Netherlands among singleton and multiple pregnancies. We focused on the different subtypes of preterm birth (spontaneous after premature prelabour rupture of membranes (pPROM), medically indicated, or spontaneous without pPROM).

Methods

This study was performed in a prospective national cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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.[22,23] The midwifery and obstetrics data collection starts at the booking visit and contain complete perinatal data from 20 gestational weeks onwards. The neonatal registry contains data on only hospital admissions of newborns. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands.[21] All data contained in the PRN are voluntarily recorded by the caregiver during prenatal care, delivery and the neonatal period. The data are annually sent to the national registry office, where a number of range and consistency checks are conducted.[24] For this study all births between 1 January 2000 and 31 December 2007 were selected.

Preterm birth was defined as birth before 37 completed weeks of gestation (< 259 days). Stillbirths were included in the analyses. Very preterm birth was defined as birth before 32 completed weeks of gestation. Following the international literature on preterm birth, all pregnancies that ended before 22.0 weeks of gestation, pregnancies with unknown gestational age and pregnancies resulting in the birth of a child weighing less than 500 grams were excluded.

Gestational age data were predominantly based on the date of last menstrual period and/or crown rump length (CRL) measured during early pregnancy ultrasound. The technique for measuring gestational age was consistent over the total study period. Preterm birth was classified in three subtypes: [1] Spontaneous preterm birth after premature prelabour rupture of membranes (pPROM) which was defined as a birth (due to spontaneous start of labour) after an interval > 24 hours between rupture of membranes and time of birth, [2] medically indicated preterm birth which was defined as delivery caused by iatrogenic intervention (primary caesarean section or induction of labour) and all other preterm deliveries were defined as [3] spontaneous preterm birth without pPROM. The latter is a category which contains all pregnancies not included in category 1 or 2.

We examined records of singleton and multiple births in the Netherlands between 2000 and 2007. Because of their known varying course of pregnancy, singleton and multiple pregnancies were also analysed separately. Secondly we investigated to what extent preterm birth and its subtypes contribute to the overall incidence of perinatal mortality in The Netherlands and to what extent risk of perinatal mortality changed over the investigated years. Perinatal mortality was defined as the number of fetal deaths from 22.0 weeks onwards (stillbirths) and neonatal deaths in the first week of life. We analysed incidence and trends in all preterm birth, as well as in the three distinct subtypes of preterm birth.

We performed an additional analysis for the following clinically relevant subgroups of gestational age: 22-23 wks, 24-27 wks, 28-29 wks, 30-31 wks, 32-33 wks and 34-36 weeks. Finally, nulliparous and multiparous women were analysed separately. To check for possible confounding factors we repeated the analyses for Caucasian women only, accounting for 84% of the total births.

To investigate whether there is a trend in preterm birth risk over time we performed a Cochran-Armitage trend test with year as the independent variable and preterm birth risk as the dependent variable. The same test was performed to check for trends in perinatal mortality risk during the same time period.

Subsequently we repeated the trend analysis by fitting a linear regression model for each series. We tested whether the regression coefficient (beta) of the fitted linear model statistically significantly deviated from 0 using the *t* -test. The statistical significance levels for both types of trend test were set at the 0.05 level. We repeated this procedure to test for temporal trends in the three preterm birth subtypes. We repeated the main trend analyses on Caucasian women only. All statistical analyses were carried out with SAS 9.2 (SAS Institute, Cary, NC). Permission for record use and analysis of data for the purpose of this study was obtained from the Netherlands Perinatal Registry (registered as data petition 09.79).

Results

There were 1,451,246 births over the 8-year study period, of which 1,394,714 singleton births and 56,532 multiple births. Table 1 shows that of all births in the Netherlands 7.7% are preterm and 1.3% are very preterm. Among the singleton pregnancies 6.0% resulted in preterm and 0.9% in very preterm deliveries. Preterm birth among singletons consisted of spontaneous preterm birth after pPROM (0.9%), medically indicated preterm birth (1.7%) and spontaneous preterm birth without pPROM (3.4%). In multiple pregnancies the total incidence of preterm and very preterm birth was respectively 48.1 and 8.7%.

Table 2 shows the contribution of preterm birth to the overall perinatal mortality rates. In singleton pregnancies the contribution of preterm birth was 62% whereas for multiple pregnancies this was even 87%. Rates of late preterm births were 5.1% among singletons with a mortality risk of 33 per 1000 whereas among multiples the rates were 39% with a lower mortality risk of 15 per 1000. In all subgroups of gestational age the subtype of medically indicated preterm birth gives the highest risk of perinatal mortality. Figure 1 shows that the total preterm birth risk for all pregnancies (singletons and multiples) decreased from 8.0% to 7.4% whilst the perinatal risk in the same study period also decreased (9.7‰ to 7.4‰). Trend analysis showed both declines to be significant (Cochran-Armitage trend test $p<0.0001$).

Table 1. Total preterm births and very preterm births among singleton and mutiple pregnancies: the Netherlands, 2000–2007

	All pregnancies			
	n	%		
Total number of deliveries	1 451 246	100		
Total preterm	111 416	7.7		
Spontaneous after pPROM	16 222	1.1		
Medically indicated	32 570	2.3		
Spontaneous without pPROM	62 624	4.3		
	Singleton pregnancies		**Multiple pregnancies**	
	n	%	*n*	%
Total number of deliveries	1 394 714	100	56 532	100
Total preterm (22–36 weeks)	84 233	6.0	27 134	48.1
Spontaneous after pPROM	13 177	0.9	3 045	5.4
Medically indicated	23 633	1.7	8 937	15.8
Spontaneous without pPROM	47 423	3.4	15 201	26.9
Total very preterm (22–31 weeks)	13 618	0.9	4 896	8.7
Spontaneous after pPROM	1 407	0.1	609	1.1
Medically indicated	6 345	0.4	999	1.8
Spontaneous without pPROM	5 866	0.4	3 288	5.8

pPROM, premature prelabour rupture of membranes.

The Cochran-Armitage trend test for the total of singleton pregnancies resulted in p<0.0001. For the subtypes of preterm birth the p-values were: 0.70 (spontaneous after pPROM [1]), 0.84 (medically indicated [2]) and <0.0001 (spontaneous without pPROM [3]). The multiple pregnancies also showed a significant trend according to the Cochran-Armitage test with p=0.047. The tests resulted is p=0.14 [1], p<0.0001 [2], and p=0.48 [3] for the subtypes of preterm birth in their respective order above.

Regression models

Risk of preterm birth in singleton pregnancies significantly decreased from 6.4 to 6.0% (p=0.049) over the years (figure 2A), which means a decrease of approximately 700 preterm deliveries per year. This decline is mainly due to significantly decreasing risk of spontaneous preterm births without pPROM from 3.6 to 3.1% (p=0.00038). There were no significant changes in risk of neither medically indicated preterm births nor spontaneous preterm birth after pPROM in singleton pregnancies. Figure 2B shows the results for multiple pregnancies. Risk of preterm birth in multiple pregnancies increased not significantly from 47.3% in the year 2000 to 47.7% in 2007 (an increase of approximately 30 preterm deliveries per year). Medically indicated preterm birth risk did show a significant increase over the years (15.0 to 17.9%), whereas spontaneous preterm birth risk (with or without pPROM) showed no significant trend.

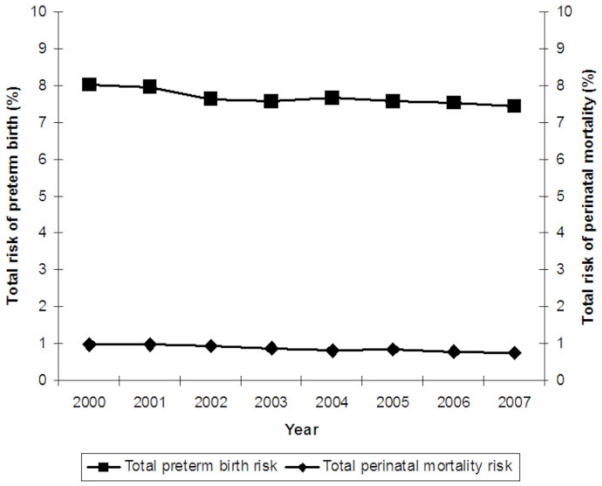

Figure 1. Risk of preterm birth and perinatal mortality in all pregnancies (singleton and multiple): the Netherlands 2000-2007.

Table 2. Incidence of preterm birth and its subtypes and related risk of perinatal mortality: the Netherlands, 2000–2007

	Singleton pregnancies			Multiple pregnancies		
	Incidence ***n*** **(%)**	**Perinatal mortality** ***n*** **(‰)**	**Contribution** ***%***	**Incidence** ***n*** **(‰)**	**Perinatal mortality** ***n*** **(%)**	**Contribution %**
Total preterm (22–27 weeks)	4 859 (0.4)	3 096 (637)	28	1 582 (2.8)	743 (469)	52
Spontaneous after pPROM	556 (0.04	318 (572)	2.8	232 (0.4)	117 (504)	8.2
Medically indicated	1 974 (0.1)	1 407 (713)	13	179 (0.3)	97 (542)	6.8
Spontaneous without pPROM	2 329 (0.2)	1 371 (589)	12	1 171 (2.1)	529 (452)	37
Total preterm (28–31 weeks)	8 759 (0.6)	1 555 (178)	14	3 314 (5.9)	169 (51)	12
Spontaneous after pPROM	851 (0.1)	76 (89)	0.7	377 (0.7)	9 (24)	0.6
Medically indicated	4 371 (0.3)	1 041 (238)	9.3	820 (1.5)	80 (98)	5.7
Spontaneous without pPROM	3 537 (0.3)	438 (124)	3.9	2 117 (3.7)	80 (38)	5.7
Total preterm (32–36 weeks)	70 615 (5.1)	2 329 (33)	21	22 287 (39.4)	329 (15)	23
Spontaneous after pPROM	11 770 (0.8)	156 (13)	1.4	2 436 (4.3)	38 (16)	2.7
Medically indicated	17 228 (1.2)	1 300 (75)	12	7 938 (14.0)	159 (20)	11
Spontaneous without pPROM	41 557 (3.0)	873 (21)	7.8	11 913 (21.1)	132 (11)	9.3
Total term (≥37 weeks)	1 310 481 (94.0)	4 193 (3.2)	38	29 349 (51.9)	184 (6.3)	13
Total number of deliveries	1 394 714 (100)	11 173 (8.0)	100	56 532 (100)	1425 (25)	100

pPROM, premature prelabour rupture of membranes

When considering subgroups of gestational age we found that in singleton pregnancies (figure 3A) the overall decrease in preterm birth risk is mostly a reflection of decreases in the 32-33 (0.8 to 0.7%) and 34-36 (4.6 to 4.2%) weeks subgroups. A similar subgroup analysis for gestational age was performed for multiple pregnancies (figure 3B). When focussing on the preterm birth subtypes in multiple pregnancies we find an increase in medically indicated preterm birth over the years in the 34-36 weeks group (11.8 to 13.0%). Finally we performed an analysis with subgroups based on parity. In singleton pregnancies the preterm birth risk was higher for nulliparous (figure 4A) than for multiparous (figure 4B) women. For nulliparous women with singleton pregnancies the total preterm birth risk decreased from 8.0% in 2000 to 7.7% in 2007, whereas for multiparous women the proportions ranged between 4.8 and 4.5%. In nulliparous and multiparous women, we found the same trend as in the overall analysis in singleton pregnancies: a significant decrease in preterm birth without pPROM.

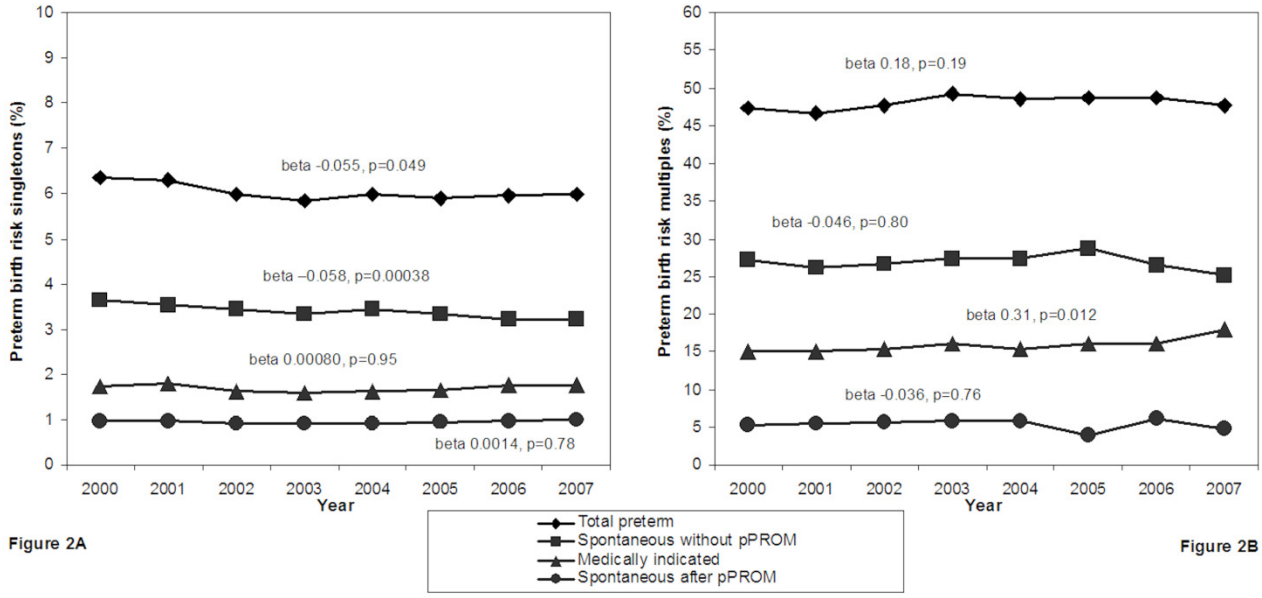

Figure 2. Risk of preterm birth per year in singleton (A) and multiple (B) pregnancies and subtypes: the Netherlands, 2000–2007. Different scales are used in (A) and (B). Beta values of trend analysis are presented for total preterm birth risk and all subtypes. pPROM, premature prelabour rupture of membranes.

However the total preterm birth risk was not significant after subdividing for parity. Figures 4C and 4D show the results of the parity subgroup analysis in multiple pregnancies. The total preterm birth risk was higher for nulliparous than for multiparous women. In nulliparous women with a multiple pregnancy the total preterm birth risk showed no significant trend over the years (54.0 to 54.4%, beta 0.48769, p=0.11) However, there was a significant increase in medically indicated preterm births (17.5 to 21.0%, beta 0.47551, p=0.024). In multiparous women with multiple pregnancies no significant trends were found. To check for possible confounding we repeated all analyses in a selection of the 1,220,489 Caucasian women (84%) and found similar trends as were found in the presented total population.

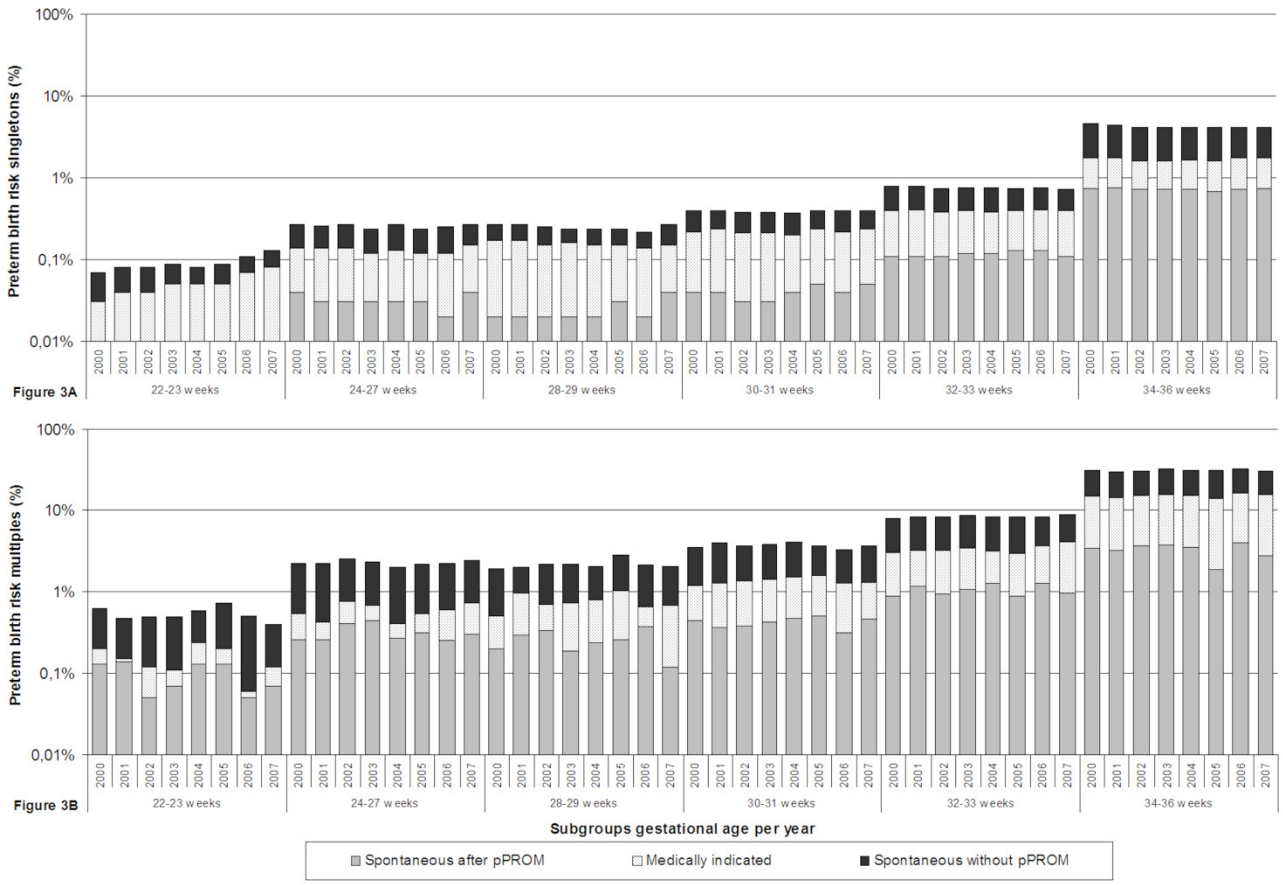

Figure 3. Risk of preterm birth per year in singleton (A) and multiple (B) pregnancies with subgroups for gestational age: the Netherlands 2000–2007 pPROM, premature prelabour rupture of membranes.

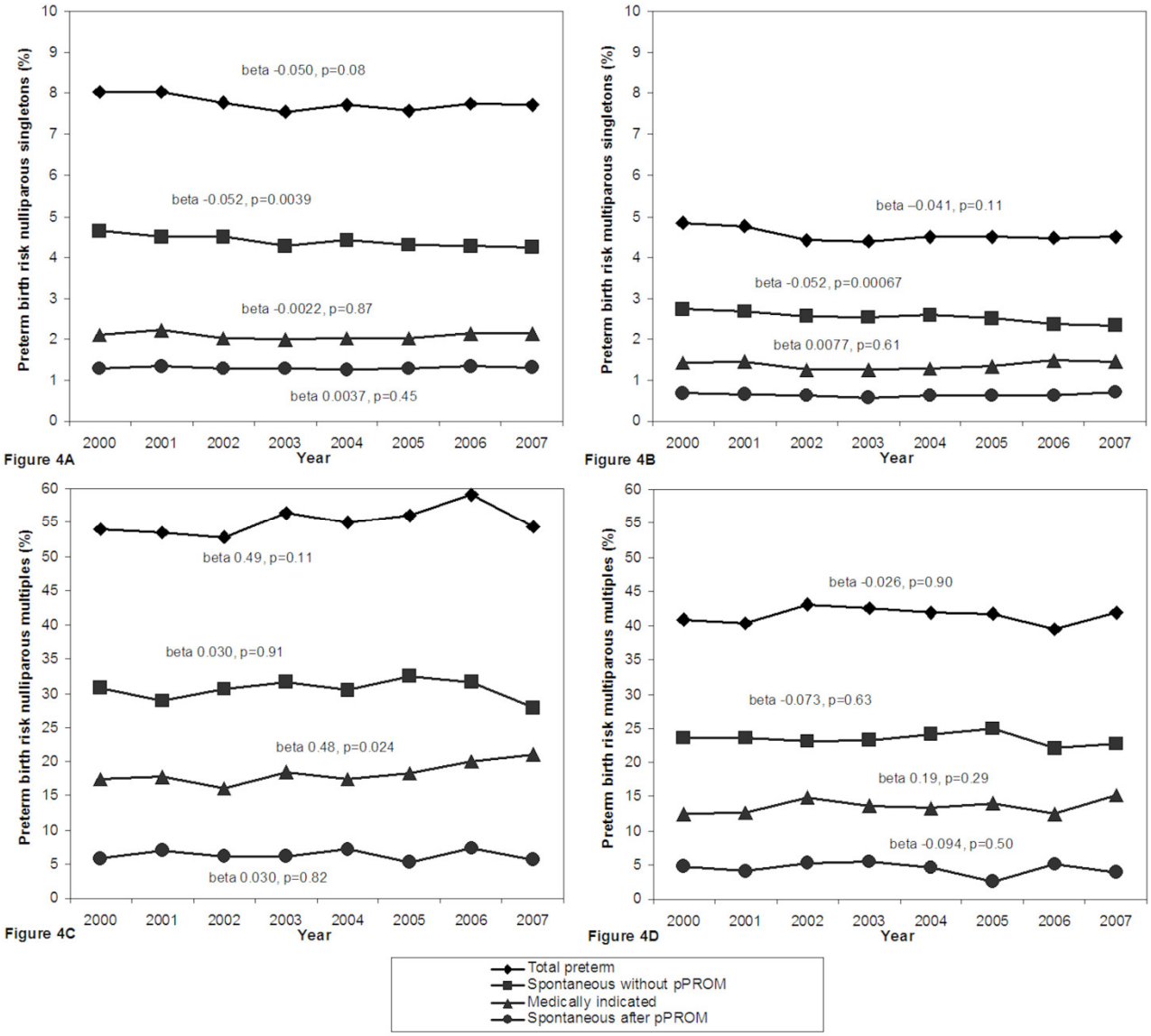

Figure 4. Risk of preterm birth per year in primiparous and multiparous singleton (A, B) and multiple (C, D) pregnancies with subtypes: the Netherlands, 2000–2007. Beta values of trend analyses are presented for total preterm birth risk and all subtypes. Trend analysis for preterm birth after premature prelabour rupture of membranes (pPROM) in (B) resulted in beta + 0.0033 (*P* = 0.60).

Principal findings

Our study shows a significant decrease in as total preterm birth risk as well as total perinatal mortality risk in the Netherlands between 2000 and 2007. For singleton pregnancies this was due to a significant decrease in spontaneous preterm birth without pPROM. This decrease was mostly seen in late preterm birth at the 32-33 and 34-36 weeks of gestational age. Risk of total preterm birth and its subtypes were higher in nulliparous women compared to multiparous women.

For multiple pregnancies there was no significant trend in total preterm birth risk although the subtype of medically indicated preterm birth did increase significantly. This trend towards increasing iatrogenic preterm birth was pronounced in the 34-36 weeks subgroup of gestational age. We observed a large contribution of preterm birth to overall incidence of perinatal mortality (68% of all perinatal deaths).

Strengths and weaknesses

Our study comprises data of a large population-based well-maintained national registry and therefore provides a reliable overview of the problem of preterm birth in the Netherlands. The sample size is large, as the PRN database consists of about 96% of all pregnancy and birth characteristics in the Netherlands. Furthermore, our study is unique in its size and design as we also investigated trends in preterm births for multiple pregnancies. To our knowledge, the latter was rarely investigated before in a population-based setting. After repeating the analyses for Caucasians only we found similar results.

The method of determining gestational age can influence the outcome of preterm birth. Nowadays the vast majority of women in the Netherlands receive an early pregnancy ultrasound to confirm or change the estimated gestational age by last menstrual period so the effect of miscalculated gestational age on the studied outcome of preterm birth should be marginal. This strategy did not change over the study period.

Four percent of all births are missing in the national perinatal registry. This is due to the 2% general practitioners and a few missing midwives practices (2%) who do not contribute data to the PRN database. However, as preterm birth is an indication for referral to an obstetrical equipped hospital (of which 99% contribute to the PRN registry), these missing data could not have influenced our results to a large degree.

Our study was performed on the available linked PRN registry data between 2000 and 2007. There are no linked LVR1, LVR2 and LNR data available yet containing information in the period before 2000. In some cases there was only little overlap in the years we investigated with respect to the previously published studies. This hinders comparison.

Relationship to other studies

The Peristat project[15] showed that the incidence of preterm birth in the Netherlands (7.4%) is average when compared to other European countries (5.4-11.4%). Ananth et al.[3] showed that the incidence in the United States is much higher (10.2%). More recently Kuehn et al.[15] reported an even higher incidence of preterm birth (13%) in the United States. Our findings on decreasing trends in preterm birth in nearly 10 years of registration do not concord with previously published studies about trends in preterm births in other developed countries. Other studies, like those performed by Ananth et al.[3] and Norman et al.[10], showed significant increasing trends in preterm birth risk through the past decades, whereas our study does not show these trends in the Netherlands. Furthermore the risk of medically indicated preterm births was only shown to increase in multiple pregnancies in our population. However, recently published data show that, after 30 years of increase, a trend of decreasing risk of preterm birth in the United States in the years 2007, 2008, and 2009.[25] Data on the incidence of preterm birth in the years after 2009 are not available yet, but these results mark the first 3-year decline (12.8% to 12.2%) in the preterm birth risk in nearly 30 years.

The Mosaic study reviewing very preterm birth in several European countries showed that the proportion of very preterm birth is ten times larger in twin pregnancies than in singleton pregnancies.[26] Our results are in accordance with this finding. A recently published study considering trends in preterm birth in Flanders (Belgium) also showed a significant increase in medically indicated preterm birth in multiple pregnancies. The study showed a similar increasing risk of preterm birth in singleton pregnancy which again is in contrast with our findings.[27] Most other studies reviewing trends in preterm birth address only singleton pregnancies.

Meaning of the results

We can assume, especially in light of the relatively high perinatal mortality risk in the Netherlands[18,19], that the Dutch women do not have a lower risk profile for preterm birth than women in other developed countries.

The lack of increasing trend in premature birth risk may be attributable to our different infrastructure for and attitude towards perinatal care. For instance, in the case of premature prelabour rupture of membranes or hypertensive disorders between 34-37 weeks, we conjecture that there is a relatively expectant approach in the Netherlands when it comes to medical intervention. In contrast, management in these conditions tends to be more proactive in most other developed countries. For instance, in the United States the risk preterm birth due to medical interventions steadily increased over the last two decades. This increase was most pronounced in the late preterm birth group (34-36 weeks).[28] Preterm obstetric care is complicated as the caregiver needs to weigh conflicting risks; The neonatal/maternal risk of progressive morbidity or even mortality when continuing pregnancy versus the neonatal risk of morbidity or mortality after being born preterm.

The risk of neonatal mortality when born after 34 weeks is relatively low. Nevertheless there is an increasing amount of evidence emphasising that infants born late preterm are less healthy than babies born later in pregnancy.[29-34]

Our relatively expectant approach was underlined by the Peristat report.[16] Combined proportion of induction of labour and primary caesarean section in the Netherlands was relatively low (21.2%) when compared to a more proactive approach presented European countries (range 14.4-52.4%).

Recent research comparing primary and secondary caesarean section rates in very preterm birth (28-31 weeks) also showed a wide range (49-88%) amongst ten developed European regions.[16] This comparison was conducted after correcting for differences in risk of preterm preeclampsia and intra uterine growth restriction. The authors of that study suggested that the observed variation is a result of socio-cultural and organisational factors and thus doctor's behaviour. The Netherlands had the lowest risk of caesarean section (49% of all very preterm births between 28-31 weeks) in that study. It is also possible that differences between guidelines pertaining neonatal care play a role in our deviating findings. Furthermore, clinician' behaviour and optimism (or lack thereof) about neonatal care might lower or raise the thresholds for medical intervention, which in turn, influence the incidence of preterm birth. This hypothesis merits testing in future research.

Differences in socio-cultural and organisational factors, resulting in varying doctor's behaviour, may at least partly explain the deviation of our results from trends in preterm birth described elsewhere.

However, this may change. We have shown that in multiple pregnancies, which are generally at higher risk than singleton pregnancies, the risk of medically indicated preterm birth significantly rose over the investigated years. Our results might indicate that, due the heightened awareness to risk, the doctor's attitude towards multiple pregnancies has become more proactive.

Fortunately we found parallel to the decreasing risk of preterm birth a decrease in the risk of perinatal mortality. Similar results were found in a previous performed study on trends in perinatal mortality in the Netherlands.[21] The exact role of decreasing preterm birth risk in the decline of perinatal mortality risk should be investigated in future research.

The fact that multiparous women have lower risk of preterm birth than nulliparous women is probably due to the fact that a risk selection has taken place. Ante partum care for multiparous women with a complicated obstetric history often differs from the care provided to nulliparous women. For instance, a selection of women with a history of spontaneous preterm birth is treated (following the national guideline[35]) with a cerclage or progesterone. Care is more likely to be provided by gynaecologists instead of midwives. Finally, some women with a complicated obstetric history might have chosen not to get pregnant again. The result is a lower proportion of preterm birth in multiparous women.

Proposals for future research

The main scope of our article was preterm birth as a clinically important outcome of pregnancy. The lower risk of medically indicated preterm birth among singletons reported in this article in combination with the higher risk of perinatal mortality seems to be paradoxical. Perhaps the more expectant treatment strategies in the Netherlands play a role in this matter. On the other hand, the scientific evidence for a more proactive intervening approach is limited. In contrast, the more proactive or sometimes even aggressive approach may lead to poorer neonatal outcome.[15]

At present, major randomized controlled trials investigate the best treatment regime for patients with premature prelabour rupture of membranes (PPROMEXIL study[36], PROMPT study[37]) and hypertensive disorders (HYPITAT II study[38]) between 34 and 37 weeks of gestation. The outcome of these studies might influence doctor's behaviour in the future.

In order to contribute to the discussion on relatively high perinatal mortality risk in the Netherlands we also aim on describing perinatal outcome after preterm birth in more detail.

Conclusions

Our study reported a significant decreasing trend in total preterm birth risk in singleton pregnancies in the Netherlands. This is in contrast with observations in many other developed countries where increasing medically indicated preterm birth led to an increasing trend of total preterm birth risk. We conjecture that our deviating findings are due to socio-cultural and organisational factors influencing the doctor's attitude towards interventions.

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CHAPTER 3

Ethnic and racial disparities in the risk of preterm birth
A systematic review and meta-analysis

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Abstract

Objectives *The aim of this study is to present a systematic review of available literature on the effect of maternal ethnicity (Africans/Blacks, Asians, Hispanics, others) on the risk of preterm birth.*

Study design *Studies investigating ethnicity (or race) as a risk factor for PTB were included if performing adjustments for confounders. A meta-analysis was performed and data were synthesized using a random effects model.*

Results *Forty-six studies met the inclusion criteria. Black ethnicity was associated with an increased risk of PTB when compared to whites (range of adjusted odds ratios (ORs) 0.6 to 2.8, pooled odds ratio 2.0 (95% Confidence interval (CI) 1.8-2.2)). For Asian ethnicity there was no significant association (range of adjusted ORs 0.6 to 2.3). For Hispanic ethnicity there also was no significant association (range of adjusted ORs 0.7 to 1.5).*

Conclusions *Ethnic disparities in the risk of preterm birth were clearly pronounced amongst black women. Future research should focus on preventative strategies for ethnic groups at high risk for preterm birth. Information on ethnic disparities in risk of preterm birth-related neonatal morbidity and mortality is lacking and is also a topic of interest for future research.*

Introduction

Preterm delivery is one of the most important factors contributing to perinatal morbidity and mortality in obstetric practice.[1] Preterm deliveries are those that occur at less than 37 completed weeks of gestation. The preterm birth risk has been reported as approximately 11% in the USA, between 5 and 7% in Europe, and 6.5% in Canada.[2] The major impact of preterm birth on public health has led to broad attention to the topic in scientific research. Many studies have reported increasing incidence of preterm birth during the last decades, mainly caused by an increase in medically indicated (iatrogenic) preterm delivery.[3-7] Unfortunately, it appears that efforts to reduce the risk of preterm birth have not resulted in lower incidence figures.

Preterm delivery results from a number of disorders, including known and unknown maternal and fetal disease. [8,9] Risk factors include specific pregnancy characteristics, obstetric history and basic maternal characteristics like maternal age, socioeconomic status and ethnicity.[10] Despite the identification of all these risk factors, the way that the risk factors interact in and contribute to the aetiology of preterm birth remains largely unknown.[11] Numerous publications have shown profound ethnic disparities in many areas of health and health care.[12] Ethnic disparities in perinatal healthcare outcomes, such as preterm birth, have been relatively intractable over the past decade.[13] Comparisons of groups in the United States, most of which compare African Americans/Blacks to Caucasians/Whites, and candidate gene approaches have suggested an ethnic predisposition of Blacks to preterm birth.[3] This predisposition could not be explained by differences in medical, social, and behavioural risk factors.[14]

However, several studies have reported contradictory findings on the relationship between ethnicity and preterm birth, mostly focusing on the ethnic groups living in the United States. To the best of our knowledge, no systematic review of the available evidence has been published on the impact of race and ethnicity on preterm birth. Therefore, the aim of this study is to present a systematic review of available literature on racial or ethnic disparities in the risk of preterm birth.

Methods

Data sources and search strategy

We used the Cochrane Collaboration's *Handbook for Systematic Reviews of Health Promotion and Public Health Interventions*[15] as a guideline for performing this review and meta-analysis.

We searched the electronic databases of MEDLINE (US National Library of Medicine, Betheshda, MD, USA) and EMBASE (Elsevier, Amsterdam, The Netherlands) from inception till August 1st 2011 for English-language articles published in peer reviewed journals.

The search strategy is summarised in Figure 1 and available on request. It combined terms for ethnicity with terms for preterm birth. Besides general terms for ethnicity or race we specified search terms for the three most frequently investigated ethnic groups, namely Blacks, Asians and Hispanics.

Study selection

Each of the initially identified articles was screened by two independent reviewers on title and abstract to determine its suitability for inclusion. The review included studies which had ethnic disparity as their main theme. We included studies which had preterm birth as their primary or secondary outcome and where the aim was to describe ethnic differences in preterm birth risk. We restricted our inclusion to studies that reported on primary data and adjusted for confounders. We considered socio-economic status, maternal age, parity and marital status as the most important confounders. All English literature was included. Gray literature – including unpublished abstracts, technical reports and dissertations – and comments, editorials and letters were excluded. We only included information available from the publications and did not seek additional information by contacting primary authors.

Definition of maternal ethnicity

The main determinant of the included articles is the ethnicity or race of the pregnant women. The terms ethnicity and race are used interchangeably in the included studies for the systematic review. In fact, the investigated determinant in most studies is often a mixture of ethnicity and race. To improve readability, we will only use the term ethnicity in this article. The definition of ethnicity is not straightforward when comparing international literature.[16] Often ethnicity is determined by the doctor's report or by self-reporting. We included all ways of determining maternal ethnicity. Studies reporting on only paternal ethnicity were excluded, but if results were available for the maternal/paternal ethnicity combination these studies were included in the present review. In this review the results will be described per ethnic group, which are *Blacks* (mostly Afro-Americans, but also Africans), *Asians* (South Asia, South East Asia, Central Asia), *Hispanics* and *others* (e.g. North Africans or aboriginals). *Whites* (Caucasians) will be used as the reference group.

Definition of preterm birth

Preterm birth is defined in de broadest sense as birth before 37 completed weeks of gestation. Studies that focused on subgroups of preterm birth (e.g. very preterm birth at less than 32 weeks of gestation) were also included and reported separately. Studies considering spontaneous as well as iatrogenic preterm births were included.

Data collection and quality assessment

The systematic review team consisted of five members. There were two master's-level researchers who acted as primary reviewers Preterm birth is defined in the broadest sense as birth before 37 completed weeks of gestation.

Furthermore there were three doctoral-level researchers, all with extensive experience in social epidemiology in general and specifically in obstetrics. If the primary reviewers could not reach consensus the expertise of the three remaining team members was used to reach agreement. The two reviewers scored the articles that were selected after screening title and abstract. Quality assessment was performed by using an adaptation of the Quality Assessment Tool for Quantitative Studies of the Effective Public Health Practice Project[17] which was modified by Blumenshine et al. for their systematic review on socioeconomic disparities in adverse birth outcomes.[18] Study quality was examined in four areas: (1) Size and representativeness of the sample; (2) study design, based on epidemiologic design and the appropriateness and clear characterisation of outcome measures; (3) data collection, based on the description of data sources, potential for bias, and data validity and reliability; (4) analysis, considering the appropriateness of analytic methods and of the presentation and interpretation of the results. All included articles were scored for all four areas resulting in an overall quality score (strong, moderate or weak). The scoring algorithm is available on request.

Data synthesis and statistical analysis

We designed a data abstraction form, and the two reviewers abstracted the data separately. We recorded data for each article on the ethnicities under investigation; the outcomes examined; and the direction, magnitude, and significance of each association, both before and after statistical adjustment for confounders (when possible). We have collected the published raw data for meta-analysis. Most studies reported only the statistically adjusted results, which provided conservative estimates of the associations of ethnicity with preterm birth. The measurements of comparison consisted of mostly adjusted odds ratios (aOR). If other types of comparisons (e.g. Hazard ratios, risk ratios) were performed then this is noted in the results. To provide a general estimate of the risk of preterm birth within each ethnic group we pooled crude data of the separate selected articles. For this meta-analysis only data on the most generic definition of preterm birth (<37 weeks) were pooled and the results are presented in a forest plot. Whites were used as the reference group. We entered and analysed the data using Review Manager 5 (Cochrane Collaboration, Oxford, UK). We used the raw data from each individual study to calculate the crude odds ratios (OR) and 95% confidence intervals (CI) before pooling the data. A random effects model was used (because of statistical heterogeneity in the outcome data) to calculate combined OR and 95% CI. Visual inspection of graphical data and I^2 test for heterogeneity were performed before pooling the data.

Summary of included studies

Table1. Summary of studies reporting on association between black ethnicity$^{\Delta}$ and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age Whites (days)	Mean gestational age Blacks (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
<37 weeks											
Getahun (2005)	USA	21 005 786	+	+	-	+	+	Whites	LMP	NR	NR
Alexander (2007)	USA	4 975 449	+	+	+	+	+	Whites	LMP	274	269
Singh (1996)	USA	2 112 607	+	+	+	+	+	Whites	NR	NR	NR
Gold (2010)	USA	1 600 000	?	?	?	?	?	Whites	NR	276	273 274
Cox (2009)	USA	292 776	+	+	-	+	+	Whites	LMP	NR	NR
Howard (2006)	USA	168 039	-	+	-	-	+	Whites	NR	NR	NR
Collins (1996)	USA	79 608	+	+	+	+	-	Whites	NR	NR	NR
Cervantes (1999)	USA	52 033	+	+	+	+	+	Whites	NR	NR	NR
Zeitlin (2004)	France	48 746	+	+	+	-	+	Whites	NR	NR	NR
Lu (2004)	USA	33 542	+	+	-	+	+	Whites	NR	NR	NR
Shiono (1986)	USA	28 330	+	+	+	+	+	Whites	LMP	NR	NR
Brown (2007)	USA	10 755	+	-	-	-	+	Whites	NR	NR	NR
Parker Frisbie (1997)	USA	8424	+	+	+	+	+	Whites	LMP	NR	NR
Goedhart (2008)	NL	7604	+	+	+	+	+	Whites	NR	NR	NR
Shen (2005)	USA	1 030 350	+	-	-	-	-	Whites	NR	NR	NR
Patel (2003)	UK	122 415	-	-	-	-	+	Whites	LMP+US	NR	NR
Leland (1995)	USA	38 551	+	+	+	+	+	Whites	NR	NR	NR
Zanconata (2011)	Italy	9026	+	-	-	-	-	Whites	NR	271	265
Blackmore-Prince (1999)	USA	6060	+	+	+	+	+	Whites	LMP	NR	NR
Barros (2001)	Brasil	5305	-	+	-	-	-	Whites	LMP	NR	NR
Collins (2007)	USA	3104	+	+	-	+	+	Whites	NR	NR	NR
Verkerk (1994)	NL	2072	+	+	-	-	+	Whites	LMP	NR	NR
Silva (2007)	Brasil	2063	-	+	-	-	-	Whites	LMP	NR	NR
Adams (1993)	USA	1868	-	-	-	-	+	Whites	US	NR	NR
Schieve (1996)	USA	32 017	-	-	-	-	-	Whites	LMP	NR	NR

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 1 continued.

Study	Definition of preterm birth	Prevalence Whites (%)	Prevalence Blacks (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
<37 weeks						
Getahun (2005)	<37 weeks	8.6%	14.8%	OR 1.7 (1.7-1.7) Black/black (maternal/paternal race)	Yes	Strong
				OR 1.4 (1.4-1.5) Black/white		
Alexander (2007)	<37 weeks	7.6%	15.0%	OR 1.9 (1.9-1.9)	Yes	Strong
Singh (1996)	<37 weeks	8.0%	18.5%	OR 1.9 (1.8-2.0)	Yes	Strong
Gold (2010)	<37 weeks	NR	NR	OR 1.1 (1.1-1.1) Black/black (maternal/paternal race)	No	Strong
			NR	OR 1.1 (1.0-1.1) Black/white		
Cox (2009)	<37 weeks	12%	19%	OR 1.6 (1.5-1.6)	Yes	Strong
Howard (2006)	<37 weeks	5.0%	12%	OR 2.3 (2.1-2.4)	Yes	Strong
Collins (1996)	<37 weeks	7.0%	14%	OR 1.5 (1.2-1.7)	Yes	Strong
Cervantes (1999)	<37 weeks	7.4%	14.7%	OR 1.6 (1.4-1.8) US-born Blacks	Yes	Strong
			12.3%	OR 1.3 (1.0-1.7) Immigrant Blacks		
Zeitlin (2004)	<37 weeks	4.6%	7.2%	OR 1.4 (1.2-1.6) Sub-Saharan Africa	No	Strong
Lu (2004)	<37 weeks	9.0%	14.3%	OR 1.7 (1.5-1.9)	Yes	Strong
Shiono (1986)	<37 weeks	6.1%	12.1%	OR 1.8 (1.6-2.1)	Yes	Strong
Brown (2007)	<37 weeks	17.7%	19.1%	OR 1.2 (1.0-1.3)	Yes	Strong
Parker Frisbie (1997)	<37 weeks	NR	NR	OR 2.8 (1.7-4.8)	No	Strong
Goedhart (2008)	<37 weeks	5.1%	9.2%	OR 1.6 (1.2-2.4) Surinamese	Yes	Strong
			8.8%	OR 2.0 (1.1-3.6) Ghanaian		
Shen (2005)	<37 weeks	2.7%	4.9%	OR 1.7 (1.6-1.8)	Yes	Moderate
Patel (2003)	<37 weeks	NR	NR	OR 0.6 (0.3-1.3) BMI <18.5	Yes	Moderate
			NR	OR 1.3 (1.2-1.6) BMI 18.5-24.9		
			NR	OR 0.9 (0.7-1.2) BMI 25.0-29.9		
			NR	OR 1.0 (0.7-1.5) BMI ≥30.0		
Leland (1995)	<37 weeks	25.4%	39.8%	OR 1.6 (1.5-1.7) maternal age 10-14 years	No	Moderate
Zanconata (2011)	<37 weeks	16.9%	25.9%	OR 1.7 (1.3-2.1) Sub-Saharan Africa	Yes	Moderate
Blackmore-Prince (1999)	<37 weeks	6.7%	17.4%	HR 2.8 (2.4-3.3)	Yes	Moderate
Barros (2001)	<37 weeks	6.7%	9.6%	OR 1.4 (1.1-1.8)	No	Moderate
Collins (2007)	<37 weeks	5.2%	11.6%	OR 1.2 (0.4-2.0)	Yes	Moderate
Verkerk (1994)	<37 weeks	5%	16%	OR 2.5 (1.0-6.1) Surinamese / Antillean	Yes	Moderate
Silva (2007)	<37 weeks	5.5%	9.7%	OR 1.8 (0.8-3.9)	Yes	Moderate
Adams (1993)	<37 weeks	10.5%	13.5%	HR 1.3 (1.0-1.7)	Yes	Moderate
Schieve (1996)	<37 weeks	11.5%	19.8%	RR 1.7 (1.6-1.9) Medicaid or Self-Pay Blacks	Yes	Weak
		7.7%	15.9%	RR 2.0 (1.7-2.2) Private insurance		

[Δ]: Ethnic group under investigation are African-Americans, unless mentioned otherwise.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio, PR= Incidence ratio, RR= Relative Risk, HR= Hazard ratio.

Table 1 continued. Summary of studies reporting on association between black ethnicity[Δ] and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age Whites (days)	Mean gestational age Blacks (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
Subgroups of preterm birth											
Getahun (2005)	USA	21 005 786	+	+	-	+	+	Whites	LMP	NR	NR
Alexander (2007)	USA	4 975 449	+	+	+	+	+	Whites	LMP	274	269
Simhan (2008)	USA	2 845 686	+	+	-	+	+	Whites	NR	NR	NR
Stein (2009)	USA	949 210	+	+	+	-	+	Whites	NR	NR	NR
Kistka (2007)	USA	711 015	+	+	-	+	+	Whites	LMP	NR	NR
Zeitlin (2004)	France	48 746	+	+	+	-	+	Whites	NR	NR	NR
Shiono (1986)	USA	28 330	+	+	+	+	+	Whites	LMP	NR	NR
Blackmore (1995)	USA	4916	+	+	+	+	+	Whites	LMP	NR	NR
Shen (2008)	USA	666 462	-	-	-	+	+	Whites	NR	275	272
Zhang (1992)	USA	185 244	+	+	+	-	+	Whites	LMP	NR	NR
Leland (1995)	USA	38 551	+	+	+	+	+	Whites	NR	NR	NR
Zanconata (2011)	Italy	9026	+	-	-	-	-	Whites	NR	271	265
Blackmore-Prince (1999)	USA	6060	+	+	+	+	+	Whites	LMP	NR	NR
Adams (1993)	USA	1868	-	-	-	-	+	Whites	US	NR	NR
Schieve (1996)	USA	32 017	N/A	N/A	N/A	N/A	N/A	Whites	LMP	NR	NR

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 1 continued.

Study	Definition of preterm birth	Prevalence Whites (%)	Prevalence Blacks (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
Subgroups of preterm birth						
Getahun (2005)	<34 weeks	2.0%	5.1%	OR 2.3 (2.3-2.3) Black/black (maternal/paternal race)	N/A	Strong
			3.9%	OR 1.8 (1.7-1.9) Black/white		
	<32 weeks	1.1%	3.1%	OR 2.7 (2.7-2.7) Black/black (maternal/paternal race)		
			2.4%	OR 2.0 (1.9-2.1) Black/white		
Alexander (2007)	<33 weeks	1.2%	3.8%	OR 2.8 (2.7-2.8)	N/A	Strong
Simhan (2008)	<34 weeks	1.6%	3.9%	OR 2.4 (2.3-2.5) Black/black (maternal/paternal race)	N/A	Strong
			2.8%	OR 1.7 (1.5-1.9) Black/white		
			3.6%	OR 2.2 (1.9-2.5) Black/hispanic		
Stein (2009)	32-36 weeks	NR	NR	OR 2.1 (2.0-2.1) African American	N/A	Strong
			NR	OR 1.6 (1.5-1.7) Sub-Saharan Africa		
		NR	NR	OR 4.9 (4.6-5.3) African American		
			NR	OR 3.1 (2.7-3.6) Sub-Saharan Afirca		
Kistka (2007)	<34 weeks	3.0%	8.8%	OR 2.2 (2.1-2.3)	N/A	Strong
Zeitlin (2004)	33-36 weeks	3.7%	5.1%	OR 1.4 (1.2-1.6) Sub-Saharan Africa	N/A	Strong
	<33 weeks	0.9%	2.1%	OR 2.4 (1.9-3.1) Sub-Saharam Afroca		
Shiono (1986)	<33 weeks	1.0%	2.7%	OR 2.4 (1.7-3.2)	N/A	Strong
Blackmore (1995)	36 weeks	2.0%	4.0%	OR 1.6 (1.0-2.5)	Yes	Strong
	34-35 weeks	1.9%	3.8%	OR 1.8 (1.1-2.7)		
	20-33 weeks	1.2%	5.2%	OR 2.9 (1.8-4.7)		
Shen (2008)	<35 weeks	0.8%	2.1%	OR 2.3 (2.0-2.5) after pPROM	N/A	Moderate
Zhang (1992)	34-36 weeks	4.5%	8.7%	PR 2.0 (1.9-2.1) idiopathic	N/A	Moderate
		0.6%	0.9%	PR 1.6 (1.5-1.8) after pPROM		
		0.9%	1.5%	PR 1.9 (1.7-2.1) iatrogenic		
	20-33 weeks	1.0%	3.5%	PR 3.5 (3.2-3.7) idiopathic		
		0.4%	1.2%	PR 3.3 (2.9-3.7) after pPROM		
		0.5%	1.0%	PR 2.5 (2.2-2.8) iatrogenic		
Leland (1995)	<32 weeks	6.3%	10.9%	OR 1.6 (1.5-1.8) maternal age 10-14 years	N/A	Moderate
Zanconata (2011)	<33 weeks	3.8%	7.6%	OR 2.1 (1.4-3.0) Sub-Saharan Africa	N/A	Moderate
Blackmore-Prince (1999)	33-36 weeks	5.3%	12.4%	HR 2.6 (2.1-3.1)	N/A	Moderate
	29-32 weeks	1.0%	2.9%	HR 3.1 (2.3-4.4)		
	20-28 weeks	0.4%	2.0%	HR 4.8 (3.3-6.9)		
Adams (1993)	<33 weeks	2.9%	4.8%	HR 1.6 (1.0-2.6)	N/A	Moderate
	<29 weeks	1.2%	2.4%	HR 2.0 (0.9-4.0)		
Schieve (1996)	<32 weeks	2.6%	5.3%	RR 2.0 (1.7-2.5) Medicaid or Self-Pay Blacks	N/A	Weak
	<37 weeks	1.4%	3.7%	RR 2.6 (2.0-3,4) Private insurance		

$^{\Delta}$: Ethnic group under investigation are African-Americans, unless mentioned otherwise.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio, PR= Incidence ratio, RR= Relative Risk, HR= Hazard ratio.

Table 2. Summary of studies reporting on association between Asian ethnicity[Δ] and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age Whites (days)	Mean gestational age Blacks (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
<37 weeks											
Alexander (2007)	USA	4 975 449	+	+	+	+	+	Whites	LMP	273	272
Singh (1996)	USA	2 112 607	+	+	+	+	+	Whites	NR	NR	NR
Li (2010)	USA	316 280	+	+	+	+	+	Whites	LMP	NR	NR
Wong (2008)	USA	202 686	+	+	+	+	+	Chinese	NR	NR	NR
Howard (2006)	USA	168 039	-	+	-	-	+	Blacks	NR	NR	NR
Zeitlin (2004)	France	48 746	+	+	+	-	-	Whites	NR	NR	NR
Yi (2011)	USA	37 751	+	+	-	-	-	Whites	NR	NR	NR
Liu (2008)	Taiwan	30 770	+	-	-	-	+	Non-aboriginal Taiwanese	NR	NR	NR
Shiono (1986)	USA	28 330	+	+	-	+	+	Whites	LMP	NR	NR
Rao. Cheng (2006)	USA	6511	+	+	+	-	+	Japanese	NR	NR	NR

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 2 continued.

Study	Definition of preterm birth	Prevalence Whites (%)	Prevalence Asians (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
<37 weeks						
Alexander (2007)	<37 weeks	7.6%	8.7%	OR 1.4 (1.4-1.4)	Yes	Strong
Singh (1996)	<37 weeks	8.0%	7.9%	OR 1.0 (0.9-1.0) Chinese	Yes	Strong
			8.5%	OR 1.1 (1.0-1.2) Japanese		
			11.9%	OR 1.5 (1.4-1.5) Filipino		
			9.8%	OR 1.4 (1.4-1.5) Other Asian		
Li (2010)	<37 weeks	8.2%	6.1%	OR 1.0 (0.9-1.0) Foreign-born Chinese Americans	Yes	Strong
			7.8%	OR 1.1 (1.0-1.2) US-borm Chinese Americans		
Wong (2008)	<37 weeks	7.7%	9.9%	OR 1.3 (1.2-1.5) Japanese	No	Strong
			12.6%	OR 1.7 (1.6-1.8) Filipina		
			10.2%	OR 1.5 (1.4-1.6) Asian Indian		
			7.4%	OR 1.1 (1.0-1.2) Korean		
			10.0%	OR 1.4 (1.3-1.6) Vietnamese		
			14.3%	OR 1.9 (1.9-1.9) Hawaiian		
			12.7%	OR 1.5 (1.2-1.9) Samoan		
			11.8%	OR 1.5 (1.4-1.6) Guamanian		
Howard (2006)	<37 weeks	11.5%	8.3%	OR 0.9 (0.7-1.1)	Yes	Strong
Zeitlin (2004)	<37 weeks	4.6%	5.1%	OR 1.0 (0.9-1.2) South/East Asia	No	Strong
Yi (2011)	<37 weeks	9.2%	6.1%	OR 0.9 (0.7-1.0) Foreign born Korean	Yes	Strong
			7.6%	OR 0.9 (0.6-1.2) US-born Korean		
Liu (2008)	<37 weeks	8.6%	6.3%	OR 0.8 (0.6-1.0) Mainland Chinese	No	Strong
			6.2%	OR 0.8 (0.7-1.1) Indonesian		
			7.7%	OR 1.1 (0.9-1.4) Vietnamese		
			13.5%	OR 1.8 (1.5-2.1) Aboriginal Taiwanese		
Shiono (1986)	<37 weeks	6.1%	7.9%	OR 1.4 (1.2-1.7)	Yes	Strong
Rao. Cheng (2006)	<37 weeks	7.6%	8.1%	OR 1.1 (0.8-1.6) Chinese	No	Strong
			12.2%	OR 1.6 (1.1-2.3) Filipino		

[Δ]: Ethnic group under investigation are Asians, unless specified in more detail.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio.

Table 2 continued. Summary of studies reporting on association between Asian ethnicity[Δ] and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age Whites (days)	Mean gestational age Asians (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
<37 weeks (continued)											
Rao (2006)	USA	3779	+	+	-	-	+	Other Asian	NR	NR	NR
Schempf (2010)	USA	NR	+	+	+	+	+	Whites	LMP	NR	NR
Shen (2005)	USA	1 030 350	+	-	-	-	-	Whites	NR	NR	NR
Patel (2003)	UK	122 415	-	-	-	-	+	Whites	LMP+US	NR	NR
Aveyard (2002)	UK	36 257	+	+	+	+	+	Whites	LMP	NR	NR
Nystrom (2008)	USA	9669	+	+	+	-	-	Whites	NR	275	274
Zanconata (2011)	Italy	9026	+	-	-	-	-	Whites	NR	271	271

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 2 continued.

Study	Definition of preterm birth	Prevalence Whites (%)	Prevalence Asians (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
<37 weeks (continued)						
Rao (2006)	<37 weeks	9.3%	7.5%	OR 0.7 (0.5-0.9) Chinese	No	Strong
			10.7%	OR 1.2 (0.9-1.6) Filipino		
			11.4%	OR 1.7 (13-2.2) Indian		
			6.6%	OR 0.6 (0.4-1.1) Japanese		
			5.3%	OR 0.6 (0.3-1.1) Korean		
			9.2%	OR 0.7 (0.4-1.1) Pacific islander		
			12.4%	OR 1.3 (0.7-2.4) Vietnamese		
Schempf (2010)	<37 weeks	7.5%	7.1%	OR 1.2 (1.1-1.2) Asian Indian	Yes	Strong
			14.0%	OR 1.7 (1.6-1.9) Cambodian		
			6.5%	OR 1.0 (0.9-1.0) Chinese		
			11.2%	OR 1.6 (1.6-1.7) Filipino		
			10.8%	OR 1.3 (1.1-1.4) Hmong		
			9.6%	OR 1.5 (1.2-1.8) Indonesian		
			7.9%	OR 1.1 (1.0-1.2) Japanese		
			5.6%	OR 0.9 (0.8-1.0) Korean		
			13.7%	OR 1.7 (1.5-2.0) Laotian		
			9.1%	OR 1.3 (1.1-1.6) Pakistani		
			9.4%	OR 1.4 (1.1-1.6) Thai		
			8.1%	OR 1.1 (1.1-1.2) Vietnamese		
Shen (2005)	<37 weeks	2.7%	2.3%	OR 0.9 (0.8-1.1)	Yes	Moderate
Patel (2003)	<37 weeks	NR	NR	OR 1.5 (1.3-1.6) Non-smoking, supported mother	Yes	Moderate
			NR	OR 1,9 (1.4-2.6) Non-smoking, unsupported mother		
			NR	OR 1.9 (1.3-2.9) Smoking, supported mother		
			NR	OR 2.3 (1.3-4.2) Smoking, unsupported morther		
Aveyard (2002)	<37 weeks	7.7%	8.5%	OR 1.1 (1.01-1.2)	Yes	Moderate
Nystrom (2008)	<37 weeks	12.6%	12.2%	OR 1.1 (0.9-1.2) Asian/Asian (maternal/paternal race)	Yes	Moderate
			12.5%	OR 1.1 (0.9-1.5) Asian/white (maternal/paternal race)		
Zanconata (2011)	<37 weeks	16.9%	16.3%	OR 0.9 (0.7-1.2)	Yes	Moderate

[Δ]: Ethnic group under investigation are Asians, unless specified in more detail.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio.

Table 2 continued. Summary of studies reporting on association between Asian ethnicity[Δ] and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age Whites (days)	Mean gestational age Asians (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
Subgroups of preterm birth											
Alexander (2007)	USA	4 975 449	+	+	+	+	+	Whites	LMP	273.7	272.2
Stein (2009)	USA	949 210	+	+	+	-	+	Whites	NR	NR	NR
Wong (2008)	USA	202 686	+	+	+	+	+	Chinese	NR	NR	NR
Zeitlin (2004)	France	48 746	+	+	+	-	-	Whites	NR	NR	NR
Shiono (1986)	USA	28 330	+	+	-	+	+	Whites	LMP	NR	NR
Rao. Cheng (2006)	USA	6511	+	+	+	-	+	Japanese	NR	NR	NR
Rao (2006)	USA	3779	+	+	-	-	+	Other Asian	NR	NR	NR
Aveyard (2002)	UK	36 257	+	+	+	+	+	Whites	LMP	NR	NR
Nystrom (2008)	USA	9669	+	+	+	-	-	Whites	NR	275	274
Zanconata (2011)	Italy	9026	+	-	-	-	-	Whites	NR	271	271

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 2 continued.

Study	Definition of preterm birth	Prevalence Whites (%)	Prevalence Asians (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
Subgroups of preterm birth						
Alexander (2007)	<33 weeks	1.2%	1.3%	OR 1.4 (1.3-1.5)	N/A	Strong
Stein (2009)	32-36 weeks	NR	NR	OR 0.9 (0.9-1.0) East Asia	N/A	Strong
			NR	OR 1.6 (1.5-1.8) Southeast Asia		
			NR	OR 1.6 (1.5-1.6) South Central Asia		
	<32 weeks		NR	OR 0.9 (0.8-1.0) East Asia		
			NR	OR 1.7 (1.3-2.0) Southseast Asia		
			NR	OR 1.7 (1.5-2.0) South Central Asia		
Wong (2008)	<32 weeks	1.0%	1.2%	OR 1.1 (0.8-1.5) Japanese	N/A	Strong
			1.7%	OR 1.6 (1.4-2.0) Filipina		
			1.4%	OR 1.6 (1.3-1.9) Asian		
			1.2%	OR 1.4 (1.1-1.9) Korean		
			1.2%	OR 1.2 (1.0-1.6) Vietnamese		
			2.2%	OR 1.4 (0.9-2-3) Hawaiian		
			2.5%	OR 2.2 (1.4-3.6) Samoan		
			1.6%	OR 1.4 (1.1-1.7) Guamanian		
Zeitlin (2004)	<33 weeks	0.9%	0.8%	OR 0.9 (0.6-1.4) South/East Asia	N/A	Strong
	33-36 weeks	3.7%	4.3%	OR 1.2 (1.0-1.4) Southeast Asia		
Shiono (1986)	<33 weeks	1.0%	1.1%	OR 1.1 (0.7-1.8)	N/A	Strong
Rao. Cheng (2006)	<34 weeks	3.1%	3.2%	OR 1.0 (0.6-1.8) Chinese	N/A	Strong
			4.8%	OR 1.7 (1.0-3.0) Filipino		
Rao (2006)	<34 weeks	1.9%	0.8%	OR 0.3 (0.2-0.7) Chinese	N/A	Strong
			2.3%	OR 1.3 (0.7-2.3) Filipino		
			3.7%	OR 4.7 (2.7-8.0) Indian		
			0.0%	NR		
			1.2%	OR 0.7 (0.2-3.0) Korean		
			1.7%	OR 0.2 (0.1-0.5) Pacific islander		
			2.9%	OR 1.6 (0.5-5.4) Vietnamese		
Aveyard (2002)	<34 weeks	2.5%	2.6%	OR 1.1 (0.9-1.3)	N/A	Moderate
			0.6%	OR 1.3 (0.9-1.9)		
Nystrom (2008)	<32 weeks	2.3%	3.2%	OR 1.3 (1.0-1.8) Asian/Asian (maternal/paternal race)	N/A	Moderate
			2.2%	OR 1.1 (0.9-1.5) Asian/White (maternal/paternal race)		
Zanconata (2011)	<32 weeks	3.8%	4.3%	OR 1.1 (0.7-1.7)	N/A	Moderate

[A]: Ethnic group under investigation are Asians, unless specified in more detail.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio.

Table 3. Summary of studies reporting on association between Hispanic ethnicity[Δ] and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age Whites (days)	Mean gestational age Hispanics (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
<37 weeks											
Alexander (2008)	USA	21 012 605	+	+	+	+	+	Whites	LMP	273	272
Howard (2006)	USA	168 039	-	+	-	-	+	Blacks	NR	NR	NR
Cervantes (1999)	USA	52 033	+	+	+	+	+	Whites	NR	NR	NR
Lu (2004)	USA	33 542	+	+	+	+	+	Whites	NR	NR	NR
Shiono (1986)	USA	28 330	+	+	+	+	+	Whites	LMP	NR	NR
Brown (2007)	USA	10 755	+	-	-	-	+	Whites	NR	NR	NR
Shen (2005)	USA	1 030 350	+	-	-	-	-	Whites	NR	NR	NR
Parker Frisbie (1997)	USA	8 424	+	+	+	+	+	Whites	LMP	NR	NR
Subgroups of preterm birth											
Alexander (2008)	USA	21 012 605	+	+	+	+	+	Whites	LMP	273	272
Simhan (2008)	USA	2 845 686	+	+	-	+	+	Whites	NR	NR	NR
Auger (2011)	Canada	2 143 134	+	+	+	+	+	Whites	US	NR	NR
Stein (2009)	USA	949 210	+	+	+	-	+	Whites	NR	NR	NR
Shiono (1986)	USA	28 330	+	+	+	+	+	Whites	LMP	NR	NR

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 3 continued.

Study	Definition of preterm birth	Prevalence Whites (%)	Prevalence Hispanics (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
<37 weeks						
Alexander (2008)	<37 weeks	8.3%	9.9%	OR 1.3 (1.3-1.3)	Yes	Strong
Howard (2006)	<37 weeks	5.0%	10.4%	OR 1.1 (1.0-1.1) West-indian/Brazilian	Yes	Strong
			7.5%	OR 0.8 (0.7-0.8) South/Central American		
			10.1%	OR 0.9 (0.8-1.0) Puerto Rican		
			11.6%	OR 1.1 (0.7-1.5) Cuban		
Cervantes (1999)	<37 weeks	7.4%	8.3%	OR 1.0 (0.8-1.2) US-born Mexican	Yes	Strong
			6.8%	OR 0.8 (0.7-0.9) immigrant Mexican		
			10.3%	OR 1.2 (1.0-1.5) US-borm Puerto Rican		
			12.3%	OR 1.5 (1.2-1.9) immigrant Puerto Rican		
Lu (2004)	<37 weeks	9.0%	8.8%	OR 1.0 (0.8-1.2)	Yes	Strong
Shiono (1986)	<37 weeks	6.1%	8.7%	OR 1.4 (1.2-1.6)	Yes	Strong
Brown (2007)	<37 weeks	17.7%	8.4%	OR 0.7 (0.5-0.8)	Yes	Strong
Shen (2005)	<37 weeks	2.7%	2.5%	OR 0.9 (0.8- 1.0)	Yes	Moderate
Parker Frisbie (1997)	<37 weeks	NR	NR	OR 0.1 (0.0-1.8)	No	Moderate
Subgroups of preterm birth						
Alexander (2008)	<33 weeks	1.3%	1.6%	OR 1.3 (1.3-1.4)	N/A	Strong
Simhan (2008)	<34 weeks	1.6%	1.9%	OR 1.1 (1.0-1.1) Hispanic/Hispanic (maternal/paternal race)	N/A	Strong
			1.7%	OR 1.1 (1.0-1.2) Hispanic/White (maternal/paternal race)		
			2.7%	OR 1.5 (1.2-1.9) Hispanic/Black (maternal/paternal race)		
Auger (2011)	32-36 weeks	NR	NR	OR 1.3 (1.2-1.3) Haiti	Yes	Strong
			NR	OR 1.3 (1.2-1.4) Other Caribbean Country		
	28-31 weeks		NR	OR 2.0 (1.7-2.3 Haiti		
			NR	OR 1.9 (1.6-2.3) Other Caribbean Country		
	< 27 weeks		NR	OR 4.0 (3.5-4.6) Haiti		
			NR	OR 3.5 (2.9-4.3) Other Caribbean Country		
Stein (2009)	32-36 weeks	NR	NR	OR 1.8 (1.7-1.8) Hispanic Caribbean	N/A	Strong
			NR	OR 1.5 (1.4-1.6) Mexico		
			NR	OR 1.6 (1.5-1.7) Central America		
			NR	OR 1.7 (1.6-1.7) South America		
			NR	OR 1.6 (1.5-1.7) Other Hispanic		
	22-36 weeks		NR	OR 2.9 (2.7-3.1) Hispanic Caribbean		
			NR	OR 1.8 (1.6-2.1) Mexico		
			NR	OR 2.8 (2.5-3.2) Central America		
			NR	OR 2.5 (2.3-2.8) South America		
			NR	OR 2.4 (2.0-2.8) Other Hispanic		
Shiono (1986)	<33 weeks	1.0%	1.3%	OR 1.3 (0.9-1.9)	N/A	Strong

$^{\Delta}$: Ethnic group under investigation are Hispanics, unless specified in more detail.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio.

Table 4. Summary of studies reporting on association between various ethnicities[Δ] and risk of preterm birth

Study	Setting	Sample Size	Adjustments *					Reference Group	Pregnancy dating	Mean gestational age reference (days)	Mean gestational age other (days)
			Maternal Age	SES †	Parity	Marital Status	Other				
<37 weeks											
Alexander (2008)	USA	21 012 605	+	+	+	+	+	Whites	LMP	273	266
Langridge (2010)	Australia	567 468	+	+	+	-	+	Non-aboriginals	NR	NR	NR
Lu (2004)	USA	33 542	+	+	+	+	+	Whites	NR	NR	NR
Goedhart (2008)	NL	7604	+	+	+	+	+	Whites	NR	NR	NR
Schempf (2010)	USA	NR	+	+	+	+	+	Whites	LMP	NR	NR
Luo (2004)	Canada	1 125 462	+	+	+	+	+	Whites	NR	NR	NR
Melamed (2000)	Israel	69 164	+	-	+	-	+	Jewish	LMP+US	NR	NR
Zanconata (2011)	Italy	9026	+	-	-	-	-	Whites	NR	271	272 270
Verkerk (1994)	NL	2072	+	+	-	-	+	Whites	LMP	NR	NR
Silva (2007)	Brasil	2063	-	+	-	-	-	Whites	LMP	NR	NR
Subgroups of preterm birth											
Alexander (2008)	USA	21 012 605	+	+	+	+	+	Whites	LMP	273	266
Stein (2009)	USA	949 210	+	+	+	-	+	Whites	NR	NR	NR
Zanconata (2011)	Italy	9026	+	-	-	-	-	Whites	NR	271	272 270

The studies are ordered by quality rating and sample size.
*: Adjustment for confounders if applied (+), if not applied (-), if not specified (?), if no adjustment applied in general (N/A)
†: Socio-economic status (SES) defined by maternal education, family income, food stamp recipient, WIC recipient, prenatal care utilization and/or maternal insurance status.

Table 4 continued.

Study	Definition of preterm birth	Prevalence reference (%)	Prevalence other (%)	Adjusted association (with 95% CI)	Data available for meta-analysis	Quality rating
<37 weeks						
Alexander (2008)	<37 weeks	8.3%	11.0%	OR 1.3 (1.3-1.3) American Indian	N/A	Strong
Langridge (2010)	<37 weeks	NR	NR	OR 1.5 (1.3-1.7) Aboriginal	N/A	Strong
Lu (2004)	<37 weeks	9.0%	8.7%	OR 0.8 (0.6-1.1) American Indian	N/A	Strong
		9.0%	9.5%	OR 1.2 (0.9-1.5) Asian pacific island		
Goedhart (2008)	<37 weeks	5.1%	5.0%	OR 0.9 (0.5-1.5) Turkish	N/A	Strong
			4.1%	OR 0.7 (0.5-1.2) Moroccan		
Schempf (2010)	<37 weeks	7.5%	11.1%	OR 1.3 (1.1-1.5) Native Hawaiian	N/A	Strong
			11.8%	OR 1.5 (1.2-1.8) Guamanian		
			18.8%	OR 2.1 (1.7-2.6) Marshallese		
			12.0%	OR 1.4 (1.3-1.6) Samoan		
			10.8%	OR 1.3 (1.1-1.6) Tongan		
Luo (2004)	<37 weeks	6.0%	10.1%	OR 1.5 (1.3-1.8) Inuit	N/A	Moderate
			5.5%	OR 0.8 (0.7-0.9) Indian		
Melamed (2000)	<37 weeks	NR	NR	OR 1.2 (1.1-1.3) Bedouins	N/A	Moderate
Zanconata (2011)	<37 weeks	16.9%	13.0%	OR 0.7 (0.5-0.9) Middle East and North Africa	N/A	Moderate
			17.8%	OR 1.0 (0.7-1.5) Central and Southe America		
Verkerk (1994)	<37 weeks	5%	3%	OR 0.2 (0.04-1.1) Turkish	N/A	Moderate
Silva (2007)	<37 weeks	5.5%	9.5%	OR 1.8 (1.2-2.5) Mulatto	N/A	Moderate
Subgroups of preterm birth						
Alexander (2008)	<33 weeks	1.3%	1.8%	OR 1.3 (1.3-1.3) American Indian	N/A	Strong
Stein (2009)	32-36 weeks	NR	NR	OR 1.1 (1.0-1.3) North Africa	N/A	Strong
	22-31 weeks			OR 1.3 (0.9-1.8) North Africa		
Zanconata (2011)	<33 weeks	3.8%	4.8%	OR 1.2 (0.8-2.0) Middle East and North Africa	N/A	Moderate
			2.3%	OR 0.6 (0.2-1.5) Central and South America		

$^{\Delta}$: Ethnic group under investigation is specified in more detail.
LMP = last menstrual period, US = ultrasound, NR = not reported
OR = Odds ratio, RR = Relative risk.

Results

Out of 2866 articles identified by our search strategy, 2791 were duplicates or were excluded on the basis of title and abstract. The full text of the remaining 75 publications was evaluated, leading to the exclusion of a further 30 studies, resulting in 45 studies (1.6%) for inclusion. Reasons for exclusion are summarized in figure 1.

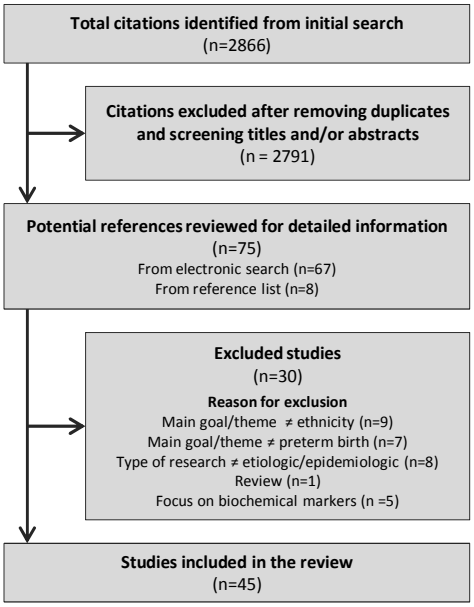

Figure 1. Flow diagram of search strategy and results.

The selected articles (tables 1-4) were published between 1983 and 2011. Most (n=32) studies were performed in the United States. Of the 45 included studies, 41 showed a significant association between at least one ethnic group and preterm birth. Two studies also included multiple pregnancies instead of singleton pregnancies only. [19,20] Most studies reported on the dichotomous outcome of preterm birth. Only six studies also reported on the mean gestational age per ethnic group. There were differences in the way gestational age was calculated. Seventeen studies performed pregnancy dating by using date of last menstrual period (LMP). Two studies achieved pregnancy dating by using a combination of LMP and ultrasonic measurement of crown-rump-length (CRL), whereas another two studies used CRL data only. The remaining 23 studies did not report which technique was used for determining gestational age. Study characteristics and quality, adjusted odds ratios (aOR) for the total of preterm birth <37 weeks, meta-analysis results and aOR for subgroups of preterm birth (e.g. <32 weeks) are reported below. All abstracted data is available upon request.

Blacks

Thirty studies reported results considering black ethnicity and preterm birth. A summary of the results is presented in table 1. The majority (18 out of 30; 60%) of these included studies were scored as *strong* after quality assessment. Most (24 out of 30; 80%) of the selected studies focused solely on Blacks living in the USA in their investigation. The remaining 6 studies focused on Sub-Saharan African Blacks, Surinamese Creole Blacks and Brazilian Blacks respectively. Twenty-seven (90%) of the selected studies reported an increased adjusted risk of preterm birth within the investigated black ethnic group when compared to whites.

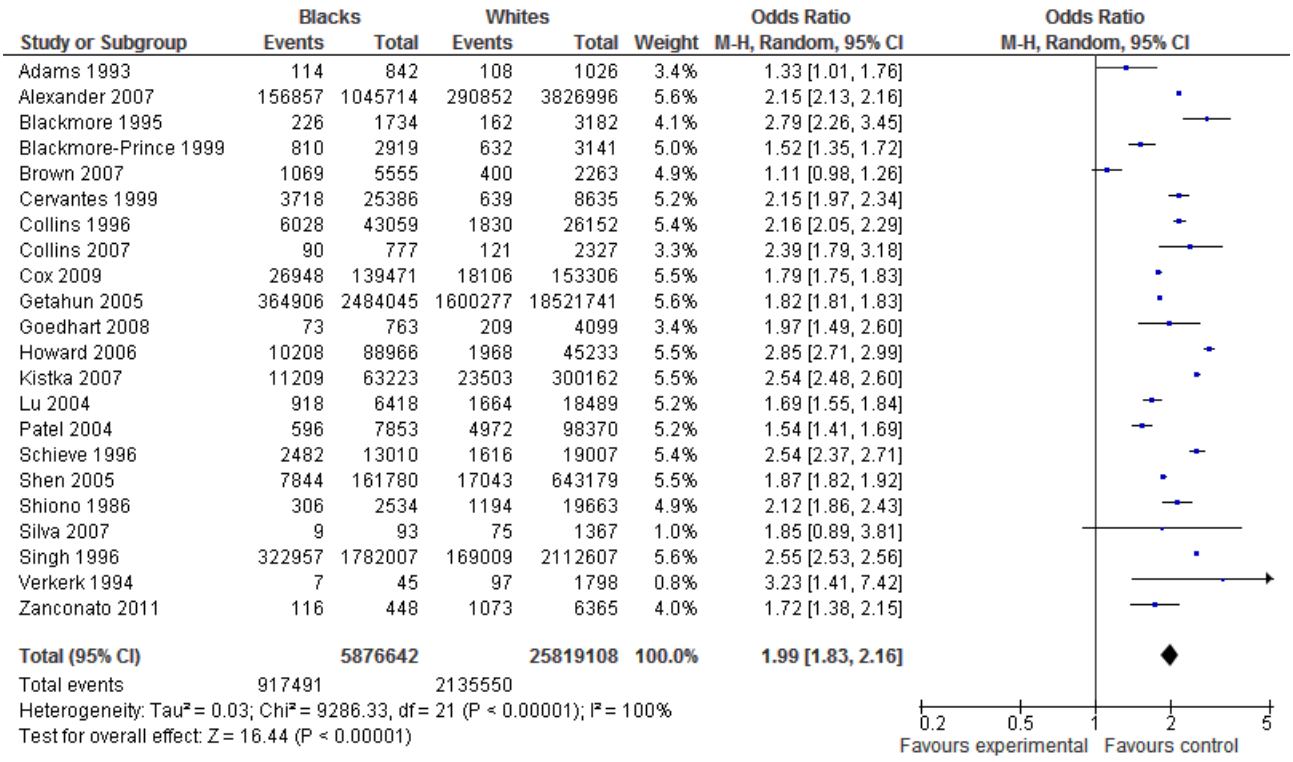

Figure 2. Forest plot of studies on preterm birth among black women.

All but one study reported adjusted estimates after controlling for at least one important confounder. Schieve at al.[21] presented results after stratifying for the type of medical insurance. Twenty-five studies published results considering the most generic definition of preterm birth, namely delivery before 37 completed weeks of gestation. Among these 25 studies the incidence of preterm birth among Blacks ranged from 4.9% to 39.8% and the reported aOR ranged from 0.6 to 2.8. Cervantes et al. [22] subdivided their results for Blacks by country of birth. The aOR is 1.6 (95% CI 1.4-1.8) for US-born Blacks and 1.3 (95% CI 1.0-1.7) for immigrant Blacks. Patel et al.[23] stratified their results for maternal BMI where the aOR for preterm birth is highest in women with a normal BMI between 18.5 and 24.9 (1.3, 95% CI 1.2-1.6). Zhang et al.[24] is the only included study that made a distinction between idiopathic, iatrogenic and spontaneous preterm birth following premature prelabour rupture of membranes (pPROM). The incidence ratio appeared to be highest for the idiopathic preterm births, especially those occurring before 34 weeks of gestation.

Then we performed a meta-analysis of 22 studies which provided crude data that allowed us to pool and extract an average (unadjusted) estimate. Figure 2 shows the results. The included observational studies appeared to be very heterogeneous (I^2 = 100%). However, visual inspection of the included studies showed that the results are comparable. The odds of delivering a child preterm are 2.0 (95% CI 1.8-2.2) for a woman of black ethnicity when compared to whites.

Various subgroups of preterm birth were investigated. Five studies reported results for preterm birth before 34 completed weeks of gestation and four studies had delivery before 32 weeks as their outcome measure. Reported adjusted relative measure of association of Blacks compared to whites varied from 1.7 to 3.7 (<34 weeks) and from 2.0 to 4.9 (<32 weeks).

Asians

Seventeen studies reported on the effect of Asian ethnicity on the risk of preterm birth. Most of these studies (71%) scored as *strong* after quality assessment. A summary of the published results is presented in table 2. The sample size of the included studies varied between 3779 and 4,975,449 women.

All included studies reported the outcome of preterm birth <37 weeks, the broadest definition of preterm birth. Seven studies showed a significant increased risk of preterm birth for the Asian ethnic group compared to whites or at least one of the reported Asian subgroups. The remaining five studies using whites as their reference group showed no significant effect. The risk of preterm birth among Asians varied between 2.3% and 16.3%. The reported relative measures of association of Asians compared to whites ranged from 0.9 to 2.3.

	Asians		Whites			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Alexander 2007	8938	102739	290852	3826996		1.16 [1.13, 1.18]	
Aveyard 2002	975	11524	1490	19241		1.10 [1.01, 1.20]	
Howard 2006	63	747	2220	45233		1.78 [1.37, 2.32]	
Li 2010	10214	165660	12175	150620		0.75 [0.73, 0.77]	
Nystrom 2008	480	3916	702	5575		0.97 [0.86, 1.10]	
Patel 2004	1049	16192	4972	98370		1.30 [1.21, 1.39]	
Schempf 2010	21406	223872	34852	464689		1.30 [1.28, 1.33]	
Shen 2005	947	41437	17043	643179		0.86 [0.80, 0.92]	
Shiono 1986	152	1923	1194	19663		1.33 [1.11, 1.58]	
Singh 1996	31315	312030	169009	2112607		1.28 [1.27, 1.30]	
Yi 2011	783	12917	2320	25834		0.65 [0.60, 0.71]	
Zanconato 2011	88	539	1073	6365		0.96 [0.76, 1.22]	

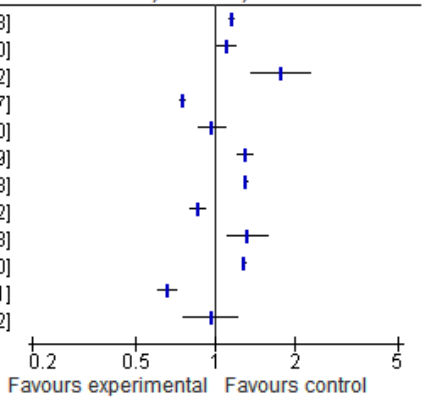

Figure 3. Forest plot of studies on preterm birth among Asian women.

Five studies specified the investigated Asian groups in more detail. Only two of these studies used Whites as their reference group. Schempf et al.[25] and Singh et al.[26] reported results for Chinese, Japanese and Filipino women separately instead of considering all Asians as one ethnic group. Between these two studies, results were comparable as can be seen in table 2. The highest risk of preterm birth was found within the Asian ethnic subgroup of Filipinos. Li et al.[27] and Yi et al.[28] presented data on Chinese and Korean women respectively. In addition they divided the population into US-born women and immigrants. Patel et al.[23] stratified their analyses into smoking versus non-smoking women and supported versus unsupported mothers. The aOR appeared to be highest for smoking, unsupported women of Asian origin when compared to smoking, unsupported white women. Twelve studies provided crude data and were included for meta-analysis. Figure 3 shows the results. The included studies appeared to be very heterogeneous (I^2 = 99%) and visual inspection did not allow us to present a pooled estimate.

Hispanics

Table 3 shows a summary of the studies reporting on Hispanic ethnicity as a risk factor for preterm birth. Eleven studies were included, of which ten were performed in the United States. After quality assessment, 82% of the studies were scored as *strong*. All but one used whites as their reference group. All studies reported adjusted estimates after controlling for at least one important confounder. Six studies reported on Hispanics without defining this group in more detail, and the reported results show great variation. The reported relative measures of association of Hispanics compared to whites ranged from 0.1 to 1.5. Three studies show a significant decreased risk of preterm birth within the Hispanic ethnic group whereas three other studies reported the opposite effect. Furthermore, seven studies provided crude data that allowed us to pool and extract an average unadjusted estimate. The included studies appeared to be very heterogeneous (I^2 = 99%). The included studies appeared to be very heterogeneous (I^2 = 99%) and visual inspection did not allow us to present a pooled estimate (figure 4). Five studies specified Hispanic ethnicity in more detail, focusing on country of birth or including paternal ethnicity. Five studies used subgroups of preterm birth (e.g. <34 weeks) as their main outcome measure.

Other ethnicities

We included eleven studies that investigated the effect of other ethnicities on the risk of preterm birth. Most of the studies were scored as *strong* (55%) or *moderate* (45%) after quality assessment. Various reference groups were used, which makes it difficult to compare the results. We included four studies investigating ethnic groups from Mediterranean countries including Turkish and Moroccan women and Middle East or North African women in general. Three of these studies showed no significant increased risk of preterm birth when compared to whites. For the subgroups of preterm birth (e.g. <32 weeks) there also appeared to be no significant effect. A summary of all the results is presented in table 4.

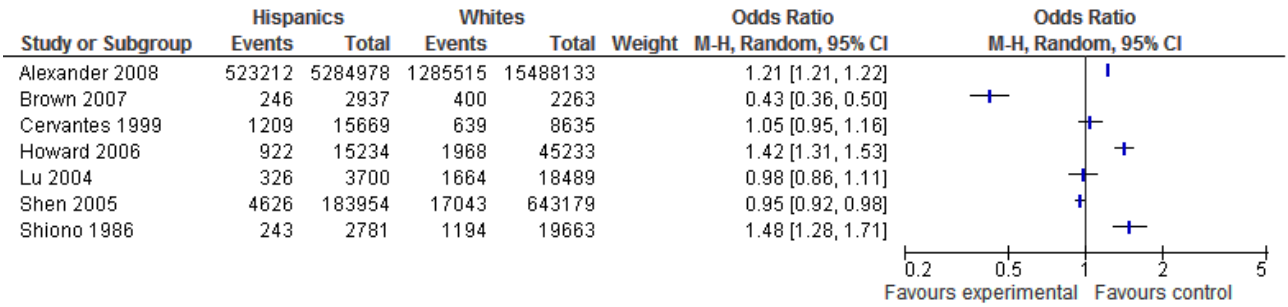

Figure 4. Forest plot of studies on preterm birth among Hispanic women.

Discussion

Principal findings

We found 45 studies on the association between maternal ethnicity and the risk of preterm birth, of which 41 reported a significant positive association between at least one ethnic group and preterm birth risk. Blacks appear to have a significantly increased (range of adjusted ORs 0.6 to 2.8, pooled odds ratio 2.0 (95% CI 1.8-2.2)) risk of preterm birth when compared to whites (30 included studies). For women of Asian ethnicity there was no significant association, with ORs ranging from 0.6 to 2.3 (17 included studies). For women of Hispanic ethnicity there was no significant difference in the risk of preterm birth when compared to whites. Currently recognized confounders do not appear to explain the increased risk of preterm birth among black women.

Strengths and weaknesses of the studies

In general, the included observational studies were scored as *strong* or *moderate* after quality assessment. There was great variation in the sample size of the included studies (range 1868 to 21,012,605), which in turn has an impact on the generalisability of the smaller studies and, inevitably, they have less statistical power.

Most studies performed adjustments for the most relevant possible confounders like socio-economic status, maternal age and parity. Nevertheless, some studies did not control for important confounders [21;23;29-32]. Since various factors other than maternal ethnicity are associated with preterm birth, it is difficult to compare and combine the results of individual outcomes across studies because of varying degrees of control for potential confounders. Less adjustment for confounding will lead to an overestimation of the effect of maternal ethnicity on preterm birth.

Unfortunately, the majority of studies did not report how pregnancy dating was achieved. The studies that did report these data mostly calculated gestational age by using last menstrual period.

Taipale et al.[33] showed that prediction of day of delivery by ultrasonically measuring crown-rump-length between 11 and 16 weeks of gestation is 1.7-3.5 days more accurate than the use of LMP. However, as in other studies,[34,35] Taipale et al. also stated that they found no difference in the number of preterm deliveries when using CRL measurement instead of LMP and therefore the lack of information on technique of pregnancy dating has not influenced our results to a large degree.

Forty-four of the included studies, all but one, only reported data on preterm birth as a single outcome. Additional information on racial disparities in the three subtypes of preterm birth (idiopathic, spontaneous after pPROM and iatrogenic) is lacking. Zhang et al.[24] is the only study that made this distinction, showing the greatest racial disparities in the subtype of spontaneous preterm birth without pPROM.

The included studies show great variation in the reported incidence of preterm birth. For instance, when looking at preterm birth rates in Blacks before 37 weeks of gestation, the incidence ranges from 4.9% reported by Shen et al.[30] to almost 40% reported by Leland et al.[36] These large differences can mostly be attributed to varying inclusion and exclusion criteria of the different studies. For instance, Leland et al. only included teenage pregnancies with a maternal age between 10-14 years. This specific subgroup is at high risk for various adverse perinatal outcomes compared to the total population.[37] Therefore, incidence figures differ and as a consequence we did not include these data for meta-analysis.

Furthermore, defining maternal ethnicity is not straightforward.[16] The main determinant investigated in the included studies was often a mixture of ethnicity and race. In most studies ethnicity was defined by the caregiver. Others used self-reported ethnicity data provided by the participating women or studies classified ethnicity by country of origin or by skin colour. Most included studies that were performed in the United States used a classification of ethnicity into non-Hispanic whites, American Blacks and Hispanics. The results presented in the studies are less applicable or difficult to translate to countries with another or mixed composition of maternal ethnicities.

We discussed the difficulties of defining ethnicity in the methods section. The problem of definition also holds, but to a lesser extent, for socio-economic status (SES). SES is a composite measurement of maternal education and family income. However, the way in which the composite variable SES was determined varied between studies.

Despite recent advances in the handling of missing data,[38] many studies that were included in this review performed a complete case analysis and did not use imputation techniques for missing data. This might have led to biased estimates. Furthermore, unfortunately not all studies reported their results in a way that allowed us to pool them for meta-analysis.

Strengths and weaknesses of this review

To the best of our knowledge this is the first review focusing solely on the subject of ethnicity or race as a risk factor for preterm birth. The search strategy was broad and thorough and designed to capture all available relevant literature. Our search strategy was designed to retrieve all studies with ethnicity as their main theme when investigating the risk of preterm birth. We used general synonyms for ethnicity in our search terms. Articles with only a specific ethnicity name (for instance 'Inuit') in their title or abstract without the words ethnicity or race might thus have been missed. The number of studies included in the 'others' section is influenced by this limitation. For instance, a recently published systematic review by Shah et al.[39] on perinatal outcomes amongst Aboriginal women contains studies on Aboriginal women that were not included in this review. On the other hand, we did specify our search terms for blacks, Asians and Hispanics as they are the three most frequently investigated ethnic groups. Finally, a narrative review Dominguez et al.[40] together with all of our included studies were checked for relevant references.

Meta-analyses are limited by biases, introduced through the individual studies as well as by the process of selecting studies for a systematic review. Before pooling the results one should investigate the heterogeneity of the different studies. This is done by eye-balling as well as by performing the I^2 test for heterogeneity. The latter showed poor results in our analyses. However it is known that the I^2 heterogeneity tends to overestimate heterogeneity in studies performed on large databases.[41] The heterogeneity might be caused by the usage of slightly varying definitions of ethnicity or the inclusion of slightly differing subgroups of a specific ethnic group.[16]

Also, in meta-analyses of observational studies secondary researchers are unable to adjust for possible confounders. However, the subject of our review does not lend itself to experimental studies such as randomized trials.

Meaning of the results and future research

This review emphasizes the independent effect of ethnicity, especially Black ethnicity, on the risk of preterm birth before 37 weeks. This effect of black ethnicity is even more pronounced in the subgroups of preterm birth (e.g. <34 of <32 weeks). The effect of Asian and Hispanic ethnicity on the risk of preterm birth is less pronounced. Risk of preterm birth appeared only to be increased in some Asian subgroups. For Hispanics we found no significant increased risk for preterm birth when compared to whites. Despite tending to be less educated, having high rates of uninsurance, low socioeconomic status and late entry into prenatal care, Hispanics have relatively low rates of preterm birth. In literature, this phenomenon is often referred to as the "Hispanic paradox".[42] The possible explanations for this phenomenon are: (1) Strong social support within the immigrant community, (2) protective factors in the immigrant culture and (3) self-selection of the healthiest immigrants.[43-45] These relatively favourable perinatal outcomes are especially reported for the first generation immigrants.

Preterm birth is defined by using the rigid cut-off of birth before 37 completed weeks. In current clinical practice this cut-off is identical for all ethnic groups. Thus we implicitly assume that mean gestational length is similar for all individuals, irrespective of maternal ethnicity. This is likely to be incorrect. Future research should focus on the question of whether there are ethnic disparities in optimal gestational length. When investigating optimal gestational length we should also incorporate perinatal outcome in the methodology of research. Optimal gestational length should namely be defined as the gestational age at which the risks of perinatal and maternal morbidity and mortality are the lowest. This issue is an important topic for future research within perinatal care.

As preterm birth is the most important cause of perinatal morbidity and mortality [1] the results presented here highlight the need for thoughtful conceptualisation of likely pathways through which ethnicity affects preterm birth risk, and in turn maternal and infant health. Subsequently we should think of possible ways to intervene in those pathways, especially among Blacks and Asians. The perinatal condition after preterm birth has a great impact on short- and long-term morbidity and short- and long-term healthcare costs. Despite the major effort of much scientific research there is no significant reduction of the risk of preterm birth over the last decades. Instead, the risk has been increasing in most developed countries.[3-7]

In order to significantly reduce the risk of preterm birth, and the strongly related risk of perinatal morbidity and mortality, we should adjust the perinatal care provided to an individual woman's risk profile. This individual risk profile should be determined using all specific maternal, including paternal and fetal characteristics known to contribute to preterm birth pathogenesis. As presented in this review, black and Asian maternal ethnicity appears to be an important factor in determining such an individual risk profile.

In this review we have demonstrated the ethnic disparities in risk of preterm birth independent of other risk factors. The causal pathway of this phenomenon is likely to be of epigenetic origin. Future research should further focus on the genetic or epigenetic components leading to the increased incidence of preterm birth. In the future, biomarkers might help us to assess the individual risk profile or provide an incentive to investigate preventive treatment strategies.

As the majority of studies in this review focus on ethnic groups living in the United States, the ethnic diversity of other countries is not well represented. Therefore epidemiologic research should be performed to investigate disparities in, for instance, ethnic groups living in Europe.[46] Information on the risk of preterm birth among ethnic minorities from North-African or Middle East origin is scarce. Goedhart et al., and Verkerk et al. showed no significant risk difference when comparing Turkish and Moroccan women to the Caucasian women, whereas Zanconata et al. showed a significant decreased risk of PTB for women from the Middle East or Northern Africa.

Expanding our knowledge on these and other ethnic groups is important, as these ethnicities form a substantial proportion of women of childbearing age in many European countries. Future research on ethnic disparities in preterm birth risk should systematically adjust for important confounders, such as socio-economic status, maternal age and history of preterm birth. This will improve the quality of research and the possibility for comparison.

Conclusions

There are clear ethnic disparities in the risk of preterm birth, with black women being at higher risk. As ethnic compositions of societies differ greatly, future prospective research should focus on ethnic groups living outside the United States. Despite the heterogeneity of the included studies in defining ethnicity and adjustment for confounding, ethnic disparities clearly exist. This merits research on the causal pathways of these differences, and on preventative measures to reduce the incidence of preterm birth.

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CHAPTER 4

Ethnic disparities in the risk of adverse neonatal outcome after spontaneous preterm birth

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Abstract

Objective *To describe ethnic disparities in the risk of spontaneous preterm birth and related adverse neonatal outcome.*

Design *Nationwide prospective cohort study.*

Setting *The Netherlands: 1999-2007.*

Population *We included 969,491 singleton pregnancies with a spontaneous onset of labour.*

Methods *We investigated ethnic disparities in perinatal outcome for European white, African, South-Asian, Mediterranean and East-Asian women. We performed multivariate logistic regression analyses to calculate the adjusted odds ratio (aOR) and confidence intervals (CI) of spontaneous preterm birth and the risk of subsequent neonatal morbidity and mortality.*

Main outcome measure *Primary outcome measure was spontaneous preterm birth before 37 completed weeks of gestation. Secondary we investigated subsequent adverse neonatal outcome which was a composite outcome of intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), infant respiratory distress syndrome (IRDS), neonatal sepsis or neonatal morality within 28 days after birth.*

Results *Compared to European whites, the aOR of delivering preterm was 1.33 (95% CI 1.26-1.41) for African women, 1.58 (95% CI 1.47-1.69) for South-Asians, 0.88 (95% CI 0.84-0.91) for Mediterraneans and 1.04 (95% CI 0.98-1.11) for East-Asians. Subsequent odds of adverse neonatal outcome were significantly lower for African (aOR 0.51; 95% CI 0.41-0.64) and Mediterranean women (aOR 0.86; 95% CI 0.75-0.99) when compared to European whites.*

Conclusions *African and South-Asian women are at higher risk for preterm birth than European white women. However, the harmful effect of preterm birth on neonatal outcome is less severe for these women.*

Introduction

Ethnicity and race are marked as an important independent risk factor for various health outcomes.[1-4] On the part of the health care providers ethnic disparities can be caused by the effect of prejudice, bias, stereotyping and clinical uncertainty. Furthermore some ethnic groups are more likely to refuse medical treatment, although this phenomenon only explains a small part of the observed ethnic disparities.[5] Current research on ethnic and racial disparities is focusing on epigenetic factors that play a role in the pathogenesis of diseases with an ethnic specific risk profile.[5]

Ethnic disparities were described for the important perinatal outcome of preterm birth with an increased risk for especially African and Hispanic women.[6-9] Preterm birth is defined as birth before 37 completed weeks of gestation. Risk of preterm birth varies between 5-20% in the USA and 5-15% in Europe.[10;11] Preterm birth has a great impact on perinatal outcome. It is the major cause of perinatal morbidity and mortality, mostly due to respiratory immaturity, intracranial haemorrhages and infections[12] Ethnic disparities in the risk of perinatal mortality were also described in various publications, but often analyzed irrespective of gestational age (preterm versus term) and subtype of perinatal mortality (fetal versus neonatal).[13-16] Furthermore, most studies on ethnic disparities were performed in the USA, focusing mainly on blacks, Hispanics and non-Hispanic whites.

There is a lack of information on ethnic disparities in spontaneous preterm birth risk in countries other than the USA and on ethnic disparities in the impact of spontaneous preterm birth on neonatal outcome. Therefore, the aim of our study is to investigate disparities in risk of spontaneous preterm birth and subsequent risk of adverse neonatal outcome for the main ethnic groups in Europe.

Material and Methods

This study was performed in a prospective nationwide cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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. The midwifery and obstetrics data collection starts at the booking visit and contain perinatal data from 20 gestational weeks onwards. The neonatal registry contains data on hospital admissions of newborns within 28 days after birth. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands. The PRN contains anonymous data, so no ethical approval was needed.

All singleton pregnancies, from 22^{+0} weeks onwards, between 1 January 1999 and 31 December 2007 were included. We excluded all cases with unknown gestational age and all cases with a birth weight <500 grams. We excluded all cases of antepartum fetal mortality (0.5%) and all cases in which maternal ethnicity was defined as "other Western", or "other non-Western", or was unknown (0.5%). As we are only interested in spontaneous births we excluded all inductions of labour or primary caesarean sections (30%). Spontaneous birth included all births after spontaneous onset of contractions with or without prelabour rupture of membranes (PROM). Our final cohort thus consisted of only spontaneous births where fetus was alive at the start of labour.

We used the classification of the Netherlands Perinatal Registry which was consistently used during the last 15 years. The classification is performed by the caregiver on the basis of race and country of birth. Maternal ethnicity is an obligatory field in the PRN. We classified maternal ethnicity/race in European white, African, South-Asian, Mediterranean and East-Asian. Classification is performed by the caregiver. With African women we refer to women of (originally) sub-Saharan African origin. With South-Asian women we refer to women who are (originally) from the Indian subcontinent. With Mediterranean we refer to non-European women from countries around the Mediterranean Sea, thus including North-African (e.g. Morocco) and Middle-East (e.g. Turkey) countries. Women from other regions in Asia (for instance China and Japan) were assigned to the "East-Asian" category.

The primary outcome measure was spontaneous preterm birth, defined as birth before 37 completed weeks of gestation. We also investigated the risk of spontaneous very preterm birth (< 32 weeks of gestation). These two outcome measures were investigated within our total cohort of pregnancies with a delivery from 22 weeks and onwards. In advance, we investigated the impact of preterm birth on adverse neonatal outcome of for all ethnic groups. Therefore, our secondary outcome measure was preterm birth-related neonatal mortality, defined as intrapartum or neonatal mortality within 28 days after (very) preterm birth. We also created a composite outcome measure for adverse neonatal mortality. This composite outcome was defined as intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), infant respiratory distress syndrome (IRDS), neonatal sepsis or neonatal morality within 28 days after birth. These neonatal outcome measures were investigated in a subset of our total cohort, namely in pregnancies with a spontaneous preterm delivery between 26 and 37 weeks of gestation. We chose the lower cut-off of 26 weeks of gestation because this was the national threshold for fully active neonatal treatment during our total study period.

Statistical analyses

We calculated the incidence of the primary and secondary outcome measures for every ethnic group. We also studied the incidence of several other risk factors associated with our primary outcome and secondary outcome measures.

These other risk factors include maternal age (categorized in <25 years, 25-29 years, 30-34 years, ≥35 years), parity (categorized in 0, 1 or ≥2 previous deliveries), socio-economic status (categorized in low (<p25), middle, high (>p75)), living in a deprived area (yes/no), late booking visit (≥ 18 weeks of gestation), use of artificial reproductive technology (ART) and male fetal gender.

To inspect the association between variables and spontaneous preterm birth and related adverse neonatal outcome we performed univariate logistic regression analysis. To obtain adjusted odds ratios (aOR), however, we performed multivariate logistics regression analysis. For the calculation of adjusted odds ratios for preterm birth related adverse neonatal outcome we entered three additional variables to the model. These included location of delivery (3^{rd} level hospital versus non-3^{rd} level), and small for gestational age (birthweight <10^{th} percentile). In the final model we also adjusted for gestational age (weeks). Data were analyzed using SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

During our 9-year study period there were 969,491 spontaneous singleton births in the Netherlands. The overall risk of spontaneous preterm birth was 5.4% (n = 52,049). Baseline characteristics of the total cohort are summarized in table 1. We studied five ethnic groups: 840,421 (87%) European white women, 21,438 (2%) African women, 10,377 (1%) South-Asian women, 78,989 (8%) Mediterranean women, and a remaining 18,266 women (2%) who were classified as being of East-Asian ethnicity. Table 1 shows the prevalence figures of other risk factors for spontaneous preterm birth.

The risk of spontaneous preterm birth was 5.3% for European white women, 7.5% for African women, 8.5% for South-Asian women, 4.7% for Mediterranean women and 5.8% for East-Asian women. The risk of spontaneous very preterm birth (before 32 weeks of gestation) is also presented in table 1 and shows that the prevalence is over 2 times higher for African women than for European white women.

Table 2 shows the results of the univariate and multivariate logistic regression and presents the unadjusted and adjusted odds ratios for spontaneous preterm birth as well as spontaneous very preterm birth. The odds ratios of preterm birth (<37 weeks), when adjusted for all other variables presented in table 2, are significantly increased for African (OR 1.33; 95% CI 1.26-1.41) and South-Asian women (OR 1.58; 95% CI 1.47-1.69). In contrast, the odds ratios were significantly decreased for Mediterranean women. When focusing on the more severe subgroup of preterm birth, namely very preterm birth (<32 weeks), we found quite similar ethnic disparities (table 2).

Table 1. Characteristics of spontaneous singleton births (>22 weeks) in the Netherlands from 1999 to 2007 according to maternal ethnicity

	Ethnicity				
	White	**African**	**South-Asian**	**Mediterranean**	**East-Asian**
Population	840,421	21,438	10,377	78,989	18,266
Maternal age					
<25 years, n (%)	77,591 (9.2)	7179 (33.5)	2399 (23.1)	22,336 (28.3)	4000 (21.9)
25-29 years, n (%)	243,045 (28.9)	5843 (27.3)	3598 (34.7)	27,045 (34.2)	5484 (30.0)
30-34 years, n (%)	358,336 (42.6)	5180 (24.2)	3028 (29.2)	19,295 (24.4)	5623 (30.8)
≥35 years, n (%)	161,449 (19.2)	3236 (15.1)	1352 (13.0)	10,313 (13.1)	3159 (17.3)
Number of previous deliveries					
0, n (%)	354,815 (42.2)	8010 (37.4)	3959 (38.2)	25,409 (32.2)	7840 (42.9)
1, n (%)	342,608 (40.8)	7110 (33.2)	3999 (38.5)	26,654 (33.7)	7104 (38.9)
≥2, n (%)	142,998 (17.0)	6318 (29.5)	2419 (23.3)	26,926 (34.0)	3322 (18.2)
Socio economic status					
High, n (%)	224,386 (26.7)	2143 (10.0)	1764 (17.0)	6311 (8.0)	3828 (21.0)
Middle, n (%)	457,304 (54.4)	4952 (23.1)	2591 (25.0)	21,543 (27.3)	7339 (40.2)
Low, n (%)	158,731 (18.9)	14,343 (66.9)	6022 (58.0)	51,135 (64.7)	7099 (38.9)
Living in deprived area, n (%)	22,371 (2.7)	7913 (36.9)	2928 (28.2)	22,110 (28.0)	2195 (12.0)
Late booking visit, n (%)	35,241 (4.2)	3365 (15.7)	1032 (10.0)	9967 (12.6)	2200 (12.0)
Artificial reproductive technology, n (%)	93,032 (11.1)	2975 (13.9)	1374 (13.2)	8952 (11.3)	1986 (10.9)
Male fetal sex, n (%)	428,133 (50.9)	10,898 (50.8)	5341 (51.5)	39,888 (50.5)	9343 (51.2)
Spontaneous preterm birth, n (%)	44,790 (5.3)	1607 (7.5)	877 (8.5)	3712 (4.7)	1063 (5.8)
Spontaneous very preterm birth, n (%)	4588 (0.6)	329 (1.5)	88 (0.9)	512 (0.7)	118 (0.7)
Mean gestational age in weeks in all deliveries (SD)	39.3 (1.7)	38.9 (2.2)	38.8 (1.9)	39.3 (1.8)	39.0 (1.7)
Mean gestational age in weeks in preterm deliveries (SD)	34.3 (2.5)	33.4 (3.6)	34.4 (2.6)	34.0 (3.0)	34.3 (2.6)
Mean gestational age in weeks in term deliveries (SD)	39.6 (1.2)	39.4 (1.2)	39.2 (1.2)	39.6 (1.2)	39.3 (1.2)
Mean birth weight in grams (SD)	3484 (538)	3254 (565)	3097 (519)	3429 (518)	3304 (501)

Then, we narrowed our scope focusing only on the women with spontaneous preterm deliveries. There were a total of 50,823 spontaneous preterm births that occurred between 26 and 37 weeks of gestation. The overall risk of neonatal mortality after spontaneous preterm birth was 9.7‰ (n = 494) and the overall risk of adverse neonatal outcome was 108‰ (n=5487). Table 3 shows the number of births for the different ethnic groups. Furthermore it shows the number (and permillages) of cases with neonatal mortality or adverse neonatal outcome after preterm and very preterm birth. The risk of neonatal mortality after spontaneous preterm birth was highest for African women (14.7‰) and lowest for Mediterranean women (8.7‰). The risk of adverse neonatal outcome was also highest for African women (124‰), but lowest in East-Asians (99‰).

Table 2. Unadjusted and adjusted odds ratios (OR) for spontaneous preterm and very preterm birth in singleton pregnancies

	Preterm birth (< 37 weeks)		Very preterm birth (< 32 weeks)	
	Unadjusted OR (95% CI)	**Adjusted OR* (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR* (95% CI)**
Ethnicity				
White	Reference	Reference	Reference	Reference
African	1.44 (1.37-1.52)	1.33 (1.26-1.41)	2.84 (2.54-3.18)	1.92 (1.69-2.17)
South-Asian	1.64 (1.53-1.76)	1.58 (1.47-1.69)	1.56 (1.26-1.93)	1.24 (1.00-1.54)
Mediterranean	0.88 (0.85-0.91)	0.88 (0.84-0.91)	1.19 (1.09-1.30)	0.92 (0.83-1.02)
East-Asian	1.10 (1.03-1.17)	1.04 (0.98-1.11)	1.19 (0.99-1.42)	0.92 (0.77-1.11)
Maternal age				
<25 years	1.13 (1.10-1.16)	0.95 (0.92-0.97)	1.54 (1.42-1.66)	1.10 (1.02-1.20)
25-29 years	Reference	Reference	Reference	Reference
30-34 years	0.85 (0.83-0.87)	0.98 (0.96-1.00)	0.87 (0.81-0.92)	1.01 (0.94-1.08)
≥35 years	0.82 (0.80-0.84)	1.03 (1.004-1.06)	0.94 (0.87-1.02)	1.10 (1.01-1.19)
Number of previous deliveries				
0, n (%)	2.20 (2.16-2.24)	2.11 (2.07-2.16)	2.25 (2.11-2.39)	2.05 (1.93-2.19)
1, n (%)	Reference	Reference	Reference	Reference
≥2, n (%)	1.00 (0.97-1.03)	0.98 (0.96-1.01)	1.30 (1.20-1.42)	1.17 (1.07-1.28)
Socio economic status				
Low	1.19 (1.16-1.22)	1.13 (1.10-1.17)	1.55 (1.44-1.67)	1.27 (1.17-1.38)
Middle	1.06 (1.04-1.09)	1.07 (1.05-1.09)	1.12 (1.05-1.21)	1.12 (1.04-1.20)
High	Reference	Reference	Reference	Reference
Living in deprived area				
Yes	1.19 (1.14-1.23)	1.07 (1.02-1.11)	1.64 (1.50-1.79)	1.10 (0.99-1.22)
No	Reference	Reference	Reference	Reference
Late booking visit				
Yes	1.19 (1.14-1.23)	1.53 (1.48-1.59)	4.40 (4.12-4.70)	4.38 (4.09-4.70)
No	Reference	Reference	Reference	Reference
Conception				
ART	2.51 (2.46-2.57)	2.37 (2.32-2.42)	2.35 (2.21-2.50)	2.42 (2.27-2.58)
Spontaneous	Reference	Reference	Reference	Reference
Fetal sex				
Male	1.28 (1.26-1.31)	1.28 (1.26-1.30)	1.44 (1.36-1.51)	1.43 (1.35-1.51)
Female	Reference	Reference	Reference	Reference

* Adjusted for all other mentioned variables.

Finally, we calculated the odds ratio for neonatal mortality and the odds ratio for adverse neonatal outcome for the different ethnic groups. Table 4 shows the results of the univariate and multivariate analyses for the outcome of neonatal mortality after preterm birth. The risk of subsequent neonatal mortality after preterm birth was significant lower for Mediterranean women (aOR 0.65; 95% CI 0.44-0.96). Due to the small number of neonatal deaths we could not calculate odds ratios for the South-Asian and East-Asian ethnic groups.

Fortunately, there was enough statistical power to calculate odds ratios for adverse neonatal outcome for all ethnic groups. Table 4 also shows that neonates of African, Mediterranean and East-Asian women have a significant decreased risk of adverse neonatal outcome after spontaneous preterm birth.

Table 3. Incidence of neonatal mortality and adverse neonatal outcome after spontaneous preterm and very preterm birth according to maternal ethnicity

	Preterm (< 37 weeks)					**Very Preterm (< 32 weeks)**				
	Births	**Neonatal mortality**		**Adverse neonatal outcome**		**Births**	**Neonatal mortality**		**Adverse neonatal outcome**	
	n	n	‰	n	‰	n	n	‰	n	‰
Ethnicity										
White	43865	423	9.6	4689	107	3663	252	68.8	2287	624
African	1494	22	14.7	185	124	216	13	60.2	121	560
South-Asian	853	7	8.2	95	111	64	4	62.5	45	703
Mediterranean	3572	33	9.2	415	116	372	23	61.8	232	624
East-Asian	1039	9	8.7	103	99	94	6	63.8	57	606
Total	50823	494	9.7	5487	108	4409	298	67.7	2742	622

Table 4. Unadjusted and adjusted* odds ratios (OR) for neonatal mortality and adverse neonatal outcome after spontaneous preterm and very preterm birth in singleton pregnancies

	Neonatal mortality after preterm birth (<37 weeks)		**Neonatal mortality after very preterm birth (<32 weeks)**	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI) ***	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI) ***
Ethnicity				
White	Reference	Reference	Reference	Reference
African	1.54 (1.00-2.36)	0.73 (0.45-1.18)	0.87 (0.49-1.54)	0.55 (0.29-1.04)
South-Asian	0.85 (0.40-1.80)	Δ	0.90 (0.33-2.50)	Δ
Mediterranean	0.96 (0.67-1.37)	0.65 (0.44-0.96)	0.89 (0.57-1.39)	0.65 (0.40-1.05)
East-Asian	0.90 (0.46-1.74)	Δ	0.92 (0.40-2.13)	Δ
	Adverse neonatal outcome after preterm birth (<37 weeks)		**Adverse neonatal outcome after very preterm birth (<32 weeks)**	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI) ***	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI) ***
Ethnicity				
White	Reference	Reference	Reference	Reference
African	1.18 (1.01-1.38)	0.51 (0.41-0.64)	0.77 (0.58-1.01)	0.44 (0.32-0.62)
South-Asian	1.05 (0.84-1.30)	0.87 (0.65-1.16)	1.43 (0.83-2.45)	Δ
Mediterranean	1.10 (0.99-1.22)	0.84 (0.72-0.98)	0.98 (0.80-1.14)	0.74 (0.57-0.97)
East-Asian	0.92 (0.75-1.13)	0.75 (0.57-0.99)	0.93 (0.61-1.41)	Δ

* Adjusted for: maternal age, number of previous deliveries (parity), socio-economic status, late booking visit, location of delivery, SGA <p10 and fetal sex and gestational age.

Overall risk of spontaneous preterm birth was 5.4% in a population cohort of 969,491 births in the Netherlands. African and South-Asian women have a significant increased risk of preterm birth, but have a decreased risk of subsequent adverse neonatal outcome. Mediterranean women had a decreased risk of preterm birth when compared to European white women, but also a significant decreased risk of subsequent adverse neonatal outcome.
Compared to European whites, other ethnic groups had a decreased risk of adverse neonatal outcome after preterm birth. For an identical pregnancy length, neonates of African, South-Asian, Mediterranean and East-Asian women seem to be better resistant to the harmful impact of preterm birth.

Our study was based on data of a large population-based, well-maintained, national perinatal registry. As the vast majority of the caregivers contribute to the PRN registry it comprises approximately 96% of all pregnancy and birth characteristics in The Netherlands. Using such a large database reduces the chances of biasing the estimates. All our analyses were based on variables that are obligatory to be filled in by the caregivers, resulting in very low numbers of missing values.

Defining maternal ethnicity or race is difficult and open for debate in international literature.[17] It is hard to strike the right balance between getting too specific in the definition on the one hand and too general on the other hand. For our analyses we were limited by the categorization that was used for over 15 years in the national PRN database. This definition is used since the mid-1980s and is in fact a mixture of ethnicity and race. The categories include all major ethnic groups living in The Netherlands and other European countries. We think that possible misclassification will not have influenced our results to a large degree. Unfortunately, the PRN database does not provide information on paternal ethnicity, migration status (e.g. categorization in 1st and 2nd generation) and age at migration. Another limitation lies within the definition of socio-economic status (SES). The SES of a woman is based on the mean SES of the 4-digit postal code of her residence neighbourhood and not on the individual socio-economic status. Although this approach is in general sufficient in large databases as ours, still the adjustment for SES might have been limited.

Studies reporting ethnic disparities in the risk of (spontaneous) preterm birth were often performed in the United States of America, thus mainly focusing on African-American, Hispanic and non-Hispanic white women.[18,19] Furthermore, it should be noted that most of the other studies on ethnic disparities did not make a distinction between spontaneous and medically indicated preterm births which hinders comparison. Getahun et al.[8] investigated risk of preterm birth in a nationwide cohort of 21,005,786 women. They reported an adjusted odds ratio of 1.7 (95% CI 1.7-1.7) for spontaneous preterm birth for black women when compared to white women.

This effect of black ethnicity was confirmed in numerous other studies in the USA and is comparable with our findings in the Netherlands (adjusted odds ratio 1.33 (95% CI 1.26-1.41).[7,20-22]

Schempf et al.[23] reported on women from South-Asian countries like India and Pakistan in the USA. They were shown to be at significantly higher risk of preterm birth than the white women. These findings are in accordance with our results on South-Asian women's risk of preterm birth. Our results on East-Asian women are in accordance with previously published data by Singh et al.[22] and Howard et al.[21] also showing no significant different risk of preterm birth for e.g. Chinese, Japanese and Filipino women when compared to white women living in the USA. Data on risk of preterm birth in Mediterranean women are scarce. Zanconata et al.[24] reported that for women from North-African and Middle-East countries the preterm birth risk is significantly decreased compared to European white women We found similar results.

Ethnic disparities in adverse neonatal outcome after preterm birth were previously described. A study performed in South Carolina (USA) by Allen et al.[25] also showed that before 37 weeks of gestation, neonatal mortality was lower for black babies at any given gestational age. Balchin et al.[26] investigated racial variation in the association between gestational age and perinatal mortality. They found that among infants born before 32 weeks' gestation perinatal mortality risk was lowest in black women. Although our findings concern intrapartum and neonatal mortality, they do concord with those presented by Balchin et al.

Our study is not only focusing on ethnic disparities in spontaneous preterm birth risk, but also on the impact of preterm birth and how this differs between the main ethnic groups living in a European country such as the Netherlands. Our study adds knowledge on ethnic groups living in Europe instead of the more frequently investigated ethnicities in the USA. We have shown that for African and South-Asian women the risk of preterm birth is significantly increased, whereas the actual impact of preterm birth on neonatal outcome is reduced for infants born preterm from European white mothers.

This apparent varying impact of preterm birth by ethnic group raises the question about defining the optimal pregnancy duration. For our research, as well as in daily clinical practice, it is assumed that the optimal period of delivery for a singleton pregnancy is 40 weeks of gestation. Furthermore a delivery before 37 weeks is considered "preterm" and a delivery after 42 weeks is "postterm". In this approach we generalise all singleton pregnancies with disregard to individual factors like maternal ethnicity. Our results suggest an ethnic variation in optimal gestational age, with children born from African, Mediterranean and East-Asian women having better outcomes at earlier gestation age than their European white counterparts. In other words, these fetuses appear to be mature at an earlier gestational age, which was previously described.[27] Apart from the clinical outcome of pregnancy, this phenomenon was also shown in the levels of biomarkers for fetal lung maturation.[28,29]

Balchin and Steer also concluded that the cause of death or morbidity before 37 weeks of gestation is 'functional immaturity at birth' instead of shortened pregnancy length per se.[30]

Therefore, future research should focus on defining ethnic-specific optimal gestational age. Optimal gestational age, in this context, is defined as the gestational age at which risk of perinatal morbidity or mortality is the lowest. This has implication on redefining thresholds for preterm and postterm pregnancies thus impacting daily obstetric practice. For instance in the Netherlands this might concern the referral pattern for women delivering before 37 weeks of gestation, but it might also imply a less expectant approach for specific ethnic groups who are having an ongoing pregnancy beyond 40 weeks of gestation.

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CHAPTER 5

Recurrence risk of preterm birth in subsequent singleton pregnancy after preterm twin delivery

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Abstract

Objective *To investigate the recurrence risk of preterm birth (<37 weeks) in a subsequent singleton pregnancy after previous nulliparous preterm twin delivery.*

Study design *We included 1957 women who delivered a twin gestation and a subsequent singleton pregnancy from the Netherlands Perinatal Registry. We compared outcome of subsequent singleton pregnancy of women with a history of preterm delivery to pregnancy outcome of women with a history of term twin delivery.*

Results *Preterm birth in the twin pregnancy occurred in 1075 (55%) women versus 882 (45%) who delivered at term. The risk of subsequent spontaneous singleton preterm birth was signifcantly higher after preterm twin delivery (5.2% versus 0.8%; odds ratio 6.9; 95% CI 3.1-15.2).*

Conclusion *Women who deliver a twin pregnancy are at greater risk for delivering prematurely in a subsequent singleton pregnancy.*

Introduction

In many developed countries twin birth rates have increased drastically during the past decades. In the USA the twin rate climbed from 1.9% in 1980 to 3.2% in 2006.[1] Similar trends were found in other developed countries.[2] The increase in twin birth rates is mainly caused by the increase in the use of assisted reproductive techniques (ART) and increasing maternal age.[1,3]

Twin pregnancies are associated with higher risks of various pregnancy complications like pre-eclampsia, intra uterine growth restriction and preterm birth.[4] These preterm births can either be a result of intervention in the case of previously mentioned obstetrical complications, or can occur spontaneously. Preterm birth, in its turn, is the most important risk factor for perinatal morbidity and mortality in developed countries.[5,6] This is mostly due to respiratory immaturity, intracranial haemorrhages and infections.[7]

Besides having a twin pregnancy, a history of previous preterm birth is the most important risk factor for spontaneous preterm birth. This recurrence risk was particularly demonstrated for singleton pregnancies in women with a preceding preterm singleton delivery.[8,9] Less is known about the recurrence risk of preterm birth after a preceding twin pregnancy. The few studies that reported on this phenomenon had contradictory findings and had access to relatively small samples.[10-14] Therefore, we aim to investigate the recurrence risk of a spontaneous preterm birth in subsequent singleton pregnancy after previous preterm twin delivery in a nationwide database.

Materials and Methods

Dataset

This study was performed in a prospective nationwide cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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[15,16]. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands. It contains pregnancies ≥ 22 weeks and a birthweight ≥ 500 grams and is primarily used for an annual assessment of the quality indicators of obstetric care.

Longitudinal linkage

The records included in the PRN registry are entered at the child's level. There is no unique maternal identifier available in the registry to follow-up on outcomes of subsequent pregnancies of the same mother.

Therefore, we performed a longitudinal probabilistic linkage procedure in which we linked records of children of the same mother in order to create a mother identifier. We subjected all children from second deliveries (n=509,559) registered in the PRN registry to linkage with their siblings born during a first delivery registered in the PRN registry. The linkage was based on the variables *birth date of mother*, *birth date of (previous) child,* and *postal code of mother* and is further described in Appendix 1. The final linked cohort with complete data on first and second deliveries of the same mother consisted of 272,551 women and 545,102 (2 x 272,551) deliveries.

Inclusion and exclusion criteria

From our linked cohort we included all women who delivered a singleton pregnancy (second delivery) after a previous twin pregnancy (first delivery) in the Netherlands between January 1st 1999 and December 31st 2007. We excluded all cases with major congenital anomalies and all cases with antepartum fetal mortality. Preterm birth was defined as birth before 37 completed weeks of gestation. We excluded iatrogenic preterm births in the subsequent singleton pregnancies as we were only interested in the subsequent risk of spontaneous preterm birth.

Statistics

We compared women with a preterm twin delivery to those with a term twin delivery. For these two groups we compared demographic and obstetric baseline characteristics like maternal age (mean ± SD), white maternal ethnicity (yes versus no), socio economic status (low (<p25) versus >p25), living in a deprived area (yes versus no) use of ART (yes versus no), and pregnancy interval (mean ± SD).

We subdivided previous preterm deliveries in iatrogenic and spontaneous deliveries. Furthermore, we subdivided previous preterm birth into three subgroups (22^{+0}-29^{+6} weeks, 30^{+0}-33^{+6} weeks and 34^{+0}-36^{+6} weeks). Univariate analyses were performed with the Student *t* test for normally distributed continuous variables and Fisher's exact test for categorical variables. Normality of continuous variables was assessed by visual inspection of Q-Q plots. All statistical tests were 2-sided and a p-value of 0.05 was chosen as the threshold for statistical significance. We measured the association between history of preterm birth and subsequent risk of spontaneous preterm birth by calculating an adjusted odds ratio (aOR). We only adjusted for variables that appeared to be unequally distributed in the baseline characteristics of the study population. The probabilistic linkage procedure was performed using the R statistical software environment version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and the data were analyzed using SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA).

In order to determine which children had similar mothers, the PRN dataset was divided into two datasets. Dataset A contained records (n = 509,559) of second deliveries and dataset B (m = 667,053) contained records of first deliveries. By performing a probabilistic record linkage procedure, we determined which second delivery from dataset A belonged to a first delivery from dataset B. After the longitudinal linkage procedure (appendix), we were able to identify 272,551 pairs of first and second deliveries. The linked dataset consisted of 254,776 (97.7%) singleton-singleton pairs, 4071 (1.6%) singleton-twin pairs, 57 (0.02%) twin-twin pairs and 2097 (0.8%) mothers who had first a twin delivery followed by a subsequent singleton delivery. For our study we selected the 2097 women with a twin delivery followed by a singleton delivery. We excluded mothers with iatrogenic preterm births in the second pregnancy (1.8%), severe congenital anomalies in first or second pregnancy (1.8% and 1.1% respectively), and antepartum fetal mortality (2.1% and 0.4% respectively).

Our final dataset consisted of 1957 women. Baseline characteristics of this cohort are presented in table 1. In the twin pregnancy 1075 (55%) women delivered before 37 completed weeks of gestation. In the majority of cases these preterm births were a result of obstetrical intervention (n=597; 56%), but occurred spontaneously in the remaining 478 (44%) women. Demographic characteristics of the women with preterm (n=1075) and term (n=882) twin deliveries were comparable when considering maternal age, socio economic status, living in a deprived area and use of artificial reproductive technology. Nonetheless, there were significantly less women with a white maternal ethnicity in the group with preterm twin deliveries (88.7% versus 91.4%, $p<0.05$). The time interval to the subsequent singleton pregnancy was statistically significantly shorter in the women who delivered their twins preterm (33 versus 36 months, $p<0.001$). As expected, the mean gestational age is also significantly different between the two groups.

Table 1. Baseline maternal characteristics of the cohort (n=1957) stratified by gestational age at the twin delivery

Characteristics of the twin delivery	**Preterm twin delivery <37 weeks** (n=1075)	**Term twin delivery ≥37 weeks** (n=882)	***p* value**
Mean gestational age at twin delivery in weeks (±SD)	32.5 ± 3.9	38.0 ± 1.1	<0.0001
Mean maternal age at twin delivery in years (±SD)	29.1 ± 4.0	29.2 ± 4.1	0.54
White maternal ethnicity (n)	982 (88.7%)	782 (91.4%)	<0.05
Low socio-economic status (n)	207 (19.3%)	185 (21.0%)	0.36
Living in a deprived area (n)	44 (4.1%)	43 (4.9%)	0.44
Artificial reproductive technology (n)	521 (48.5%)	426 (48.3%)	0.96
Interval to subsequent singleton delivery in months (±SD)	33 ± 17	36 ± 16	<0.001

Table 2. Risk of spontaneous preterm birth of singleton pregnancy in women with a history of twins (n=1957)
Stratification by subtype of preterm birth and gestational age at time of previous twin delivery

Twin delivery (n=1957)		**Subsequent singleton delivery** (n=1957)		
Gestational age at delivery (weeks)	**Number**	**Spontaneous preterm birth**		**Odds ratio* (95% CI)**
		n	**%**	
Total term delivery ≥ 37 weeks	**882**	**7**	**0.8%**	**Reference**
Total preterm delivery < 37 weeks	**1075**	**56**	**5.2%**	**6.9 (3.1-15.2)**
Spontaneous preterm delivery				
< 37 weeks	**478**	**35**	**7.3%**	**9.9 (4.4-22.4)**
34^{+0}-36^{+6} weeks	199	7	3.5%	4.6 (1.6-13.3)
30^{+0}-33^{+6} weeks	116	9	7.8%	10.7 (3.9-29.5)
22^{+0}-29^{+6} weeks	163	19	11.7%	17.8 (7.2-44.1)
Iatrogenic preterm delivery				
< 37 weeks	**597**	**21**	**3.5%**	**4.6 (1.9-10.8)**
34^{+0}-36^{+6} weeks	407	9	2.2%	2.8 (1.04-7.6)
30^{+0}-33^{+6} weeks	144	7	4.9%	6.4 (2.2-18.5)
22^{+0}-29^{+6} weeks	46	5	10.9%	16.2 (4.9-54.1)

* Adjusted for: maternal ethnicity and pregnancy interval

Of the 1075 women who had a preterm twin delivery, 56 women (5.2%) had a spontaneous preterm birth in the subsequent singleton pregnancy and 1019 (94.8%) women delivered at term. The spontaneous singleton preterm birth rate in the 882 women who delivered their twins at term was 0.8% (n=7). Delivery of preterm twins was thus associated with a significant increased risk of spontaneous preterm birth in a subsequent singleton pregnancy (aOR 6.9; 95% CI 3.1-15.2). Table 2 shows the subdivision in spontaneous versus iatrogenic preterm twin delivery. It shows that the increased risk of subsequent singleton preterm birth is even higher after a spontaneous preterm twin delivery (aOR 9.9; 95% CI 4.4-22.4) instead of an iatrogenic preterm twin delivery. Nevertheless, even after an iatrogenic preterm twin delivery there is still an increased risk of spontaneous preterm birth in the next singleton pregnancy (aOR 4.6; 95% CI 1.9-10.8).

Table 2 shows that for both spontaneous as well as iatrogenic preterm twin deliveries the recurrence risk also depends on the gestational age at the time of preterm twin delivery. The risk of preterm birth increases as the gestational age at preterm twin delivery decreases. The odds ratios in table 2 are adjusted for maternal ethnicity and pregnancy interval.

Comment

Principal findings

We investigated the risk of spontaneous preterm (<37 weeks) singleton birth in women with a history of twin delivery. We found that the risk of subsequent singleton preterm birth is significantly increased after a previous preterm twin delivery when compared to a previous term twin delivery. Twin gestation is thus not only a risk factor for preterm birth in the current pregnancy, but also accounts for an increased risk of preterm birth in a subsequent singleton pregnancy (5.2% versus 0.8%).

Strengths and weaknesses

Our study was based on data of a large, well maintained, population-based national perinatal registry. The vast majority of the caregivers contribute to the PRN registry and it thus comprises approximately 96% of all pregnancy and birth characteristics in the Netherlands. The 4% missing birth data are due to 1-2% non-reporting general practitioners and 2-3% non-reporting midwives. As (threatened) preterm delivery and multiple gestation are an indication for referral to an obstetrician and the registration by obstetricians is nearly complete (>99%), we would not have missed many cases due to non-reporting. Because of the magnitude of the PRN database we did not perform an a priori power calculation. Unfortanately, the PRN does not contain information on possible confounders like chorionicity, tobacco use, highest level of education, history of cervical surgery, cervical length measurements, and the use of progesterone or cerclage.

For our analyses we performed a probabilistic linkage method to follow-up mothers in a subsequent pregnancy. Of the 509,559 second deliveries in the PRN registry we were able to find the matching first delivery in 272,551 (53%) cases. Non-linkage could be due to missing values of the linkage variables as well as by the fact that the first child was born before the start of the PRN registry in 1999. Finally, as *postal code of mother* is one of the linkage variables, changes of home address over time will also have led to non-linkage. We found that our linked dataset of 272,551 women are comparable to the national figures on the level of demographic characteristics (e.g. maternal age) and pregnancy outcomes (e.g. pregnancy length, preterm birth rates, and congenital malformations). Only the twin pregnancy rate and the perinatal mortality rate in the linked dataset seem to be different from the original dataset in the first pregnancy (appendix). However, we do not think that the non-linked twin pregnancies have influenced our results to a large degree as non-linkage is not related to gestational age at nulliparous twin delivery, nor to our primary outcome measure.

Relation to other studies

The five previous publications on this subject have reported conflicting results and conclusions. However, they are based on relatively small sample sizes of less than 300 women.

The most recent published study was performed by Rafael et al. and they investigated 255 women in a retrospective study.[14] The risk of spontaneous preterm singleton birth was 11.1% after previous spontaneous preterm twin birth versus 1.8% after previous term twin birth (odds ratio 6.81; 95% CI 1.53-30.29). However they did not find a significant increased risk when the preterm twins were born between 34^{+0}-36^{+6} weeks. The latter is in contrast with our findings, but is probably due to a lack of statistical power in the study by Rafael et al. Our results are also consistent with those presented by Facco et al.[11] They investigated 167 women with twin deliveries followed by a singleton gestation in a retrospective cohort study. The odds ratio for spontaneous preterm birth in the singleton pregnancy was 5.0 (95% CI 1.1-22.9) for women with a preceding preterm twin delivery compared to women with a term twin delivery. Similar results were found by Menard et al.[12] Their retrospective cohort consisted of 144 women and the relative risk of subsequent singleton preterm birth after preterm twin delivery was 2.87 (95% CI 1.02-8.09). All three studies also included women who had delivered before their index twin pregnancy, whereas in our study the women were nulliparous at the time of twin pregnancy. Another conclusion, compared to ours, was drawn by Bloom et al.[10] The authors concluded that previous preterm twin delivery (<35 weeks) did not significantly increase the risk of subsequent singleton preterm birth (OR 1.9; 95% CI 0.46-8.14). The analyses were performed in a cohort of only 82 women, thus probably lacking sufficient power to detect the difference in risk of subsequent preterm delivery. In another study on this topic the authors also concluded that in the great majority of cases a singleton pregnancy will proceed to term, irrespective of the gestational length of the preceding twin pregnancy.[13] However, the authors base their conclusion on a frequency table without statistically comparing the two groups. They also analyzed previous preterm births as a whole, instead of subdividing them into iatrogenic and spontaneous preterm births. As our results showed, the recurrence risk after iatrogenic preterm birth is much smaller than in the case of a spontaneous preterm twin delivery. Combining iatrogenic and spontaneous preterm birth might have led to their different conclusion.

Previous studies showed that the overall incidence of preterm birth is 6.0% in singleton pregnancies and 48.1% in twin pregnancies.[17] Furthermore, there is a relatively expectant approach towards obstetric interventions in the preterm period in the Netherlands.[17,18] This is also reflected in the low incidence of iatrogenic preterm births in our study population (30.1% in the nulliparous twin delivery and 1.8% in the excluded multiparous singleton delivery). The expectant approach is embedded in Dutch guidelines. For instance, in the case of premature prelabour rupture of membranes (pPROM) it is often decided to provide expectant monitoring until 37 weeks instead of routinely induction of labour.[19] The low incidence figures in the Netherlands are thus not a result of a healthier population of pregnant women (which would limit the external validity), but rather a result of different doctor's behaviour.

Meaning of the results and future research

To the best of our knowledge our study has the largest sample size in the investigation of recurrence risk of singleton preterm birth after preterm twin delivery. The evidence of an increased risk of singleton preterm birth after a previous preterm singleton delivery is substantial and consistent.[8,9]

We have now demonstrated a similar increased recurrence risk after preterm twin delivery. This increased risk is found after spontaneous as well as iatrogenic preterm delivery. The latter might be explained by the presence of risk factors (e.g. maternal age of maternal ethnicity) that both contributed to the need of medical intervention in the first twin pregnancy, as well as to the pathogenesis of spontaneous preterm birth in the next singleton pregnancy. Given the very low risk (0.8%) of spontaneous preterm birth after previous term twin delivery one could also state the inversed conclusion: The risk of subsequent singleton preterm birth is significantly decreased after a previous term twin delivery when compared to a previous preterm twin delivery.

The increased risk of preterm birth in twin pregnancies, which are often a result of artificial reproductive technology, is thus not only applicable to the current pregnancy but also impacts subsequent singleton pregnancies. These results can help clinicians to counsel their patients with a history of spontaneous or iatrogenic preterm delivery of twins and quantify their recurrence risks for spontaneous preterm birth.

Previous singleton preterm birth is often an indication for the use of 17-alpha-hydroxyprogesterone in the next singleton pregnancy as a preventive measure for recurrence of preterm birth.[20] With these and previous findings, one should investigate the effectiveness of 17-alpha-hydroxyprogesterone in singleton pregnancies following preterm twin deliveries as well.

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Appendix

In order to determine which children had similar mothers, the PRN dataset was divided into two datasets. Dataset A contained records (n = 509.559) of second deliveries and dataset B (m = 667.053) contained records of first deliveries. By performing a probabilistic record linkage procedure [1], we determined which second delivery from dataset A belonged to a first delivery from dataset B. Similarly to Tromp et al. [2], records from A and B that belong to the same mother are called matches and non-matches otherwise. Note that from the information on the deliveries that belonged to each other, we determined which children had similar mothers.

We defined three linking variables, v_1, v_2, and v_3, that were compared to each other to determine if the i^{th} delivery from dataset A belonged to the same mother as the j^{th} delivery from dataset B. Firstly, postal code (v_1) and the date of birth (v_2) of the mother were registered in both datasets. In addition to these characteristics of the mother, the date of the previous (first) delivery was registered in dataset A. This variable was compared with the date of the delivery registered in dataset B (v_3). Note that the outcome of the comparison of the p^{th} linking variable could be either an agreement or disagreement (i.e. $y_{ijp} = 1$ or $y_{ijp} = 0$) or missing (i.e. $\delta_{ijp} = 1$ or $\delta_{ijp} = 0$).

To calculate the posterior probability the following likelihood formula was maximized

$$\prod_{ij=1}^{nm} \left\{ \pi \prod_{p=1}^{3} \left[\mu_p^{y_{ijp}} (1-\mu_p)^{(1-y_{ijp})} \right]^{\delta_{ijp}} + (1-\pi) \prod_{p=1}^{3} \left[\upsilon_p^{y_{ijp}} (1-\upsilon_p)^{(1-y_{ijp})} \right]^{\delta_{ijp}} \right\}$$

where μ_p and υ_p are the probabilities of agreement of the p^{th} variable among respectively matches and non-matches. In addition, π is the relative frequency of matches among the nm records-pairs.

Table 1. Estimated parameters derived from maximizing the total likelihood function.

Linkage Variable	Parameters Likelihood	
	logit (μ)	logit (υ)
v_1	4.66	-8.8
v_2	2.16	-8.3
v_3	1.19	-7.50
π	-13.80	

The estimated parameters derived from the total likelihood maximization have been summarized in table 1. With these estimates, the posterior probability that record i from dataset A and record j from dataset B belong to each other was calculated. A posterior probability higher than 80% was considered high enough to assume that both deliveries belonged to the same mother. With this (arbitrary) threshold, we were able to identify 304.130 potential record pairs (table 2).

Table 2. Number of patterns with the highest posterior probability

Outcome comparison of			Frequency	P(Match)	
v_1	v_2	v_3			
0	1	1	25262	0.04	
1	0	1	28952	0.49	← Threshold for linkage
missing	1	1	3	0.83	
1	1	0	42963	0.84	
1	missing	1	139359	0.90	
1	1	missing	315	0.96	
1	1	1	121490	0.99	

Patterns with a posterior probability > 0.80 were considered as a linkage.

After the linkage the dataset was checked. Some deliveries from dataset A were wrongly linked to deliveries from dataset B. We reduced the number of false positive pairs of second and first deliveries with the following steps:

1. Exclude pairs in which deliveries from dataset A were linked to more than one delivery in dataset B
2. Exclude pairs of deliveries in which the second delivery (from dataset A) happened less than 10 months after the first one (from dataset B)

We validated our longitudinal linkage in a random sample of 200 deliveries within the Academic Medical Center Amsterdam and found that the calculated posterior probability is similar to the actual chance of a correct linkage of 2 subsequent deliveries.

After these steps, we were able to identify 272.551 pairs of first and second deliveries. Table 3 shows that basic baseline and pregnancy characteristics are comparable between the original and linked datasets. Differences in baseline characteristics were assessed with the Student *t* test for normally distributed continuous variables and chi-square test for categorical variables.

Table 3. Comparison of baseline characteristics original dataset and linked dataset for first and second deliveries

Characteristics	**First delivery**		**Second delivery**	
	Original dataset n=667,053	**Linked dataset** n=272,551	**Original dataset** n=509,559	**Linked dataset** n=272,551
Mean birthweight in grams (±SD)	3315 (615)	3346 (608)*	3510 (581)	3539 (573)*
Mean maternal age in weeks (±SD)	28.8 (4.8)	28.6 (4.2)*	31.2 (4.3)	31.2 (4.2)
White maternal ethnicity, n (%)	574,809 (86.2%)	242,907 (89.1%)*	437,832 (85.9%)	242,801 (89.1%)*
Twin pregnancy, n (%)	14,138 (2.1%)	4346 (1.6%)*	10,065 (2.0%)	5383 (2.0%)
Preterm birth <37 weeks, n (%)	58,791 (8.8%)	22,080 (8.1%)*	26,162 (5.1%)	13,185 (4.8%)*
Very preterm birth <32 weeks, n (%)	9772 (1.5%)	3760 (1.4%)*	3911 (0.8%)	1757 (0.6%)*
Congenital malformations, n (%)	16,983 (2.6%)	6777 (2.5%)	11,104 (2.2%)	6120 (2.3%)
Perinatal mortality, n (‰)	6203 (9.3‰)	3664 (13.4‰)*	3448 (6.8‰)	1666 (6.1‰)*

* p<0.05 compared to the original dataset.

Due to the large datasets we found several statistically significant differences between the linked and original datasets. However, only the differences in multiple pregnancy rate and perinatal mortality rate in the first pregnancy appear to be also clinically significant differences.

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CHAPTER 6

Recurrence risk of preterm birth in subsequent twin pregnancy after preterm singleton delivery

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Abstract

Objective *In women with a multiparous singleton pregnancy, previous preterm birth is the most important risk factor for subsequent preterm birth. Little is known whether this recurrence risk also holds if the next pregnancy is a twin gestation. We aim to determine the risk of preterm birth in a subsequent twin pregnancy after previous singleton preterm birth.*

Design *Cohort study*

Setting *Nationwide study in the Netherlands*

Population *We studied 4071 nulliparous women who had a singleton delivery followed by a subsequent twin delivery between the years 1999 and 2007.*

Methods *We compared outcome of subsequent twin pregnancy of women with a history of preterm singleton delivery to pregnancy outcome of women with a history of term singleton delivery. We subdivided first delivery in iatrogenic and spontaneous preterm deliveries. Furthermore we performed analyses by subgroups for gestational age at the time of singleton delivery.*

Main outcome measure *Spontaneous preterm birth (<37 weeks) in subsequent twin pregnancy.*

Results *In the index singleton pregnancy, preterm birth occurred in 232 (5.7%) of 4071 women. The risk of subsequent twin preterm birth was significantly higher after previous singleton preterm delivery (56.9% versus 20.9%; odds ratio 5.0; 95% CI 3.8-6.6). Risk of subsequent twin preterm birth was dependent on the severity of previous singleton preterm birth and was highest after preceding spontaneous instead of iatrogenic singleton preterm delivery.*

Conclusion *Preterm birth of a singleton gestation is associated with an increased risk of spontaneous preterm birth in a subsequent twin pregnancy.*

Introduction

Preterm birth, defined as birth before 37 completed weeks of gestation, is one of the major concerns in modern obstetric healthcare. It is the most common cause of perinatal morbidity and mortality in developed countries.[1,2] This is often due to respiratory immaturity, intracranial haemorrhages and infections.[3] Preterm birth can occur spontaneously or can be a result of medical intervention in the case of severe pregnancy complications like pre-eclampsia or intra uterine growth restriction.[4] The incidence of preterm birth has been steadily rising in most developed countries during the last decades, mainly caused by an increase in iatrogenic preterm births.[5-7] Risk of preterm birth varies between 5-15% in developed countries. Preterm birth is associated with an increased risk of preterm birth in the subsequent pregnancy. In fact, a history of previous preterm birth is, together with multiple gestation, the most important risk factor in the aetiology of preterm birth. This increased risk is well established and reconfirmed in several studies reporting odds ratios of approximately 3 for the recurrence of preterm birth.[8,9] However, these studies only focused on the risk of singleton preterm birth after a previous singleton birth. Little is known whether the recurrence risk also holds for twin pregnancies following a preceding singleton preterm birth. To our knowledge, only four studies reported on this subject using different methodological approaches.[10-13] Therefore, we aim to further investigate the recurrence risk of preterm birth in subsequent twin pregnancy following previous preterm singleton delivery.

Materials and Methods

Dataset

This study was performed in a nationwide prospective cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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.[14,15] The coverage of the PRN registry is about 96% of all deliveries in The Netherlands. It contains pregnancies ≥ 22 weeks and a birthweight ≥ 500 grams. The records included in the PRN are entered at the child's level.

Longitudinal linkage

There is no unique maternal identifier available in the registry to follow-up on outcomes of subsequent pregnancies of the same mother. Therefore, we performed a probabilistic linkage procedure in which we longitudinally linked records of children of the same mother in order to create a mother identifier.

We subjected all children from second deliveries (n=509,559) registered in the PRN registry to linkage with their siblings born during a first delivery (nulliparous woman) registered in the PRN registry. The longitudinal linkage was based on the variables *birth date of mother*, *birth date of (previous) child,* and *postal code of mother* and is further described in the Appendix (see Chapter 5) . The final linked cohort with complete data on first and second deliveries of the same mother consisted of 272,551 women and 545,102 (2 x 272,551) deliveries.

Inclusion and exclusion criteria

From our linked cohort we included all multiparous women who delivered a twin pregnancy (second delivery) after a previous singleton pregnancy (first delivery) in the Netherlands between January 1st 1999 and December 31st 2007. We excluded all cases with antepartum fetal mortality and all cases with major congenital anomalies. Furthermore we excluded iatrogenic preterm births in the subsequent twin pregnancies as we were only interested in the subsequent risk of spontaneous preterm birth. Preterm birth was defined as birth before 37 completed weeks of gestation.

Statistics

We compared baseline characteristics of women with a preterm singleton delivery to those with a term singleton delivery. For these two groups we compared demographic and obstetric baseline characteristics like maternal age (mean ± SD), socio economic status (low (<p25) versus >p25), white maternal ethnicity (yes versus no), living in a deprived area (yes versus no) use of ART (yes versus no), and pregnancy interval (mean ± SD).

We subdivided nulliparous singleton preterm deliveries in spontaneous and iatrogenic deliveries. We also subdivided previous preterm birth into three subgroups (22^{+0}-29^{+6} weeks, 30^{+0}-33^{+6} weeks and 34^{+0}-36^{+6} weeks). Univariate analyses of the baseline characteristics were performed with the Student *t* test for normally distributed continuous variables and chi-square test for categorical variables. Normality of continuous variables was assessed by visual inspection of Q-Q plots. All statistical tests were 2-sided and a p-value of 0.05 was chosen as the threshold for statistical significance. We measured the association between history of preterm birth and subsequent risk of spontaneous preterm birth by calculating an adjusted odds ratio (aOR). We only adjusted for variables that appeared to be differently distributed in the baseline characteristics of the study population.

The probabilistic linkage procedure was performed using the R statistical software environment version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and the data were analyzed using SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA).

After the longitudinal linkage procedure (see Appendix Chapter 5) we were able to identify 5307 mothers who had a twin delivery following a previous index singleton delivery. After excluding mothers with iatrogenic preterm births in the second pregnancy (21%), severe congenital anomalies in first or second pregnancy (1.0% and 1.2% respectively), and antepartum fetal mortality (1.1% and 0.5% respectively) we had 4071 women with complete follow-up data.

Baseline characteristics of this cohort are presented in table 1. In the singleton pregnancy 232 (5.7%) women delivered before 37 completed weeks of gestation. In the majority of cases these preterm births occurred spontaneously (n=147; 63%), but were a result of obstetrical intervention in the remaining 85 (37%) women. Demographic characteristics of the women with preterm (n=232) and term (n=3839) singleton deliveries were comparable when considering maternal age, maternal ethnicity, socio economic status, living in a deprived area, and pregnancy interval. Nonetheless, there were significantly more women who used artificial reproductive technology in the group with preterm singleton deliveries (35.3% versus 27.9%, p<0.05).

Figure 1 visualises the relation between gestational age in the nulliparous singleton delivery and subsequent twin delivery. Of the 232 women who had a preterm singleton delivery, 132 women (56.9%) had a spontaneous preterm birth in the subsequent twin pregnancy and 100 (43.1%) women delivered at term. The spontaneous twin preterm birth rate in the 3839 women who delivered their singleton at term was 20.9% (n=804). Delivery of preterm singleton was thus associated with a significant increased risk of spontaneous preterm birth in a subsequent twin pregnancy (aOR 5.0; 95% CI 3.8-6.6).

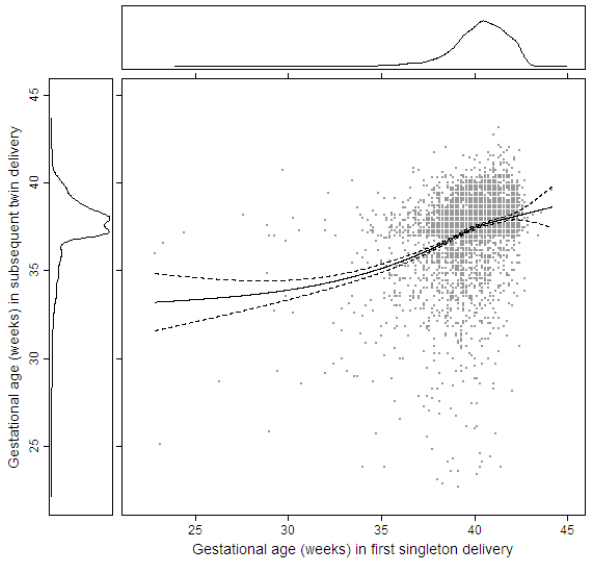

Figure 1. Distributions of gestational age (in weeks) in nulliparous singleton delivery and subsequent twin delivery. To illustrate the relation between the two gestational ages, we predicted the gestational age at the second delivery using the gestational age of the first delivery. The estimated mean (continuous line) and its corresponding 95% confidence interval (dotted line) are presented.

Table 1. Baseline maternal characteristics of the cohort (n=4071) stratified by gestational age at the singleton delivery

Characteristics of the singleton delivery	Preterm singleton delivery <37 weeks (n=232)	Term singleton delivery ≥37 weeks (n=3839)	*p* value
Mean maternal age at twin delivery in years (±SD)	29.8 ± 3.8	29.4 ± 4.0	0.19
White maternal ethnicity (n)	219 (94.4%)	3526 (91.9%)	0.16
Low socio-economic status (n)	36 (15.5%)	775 (20.2%)	0.08
Living in a deprived area (n)	5 (2.2%)	154 (4.0%)	0.16
Artificial reproductive technology (n)	82 (35.3%)	1072 (27.9%)	<0.05
Median interval to subsequent twin pregnancy in months (IQR)	28 (21-39)	28 (22-37)	

Table 2 shows the subdivision in spontaneous versus iatrogenic preterm singleton delivery. It shows that the increased risk of subsequent twin preterm birth is highest after a spontaneous preterm singleton delivery (aOR 7.8; 95% CI 5.5-11.2) instead of an iatrogenic preterm singleton delivery. Nevertheless, even after an iatrogenic preterm singleton delivery there is still an increased risk of spontaneous preterm birth in the next twin pregnancy (aOR 2.4; 95% CI 1.5-3.8). Table 2 shows that for iatrogenic preterm singleton deliveries the recurrence risk also depends on the gestational age at the time of preterm singleton delivery. The risk of preterm birth increases as the gestational age at preterm singleton delivery decreases. The odds ratios in table 2 are adjusted for artificial reproductive technology and socio-economic status.

Table 2. Risk of spontaneous preterm birth of twin pregnancy in women with a history of singleton delivery (n=4071)
Stratification by subtype of preterm birth and gestational age at time of previous singleton delivery

Singleton delivery (n=4071)		Subsequent twin delivery (n=4071)			
Gestational age at delivery (weeks)	Number	Spontaneous preterm birth		Odds ratio* (95% CI)
		n	%	
Overall term delivery ≥ 37 weeks	**3839**	**804**	**20.9%**	**Reference**
Overall preterm delivery < 37 weeks	**232**	**132**	**56.9%**	**5.0 (3.8-6.6)**
Spontaneous preterm delivery				
< 37 weeks	**147**	**99**	**67.3%**	**7.8 (5.5-11.2)**
34^{+0}-36^{+6} weeks	126	83	65.9%	7.3 (5.0-10.6)
30^{+0}-33^{+6} weeks	14	11	78.6%	14.0 (3.9-50.5)
22^{+0}-29^{+6} weeks	7	5	71.4%	9.5 (1.8-48.9)
Iatrogenic preterm delivery				
< 37 weeks	**85**	**33**	**38.8%**	**2.4 (1.5-3.8)**
34^{+0}-36^{+6} weeks	64	22	34.4%	1.9 (1.2-3.4)
30^{+0}-33^{+6} weeks	12	6	50.0%	3.8 (1.2-11.7)
22^{+0}-29^{+6} weeks	9	5	55.6%	4.7 (1.3-17.7)

* Adjusted for: artificial reproductive technology and socio-economic status

Principal findings

We investigated the risk of spontaneous preterm twin birth in women with a history of singleton delivery. We found that the risk of subsequent twin preterm birth is significantly increased after a previous preterm singleton delivery when compared to a previous term singleton delivery.

Strengths and weaknesses

Our study was based on data of a large population-based national perinatal registry. The majority of the caregivers contribute to the PRN registry and it thus comprises approximately 96% of all pregnancy and birth characteristics in the Netherlands. The 4% missing birth data are due to 1-2% non-reporting general practitioners and 2-3% non-reporting midwives. As (threatened) preterm delivery and multiple gestation are an indication for referral to an obstetrician and the registration by obstetricians is nearly complete (>99%), we would not have missed many cases due to non-reporting.

For our analyses we performed a probabilistic linkage method to follow-up mothers in a subsequent pregnancy. Of the 509,559 second deliveries in the PRN registry we were able to find the matching first delivery in 272,551 (53%) cases. Non-linkage could be due to missing values of the linkage variables, but is mainly due to the fact that the first child was born before the start of the PRN registry in 1999. The latter argument accounts for approximately half of the non-linked deliveries. Furthermore, the small number of available linkage variables also influenced the linkage rate. Finally, as *postal code of mother* is one of the linkage variables, changes of home address over time will also have led to non-linkage. We found that our linked dataset of 272,551 women are comparable to the national figures for demographic characteristics (e.g. maternal age) and pregnancy outcomes (e.g. congenital abnormalities, pregnancy length and preterm birth rates). Only the twin pregnancy rate and the perinatal mortality rate in the linked dataset seem to be different from the original dataset. This only holds for the incidence rates in the first pregnancy (appendix S1). However, we do not think that non-linked pregnancies have influenced our results to a large degree as non-linkage is not related to gestational age at nulliparous singleton delivery, nor to the primary outcome measure.

Relation to other studies

To the best of our knowledge, four previous studies on this topic were published presenting conflicting results and conclusions. The most recent study was performed by Facco et al. where they investigated 193 women in a 10-year hospital-based retrospective cohort.[12] The risk of spontaneous preterm twin birth was 73.9% after previous spontaneous singleton preterm birth and 44.4% after previous term singleton delivery (odds ratio 3.5, 95% CI 1.4-9.3). These results are in accordance with our findings. Another study performed by Ananth et al. also concluded that women with a history of singleton preterm birth carry an increased risk of preterm birth in the subsequent twin pregnancy.[10]

This population-based retrospective study included 2329 women in the state of Missouri between 1989 and 1997. The risk of spontaneous preterm twin birth was 43.6% after previous spontaneous singleton preterm birth and 31.2% after previous term singleton delivery. They also found that the risk of subsequent preterm birth increased based on the severity of the previous preterm birth. Bloom et al. found that of the 179 women with a preterm (<35 weeks) twin deliveries included in their study, 16% had a history of prior preterm birth compared to 5% of those who delivered beyond 35 weeks. Unfortunately, the investigators did not describe any baseline characteristics, nor did they specify whether the prior preterm birth had a spontaneous or iatrogenic onset of labour. Finally, our findings show similarities with those presented by Rydhstroem.[13] The author also analyzed previous preterm births as a whole, instead of subdividing them into iatrogenic and spontaneous preterm births.

Meaning of the results and future research

The evidence of the recurrence risk of preterm birth after a previous singleton preterm birth is consistent and substantial.[8,9] We have now demonstrated a similar increased recurrence risk for a twin pregnancy following preterm singleton delivery. This increased risk is found after spontaneous as well as iatrogenic preterm delivery. The latter might be explained by the presence of risk factors that both contributed to the need of medical intervention in the first singleton pregnancy, as well as to the pathogenesis of spontaneous preterm birth in the next twin pregnancy. To the best of our knowledge our study has the largest sample size in the investigation of twin preterm birth after preceding singleton delivery.

Twin pregnancy is one of the most important risk factors for preterm birth. The pathogenesis of preterm birth in twins remains largely unknown, but is claimed to be partly caused by excessive myometrial stretch.[16] However, our findings implicate that other mechanisms must also exist as the risk of preterm twin birth is even further increased in the case of previous singleton preterm birth. This merits further research on other underlying risk factors that cause preterm birth in twin pregnancies. Our study can also have implications for patient counselling and can help obstetric caregivers better quantify the risk of preterm delivery.

Conclusion

Women with a history of singleton preterm birth are at increased risk for spontaneous preterm birth in a subsequent twin pregnancy.

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CHAPTER 7

Development of a prognostic model for predicting spontaneous singleton preterm birth

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Abstract

Objective

To develop and validate a prognostic model for prediction of spontaneous preterm birth.

Study Design

Prospective cohort study using data of the nationwide perinatal registry in the Netherlands. We studied 1,524,058 singleton pregnancies between 1999 and 2007. We developed a multiple logistic regression model to estimate the risk of spontaneous preterm birth based on maternal and pregnancy characteristics. We used bootstrapping techniques to internally validate our model. Discrimination (AUC), accuracy (Brier score) and calibration (calibration graphs and Hosmer-Lemeshow C-statistic) were used to assess the model's predictive performance. Our primary outcome measure was spontaneous preterm birth <37 completed weeks.

Results

Spontaneous preterm birth occurred in 57,796 (3.8%) pregnancies. The final model included 13 variables for predicting preterm birth. The predicted probabilities ranged from 0.01-0.71 (IQR 0.02-0.04). The model had an area under the receiver operator characteristic curve (AUC) of 0.63 (95% CI 0.63-0.63), the Brier score was 0.04 (95% CI 0.04-0.04) and the Hosmer Lemeshow C-statistic was significant (p <0.0001). The calibration graph showed overprediction at higher values of predicted probability. The positive predictive value was 26% (95% CI 20-33%) for the 0.4 probability cut-off point.

Conclusions

The model's discrimination was fair and it had modest calibration. Previous preterm birth, drug abuse and vaginal bleeding in the 1st half of pregnancy were the most important predictors for spontaneous preterm birth. Although not applicable in clinical practice yet, this model is a next step towards early prediction of spontaneous preterm birth that enables caregivers to start preventive therapy in women at higher risk.

Introduction

Preterm birth, defined as birth before 37 completed weeks of gestation, is an important healthcare concern. An estimated 13 million infants are annually born preterm worldwide. Preterm birth is the leading cause of perinatal mortality in developed countries and is responsible for an estimated million neonatal deaths world-wide each year.[1,2] Furthermore, preterm birth leads to severe perinatal morbidity which, in turn, can influence health status upon to adulthood.[3,4] Because of its impact on neonatal outcome and costs, much effort has been expended in revealing the pathogenesis of preterm birth and in finding preventive measures that reduce its risk. On the one hand, the intensive care for preterm infants has improved significantly over the last decades leading to better prognosis for the neonates. On the other hand there was less success in attempts to reduce the incidence of preterm birth. Instead, risk of preterm birth has been rising in most developed countries during the past decades.[5-7]

Extensive research has identified many risk factors for spontaneous preterm birth.[2,8,9] These include maternal demographic characteristics as ethnicity, age and socio-economic status, but also pregnancy characteristics as multiplicity, shortened cervix and urogenital tract infections.[9-11] Despite the identification of all of these risk factors, the prognostic value of their combination is not well understood. As a result one is often unable to assign risk of spontaneous preterm birth to individual women. This hinders caregivers from selecting women at higher risk of spontaneous preterm birth for (trials on) preventive measures.

Prognostic models are promoted as helpful tools to support clinicians: by producing an individual's risk score they can be applied in selecting patients for clinical trials, clinical decision making and counselling patients.[12,13] In literature, few clinical scoring systems have been presented for assigning risk of spontaneous preterm birth to individual women, but none of them was accurate enough to be applied in daily practice.[14] Most of the risk assessment tools were based on small datasets or did not present predictions in a quantitative manner.

The aim of this study is to develop and internally validate a prognostic model for predicting spontaneous preterm birth in singleton pregnancies based on information known around 20 weeks of gestation.

Materials and Methods

Dataset

This study was performed in a prospective nationwide cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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.[15,16] The midwifery and obstetrics data collection starts at the booking visit and contain perinatal data from 20 gestational weeks onwards. The neonatal registry contains data on hospital admissions of newborns within 28 days after birth. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands. The incompleteness is due to non-registering general practitioners (2%) and a few non-registering midwifery practices (2%). All data contained in the PRN are voluntarily recorded by the caregiver during prenatal care, delivery, and the neonatal period. The data are annually sent to the national registry office, where a number of range and consistency checks are conducted.[17]

Inclusion and exclusion criteria

For this study all singleton pregnancies between 1 January 1999 and 31 December 2007 resulting in birth where fetus was alive at the start of labour were selected. We excluded all pregnancies ending before 22 completed weeks of gestation, all cases with unknown gestational age (1.2%) and all cases with a birth weight <500 g (0.2%). Furthermore we excluded all multiple pregnancies (2.0%), all cases of antepartum fetal mortality (0.5%) and all cases in which maternal ethnicity was unknown (0.5%). Finally, we excluded all preterm inductions of labour and preterm primary caesarean sections (2.4%).

Outcome and predictors

Our primary outcome measure was spontaneous preterm birth (sPTB), defined as birth before 37 completed weeks of gestation. Spontaneous preterm birth included all births after spontaneous onset of contractions with or without prelabour rupture of membranes (PROM). Gestational age was predominantly based on the date of last menstrual period (LMP) and confirmed (or adjusted in case of discrepancy ≥ 7 days) by crown rump length (CRL) measurement during early pregnancy.

As potential early predictors we used all available variables in the PRN database whose value could be known before the 20th week of gestation. The potential predictors included maternal age (categorized in <25, 25-29, 30-34 and ≥35 years), maternal ethnicity (categorized in Caucasian, Mediterranean, Blacks, South-Asian and East-Asian), socio-economic status (categorized in high, middle and low), living in a deprived area, parity (categorized in 0, 1, and ≥ 2 previous births), late booking visit (after 18 weeks of gestation) and fetal sex.

Both socio-economic status and deprived area classifications are based on national governmental standards using the postal code of the women's home address. The above described variables are obligatory fields in the PRN database to be filled in by the caregiver. The remaining dichotomous variables are non-obligatory fields: pre-existent diabetes mellitus, essential hypertension, history of previous preterm birth, and history of recurrent urinary tract infections, history of cervical surgery, psychiatric disorder, drug abuse and vaginal bleeding in the first half of pregnancy.

Model development and validation

To inspect the individual variables that significantly contribute to the risk of sPTB we performed univariate logistic regression analysis. To obtain the model, however, we performed multivariate logistic regression analysis with backward stepwise elimination of variables. Discrimination (area under the receiver operator characteristic; AUC), accuracy (Brier score and Brier skill score) and calibration (calibration graphs and Hosmer-Lemeshow C-statistic) were used to assess the model's predictive performance. The Brier score measures the mean squared residuals and the Brier skill score measures the improvement of the predictions relative to a model that gives all women the same probability that equals the incidence of the outcome; the skill score hence "adjusts" for the prevalence of the outcome. The goodness of fit was also evaluated by the Hosmer Lemeshow C-statistic (a p-value below 0.05 indicates an overall poor fit) [18]. To provide unbiased estimates for the abovementioned performance measures we internally validated the model using the standard bootstrap method with 100 bootstrap samples.[19]

Data were analyzed using the R statistical software environment version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

We included 1,524,058 singleton pregnancies in our 9-year nationwide cohort. Incidence of sPTB was 3.8% (n= 57,796). Baseline characteristics of the study population are presented in table 1.Stepwise backward selection eliminated two of the introduced variables, namely essential hypertension and recurrent urinary tract infections. The results of univariate and multivariate analyses are presented in table 2. The multivariate model showed that a low socio-economic status (OR 1.10, 95% CI 1.07-1.13) and nulliparity (OR 1.75, 95% CI 1.72-1.79) increased the risk of preterm birth. The strongest predictors were drug abuse (OR 4.23, 95% CI 3.54-5.06), vaginal bleeding in the first half of pregnancy (OR 4.10, 95% CI 3.65-4.61) and a history of previous preterm birth (OR 9.53, 95% CI 9.03-10.06).

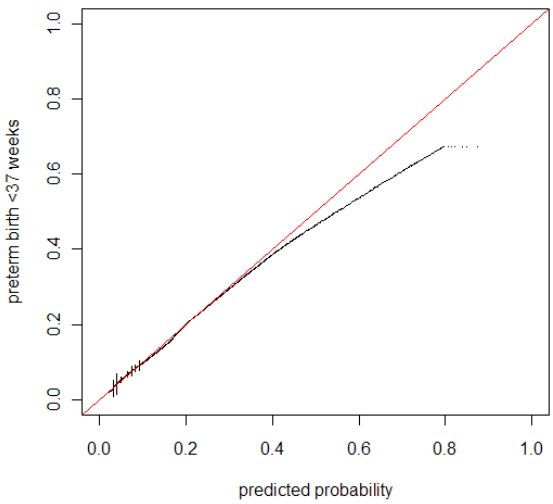

Figure 1. Calibration graph of the prognostic model.

The predicted probabilities derived from our multivariate model ranged from 0.01 to 0.71 (inter quartile range (IQR) 0.02-0.04). The area under the receiver operating characteristic (AUC) curve was 0.63 (95% CI 0.63-0.63), demonstrating a fair capacity to discriminate between women with and without preterm birth. The Brier score was 0.04 (95% CI 0.04-0.04) corresponding to a Brier skill score of 0.05. Figure 1 shows the model's calibration graph that reveals modest calibration for most predicted probabilities and a structural overestimation at higher values of predicted probability. Accordant with the presented calibration graph, the p-value for the Hosmer Lemeshow C- statistic was <0.0001, indicating poor agreement between the mean predicted probabilities and the observed probability of preterm birth. Our actual final model, including the performance measures, is presented in table 3.

Finally we calculated the predictive value, sensitivity and specificity of the model by showing the positive (PPV) and negative (NPV) predictive values at two arbitrary cut-off points of predicted probability. At a predicted probability of 0.1 the PPV is 19.4% (95% CI 18.7-20.1%) and the NPV is 96.3% (96.3-96.4%). At this cut-off the sensitivity of our model is 4.2% (95% CI 4.2-4.2%) and the specificity is 99.3% (95% CI 99.3-99.3%). At the different cut-off of 0.4 the PPV is 25.8% (95% CI 19.6-33.1%) and the NPV is 96.2% (95% CI 96.2-96.3%).

Table 1. Baseline maternal and obstetric characteristics of deliveries: the Netherlands 1999-2007

Characteristics	Preterm delivery <37 weeks n = 57,796 (3.8%)		Delivery ≥ 37 weeks n = 1,466,262 (96.2%)		Total n = 1,524,058 (100%)	
	n	%	n	%	n	%
Maternal						
Maternal age						
<25 years, n (%)	8455	14.6	170,847	11.7	179,302	11.8
25-<30 years, n (%)	18,232	31.6	426,956	29,1	445,188	29.2
30-<35 years, n (%)	21,326	36.9	583,382	39.8	604,708	39.7
≥35 years, n (%)	9783	16.9	285,077	19.4	294,860	19.4
Maternal ethnicity						
Caucasian, n (%)	48,288	83.5	1,239,633	84.5	1,287,921	84.5
Mediterranean, n (%)	4115	7.1	115,466	7.9	119,581	7.9
Black, n (%)	1817	2.3	33,521	2.3	35,338	2.3
South-Asian, n (%)	950	1.1	16,001	1.1	16,951	1.1
East Asian, n (%)	1138	2.0	26,811	1.8	27,949	1.8
Other, n (%)	1488	2.6	34,830	2.4	36,318	2.4
Socio economic status						
High, n (%)	13,129	22.7	359,230	24.5	372,359	24.4
Middle, n (%)	28,606	49.5	741,088	50.5	769,694	50.5
Low, n (%)	16,061	27.8	365,944	25.0	382,005	25.1
Living in a deprived area, n (%)	4229	6.1	88,266	6.0	92,455	6.1
General and obstetric history						
Parity						
Nulliparous, n (%)	34,084	59.0	668,100	45.6	702,184	46.1
Primiparous, n (%)	15,961	27.6	531,932	36.3	547,893	36.0
Multiparous, n (%)	7751	13.4	266,230	18.2	273,981	18.0
Pre-existent diabetes mellitus , n (%)	160	0.3	2091	0.1	2251	0.2
Essential hypertension, n (%)	274	0.5	7054	0.5	7328	0.5
Previous preterm birth, n (%)	1891	3.3	6283	0.4	8174	0.5
Recurrent urinary tract infections, n (%)	62	0.07	1021	0.11	1083	0.07
History of cervical surgery, n (%)	78	0.06	841	0.13	919	0.06
Psychiatric disorder, n (%)	225	0.4	3803	0.3	4028	0.3
Drug abuse, n (%)	158	0.3	716	0.1	874	0.1
Current pregnancy						
Booking visit ≥18 weeks of gestation, n (%)	19,123	33.1	334,785	22.8	353.908	23.2
Vaginal bleeding <20 weeks of gestation, n (%)	350	0.6	2011	0.1	2361	0.2
Male fetal sex, n (%)	32,906	56.9	749,476	51.1	782,382	51.3

Table 2. Logistic regression model for the prediction of spontaneous preterm birth before 37 weeks of gestation: the Netherlands 1999-2007

Characteristics	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Maternal				
Maternal age				
<25 years	1.16	1.13-1.19	1.01	0.98-1.04
25-<30 years	Reference		Reference	
30-<35 years	0.86	0.84-0.87	0.95	0.93-0.97
≥35 years	0.80	0.78-0.82	0.93	0.91-0.96
Maternal ethnicity				
Caucasian	Reference		Reference	
Mediterranean	0.92	0.89-0.95	0.88	0.85-0.91
Black	1.39	1.33-1.46	1.22	1.16-1.28
South-Asian	1.52	1.43-1.63	1.36	1.27-1.46
East Asian	1.10	1.03-1.16	1.02	0.96-1.08
Other	1.10	1.04-1.16	1.01	0.95-1.06
Socio economic status				
High	Reference		Reference	
Middle	1.06	1.03-1.08	1.04	1.02-1.06
Low	1.20	1.17-1.23	1.10	1.07-1.13
Living in a deprived area	1.23	1.19-1.27	1.10	1.06-1.14
General and obstetric history				
Parity				
Nulliparous	1.70	1.67-1.73	1.75	1.72-1.79
Primiparous	Reference		Reference	
Multiparous	0.97	0.94-1.00	0.93	0.90-0.95
Pre-existent diabetes mellitus	1.17	1.08-1.28	1.67	1.42-1.97
Essential hypertension	0.92	0.89-0.95	N/A	N/A
Previous preterm birth	7.86	7.46-8.28	9,53	9.03-10.06
Recurrent urinary tract infections	1.55	1.20-2.00	N/A	N/A
History of cervical surgery	2.36	1.87-2.98	1,90	1.50-2.41
Psychiatric disorder	1.51	1.32-1.73	1,22	1.06-1.40
Drug abuse	5.61	4.72-6.67	4.23	3.54-5.06
Current pregnancy				
Booking visit ≥18 weeks of gestation	1.67	1.64-1.70	1.59	1.56-1.62
Vaginal bleeding <20 weeks of gestation	4.44	3.96-4.97	4,10	3.65-4.61
Male fetal sex	1.26	1.24-1.29	1.26	1.24-1.29

Table 3. Regression coefficients and standard errors (SE) in a logistic regression model to predict the probability of spontaneous singleton preterm delivery before 37 weeks of gestation

Characteristics	Prognostic model		
	Regression coefficent	SE	p-value
Intercept	-3,8322	0,0146	<0.0001
Maternal			
Maternal age			
<25 years	0,0078	0,0139	0,5772
25-<30 years	0,0000	X	X
30-<35 years	-0,0512	0,0105	<0.0001
≥35 years	-0,0679	0,0134	<0.0001
Maternal ethnicity			
Caucasian	0,0000	X	X
Mediterranean	-0,1331	0,0179	<0.0001
Black	0,1946	0,0259	<0.0001
South-Asian	0,3078	0,0345	<0.0001
East Asian	0,0150	0,0309	0,2337
Other	0,0055	0,0274	0,8398
Socio economic status			
High	0,0000	X	X
Middle	0,0396	<0.001	<0.0003
Low	0,0915	0,0134	<0.0001
Living in a deprived area	0,0961	0,0191	<0.0001
General and obstetric history			
Parity			
Nulliparous	0,5617	0,0102	<0.0001
Primiparous	0,0000	X	X
Multiparous	-0,0757	0,0145	<0.0001
Pre-existent diabetes mellitus	0,5137	0,0840	<0.0001
Essential hypertension	N/A	N/A	N/A
Previous preterm birth	2,2546	0,0274	<0.0001
Recurrent urinary tract infections	N/A	N/A	N/A
History of cervical surgery	0,6409	0,1216	<0.0001
Psychiatric disorder	0,1974	0,0706	0,0052
Drug abuse	1,4427	0,0908	<0.0001
Current pregnancy			
Booking visit ≥18 weeks of gestation	0,4662	0,0092	<0.0001
Vaginal bleeding <20 weeks of gestation	1,4117	0,0597	<0.0001
Male fetal sex	0,2341	0,0086	<0.0001

Performance measures
AUC (95% CI)
0.63 (0.63-0.63)
Hosmer Lemeshow goodness-of-fit-test
<0.0001
Brier score (95% CI)
0.04 (0.04-0.04)

Comment

Principal findings

We developed and internally validated a prognostic model for predicting the adverse pregnancy outcome of spontaneous preterm birth (<37 weeks). Our model consisted of 13 variables, had an AUC of 0.63 (95% CI 0.63-0.63), and exhibited over-prediction at high predicted probabilities. Our prognostic model combines all mentioned predictors and has the potential to facilitate the process of indentifying individual women at higher risk for preterm birth after spontaneous onset of birth.

Strengths & weaknesses

For the development of the prognostic model we had access to the large database of the Netherlands Perinatal Registry. This nationwide registry contains information on 96% of all pregnancies in The Netherlands and thus gives us a valuable insight in many important pregnancy characteristics and related perinatal outcome. Using such a large prospective cohort reduces the chances of overestimating or underestimating effects. We further used the bootstrap procedure to provide unbiased estimates.

The presented predictors are all available in the first or early second trimester, which allows it for calculating an individual risk around 20 weeks of gestation. This enables one to select patients for trials on, or provide them with preventive strategies in the current pregnancy.

Our study has some limitations. First, unfortunately, the Netherlands Perinatal Registry does not contain data on ultrasound or laboratory results. The same holds for possibly relevant other biomarkers.[20-22] Second, some of the included predictors were based on non-obligatory variables in our database. This phenomenon explains the low prevalence figures for these types of variables (presented in table 1) and it might have led to some underestimation of the effects (table 2). Unfortunately we are unable to calculate the proportion of patients that did not have the non-obligatory fields completed. Third, the admission of progesterone in women with a history of preterm birth is also not registered in the PRN dataset. The effect of the predictor 'previous preterm birth' is influenced by these preventive measures and is thus probably underestimated in our model. Finally, the PRN does not contain information on the indication for preterm induction of labour or primary caesarean section. Therefore, we had to exclude all iatrogenic preterm births to be able to predict the remaining spontaneous preterm births, instead of selecting our cohort based on the actual indication for preterm obstetric interventions. The latter would have been more accurate.

Relation to other studies

Studies on individual risk assessment for preterm birth were first introduced in the 70s of the 20th century.

Honest et al.[14] systematically reviewed literature on risk assessment tools and concluded that there is need for better quality information of the tools and that new tools should be developed with more robust methods in order to make them applicable in clinical practice.

To et al.[23] and Celik et al.[24] developed prognostic models in a more sophisticated manner similar to our approach. In both studies the prediction models were developed using logistic regression methods. These models included data on patient history as well as on ultrasound results for cervical length measurements. Celik et al.[24] included 58,807 women in their study cohort. This cohort was divided in two: The one part for development of the model and the other part for internal validation of the model. Their model consisting of information on only patient history and maternal characteristics showed similar performance to the model presented in our study (AUCs respectively 0.65, 0.69, 0.68 and 0.61). However, their primary model which also included cervical length measurements showed even better performance.

More recent work on prediction of preterm birth was performed by Beta et al.[22]. Apart from using obstetric history and maternal characteristics they investigated whether the addition of several biomarkers would improve the performance of the model. The AUCs of different combinations of predictors varied between 0.61 (95% CI 0.57-0.65) and 0.71 (95% CI 0.67-0.76). Addition of biomarkers like PAPP-A, MoM and PIGF appeared not to be improving the performance of the model. Like the previously described models for predicting preterm birth, the performance of our model hinders actual implementation in current patient care.

Meaning of the results

Although the development and validation of our prognostic model is an important next step towards individual risk assessment for sPTB, the moderate performance of the model limits its clinical usefulness. In future, our model and its successors with additional predictors should help clinicians indentify women at high risk. To apply such a screening test we should fulfil the criteria of the World Health Organisation (WHO)[25]. To et al.[23] already pointed out that the only point of concern is the availability of effective medical intervention for the high-risk group. Actually, these women should be provided with better counselling and more frequent obstetric follow-up. The improved counselling of women should focus on the modifiable predictors during pregnancy and should help patients recognize the early symptoms of threatening preterm labour. Another application of our model is the selection of women at higher risk for trials on preventive treatments strategies. Progesterone[26] and Cerclage procedure[27] have been shown to significantly reduce the risk of preterm birth in patients with a history of preterm birth. Using our prognostic model we can investigate whether these treatments are beneficial for a broader group of pregnant women as well. For such an application prediction models should be well calibrated. Unfortunately, the existing prediction models for preterm birth, including ours, showed modest calibration.

Finally, we have identified demographic and social predictors that might be modifiable by specialized programmes.

Proposal for future research

A limitation of our model development method is that we are not taking into account the competing risks that are present during pregnancy. For example in the case of women who develop early-onset pre-eclampsia the caregivers will intervene and induce preterm birth. This type of preterm birth was not included in our study. This risk of iatrogenic preterm birth is in competition with the risk of a spontaneous (preterm) birth later in pregnancy. More advanced methods like with time-to-event analysis (e.g. Cox proportional hazards model) with competing risk assessment could address this problem in future research.

Although the difficulties in individual preterm birth risk assessment are evident, we should still focus on expanding the development, validation and implementation of prognostic models. To this end we need the inclusion of much more potentially relevant variables and the standardization of the collection of well-defined variables. In particular the combination of maternal demographic and pregnancy characteristics, ultrasound and laboratory results, and other biomarkers merits more research. Finally, external validation of developed models should be performed to assess the predictive performance in other populations [28]. Such a constructive strategy is indispensable when it comes to reducing the incidence of preterm birth and its associated adverse neonatal outcomes.

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CHAPTER 8

Antenatal prediction of neonatal mortality in very premature infants

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Abstract

Objective *To develop a prognostic model for antenatal prediction of neonatal mortality in infants threatened to be born very preterm.*

Study Design *Nationwide cohort study in the Netherlands between 1999 and 2007. We studied 8,500 singletons between 25^{+0} and 31^{+6} weeks of gestation where fetus was alive at birth. We developed a multiple logistic regression model to estimate the risk of neonatal mortality within 28 days after birth based on characteristics that are known before birth. We used bootstrapping techniques for internal validation. Discrimination (AUC), accuracy (Brier score) and calibration (graph, c-statistics) were used to assess the model's predictive performance.*

Results *Neonatal mortality occurred in 766 (90 per 1000 cases). The final model consisted of seven variables. The predicted probabilities ranged from 0.0035-0.675 (IQR 0.11-0.18). The model had an AUC of 0.84, the Brier score was 0.067. The calibration graph showed good calibration, and the test for the Hosmer Lemeshow c-statistic showed no lack of fit (p=0.16).*

Conclusions *Neonatal mortality can be predicted for very preterm births based on antenatal factors; gestational age, antenatal corticosteroids, fetal gender, SGA, age, ethnicity and level of hospital. This model can be very helpful for antenatal counselling.*

Introduction

Preterm birth, is the leading cause of neonatal morbidity and mortality in high income countries.[1] It is estimated that preterm birth is responsible for a million neonatal deaths world-wide each year.[2] The consequences of preterm birth arise from the fact that the immature organ systems of the neonate are not yet prepared to support extrauterine life. This is expressed in respiratory insufficiency, intracranial haemorrhage and infections. The impact of very preterm birth, defined as birth before 32 completed weeks of gestation, on neonatal morbidity and mortality risk is dependent on the actual length of gestation as the risk decreases when pregnancy prolongs.[3,4,5] The risk of neonatal complications in very preterm births influence antenatal clinical decision making concerning the administration of tocolytics/ corticosteroids and/or referral to a 3rd level perinatal centre.[6,7]

Prediction models can be a helpful tool to clinicians working in perinatal care.[8,9,10] To assess the risk of neonatal mortality in very premature infants there are around 40 prediction models available to clinicians.[11] Medlock et al. systematically reviewed all of these models and found that besides gestational age and birth weight, seven other variables were recurrently found to be independent predictors for neonatal mortality after very preterm birth. These predictors were: being small for gestational age (SGA), male gender, white ethnicity, congenital anomalies, no use of antenatal corticosteroids, lower Apgar score, neonatal hypo- or hyperthermia at time of admission and clinical or biochemical signs of respiratory insufficiency.[11] The majority of these models were only applicable after birth as they included predictors that are not known antenatally, including birth weight and Apgar score. Prediction models for neonatal mortality after very preterm birth based solely on antenatal factors are rare; only two models were developed for infants threatened to be born before 26 weeks of gestation.[12,13] The lack of antenatal prediction models for very preterm births after threshold of viability hinders counselling of patients who are confronted with this threat. Therefore, the aim of this study was to develop a prognostic model for obstetricians to be used during gestation predicting neonatal mortality after very preterm birth based on only information known before birth.

Methods

Dataset

This study was performed in a prospective nationwide cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions 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.[14,15]

The midwifery and obstetrics data collection starts at the booking visit and contain perinatal data from 20 gestational weeks onwards. The neonatal registry contains data on hospital (re)admissions of newborns within 28 days after birth. The coverage of the PRN registry is about 96% of all deliveries in the Netherlands. The incompleteness is due to non-registering general practitioners (1-2%) and non-registering midwifery practices (2-3%). All data contained in the PRN are voluntarily recorded by the caregiver during prenatal care, delivery, and the neonatal period. The data are annually sent to the national registry office, where a number of range and consistency checks are conducted.[16]

Inclusion and exclusion criteria

All live borns between 25^{+0} and 31^{+6} weeks of gestation and a birth weight of 500 grams or more were included in our study. Neonates were born between January 1st 2000 and December 31st 2007. Fetuses with a congenital abnormality were excluded as well as children born from multiple births. In the Netherlands 24^{+0} weeks is the limit of viability and active treatment of newborns was performed from 25^{+0} weeks onwards during our study period.

Outcome and candidate predictors

The primary outcome measure was neonatal mortality within 28 days after birth. Candidate predictors, which should be available antenatally, were specified using evidence from clinical guidelines, literature and expert opinions. These potential predictors registered in the national registration were gestational age (days), fetal gender (male), use of antenatal corticosteroids, maternal age (<25,25-34,≥ 35 years), parity (primiparous/multiparous), Caucasian maternal ethnicity (yes/no), socio-economic status (SES)(p25), hypertension/pre-eclampsia, prelabour rupture of the membranes (PROM), history of preterm birth, bleeding in the second half of pregnancy, level of hospital for delivery (3rd level versus non 3rd level hospital) and small for gestational age (p10). Predictors known at or after birth like non-cephalic fetal presentation, birth weight and 5-minute Apgar score will only be presented in the baseline characteristics of the study population. The SES score is based on the mean income, the percentage of people with a paid job and the percentage of household on a low education in a postal code area.

Model development and validation

First we measured the baseline characteristics. To inspect the individual variables that significantly contribute to the risk of neonatal mortality we performed univariate logistic regression analysis. To obtain the prediction model we performed multivariate logistic regression analysis with backward selection based on the Akaike Information Criterion.

We evaluated the discriminative performance of the prognostic model by the area under the receiver operating characteristic curve; the AUC.[17] The AUC can be interpreted as the probability that a randomly selected patient with the outcome (in our case neonatal mortality) is assigned a higher probability than a randomly selected patient without the outcome. The accuracy of the prognostic model's predictions was assessed by the Brier score and Brier skill score.

The Brier score (the mean squared deviation between the predicted probabilities and their respective outcomes) for a model can range from 0 for a perfect model and 0.25 for a non-informative model.[17] The Brier skill score measures the improvement of the predictions relative to a non informative model and thus "adjusts" for the prevalence of the outcome.

We assessed the calibration of the model by plotting a smoothed calibration graph. The goodness of fit was also evaluated by the Hosmer Lemeshow C-statistic (a p-value below 0.05 indicates an overall poor fit).[18] To provide unbiased estimates for the abovementioned performance measures we internally validated the model using the standard bootstrap method of Efron with 100 bootstrap samples.[19] Along with the sensitivity and specificity, we evaluated the clinical applicability of our model by calculating the positive and negative predictive values at arbitrary chosen cut-off points.

Data were analyzed using SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA) and for the bootstrapping the R statistical software environment version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) was used.

Results

Between January 1st 2000 and December 31st 2007 1,357,628 children were born, of which 12,391 live born between 25^{+0} and 31^{+6} weeks of gestation and a birth weight of 500 grams or more without congenital abnormalities. Children born from multiple births (n=3,938, 31.4%) were excluded. Hence the resulting study population consisted of 8,500 live born singleton infants without congenital anomalies.

Neonatal mortality within 28 days occurred in 766 cases; 90 per 1000 (‰). Neonatal mortality was largely dependent on gestational age and ranged from 546‰ at 25 weeks to 18‰ at 31 weeks of gestation (figure 1). The mean birth weight was 1264 gram. Baseline characteristics of the study population are presented in table 1.

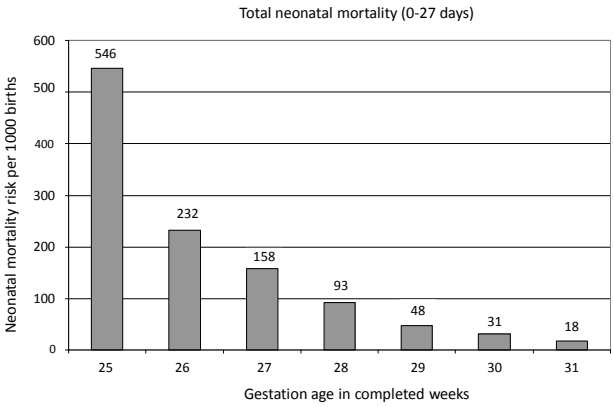

Figure 1. Neonatal mortality risk by week of gestation for 8500 singleton live born births

Table 1. Characteristics of the live born singleton very preterm infants (n=8.500)

	n (%) mean (SD)	
Maternatal characteristics		
Multiparous	3295	38,8%
Maternal age (years)	29,7	(5.4)
Caucasian maternal ethnicity	6764	79,6%
Low SES	2299	27,1%
Pregnancy characteristics		
Hypertension/(pre)eclampsia	2530	29,8%
Previous preterm birth	517	6,1%
Blood loss in 2nd half of pregnancy	586	6,9%
Prelabour rupture of membranes	931	11,0%
Labour		
non-3rd level hospital at birth	5721	37,3%
Antenatal corticosteroids	2810	33,1%
Non cephalic fetal presentation	2380	28,0%
Spontanous start labour	4367	51,4%
Neonatal characteristics		
Gestational age (days)	207	(12.8)
Birth weight (grams)	1264	(383)
Small for gestational age	739	8,7%
5-minute APGAR score	8,0	(2.1)
Male gender	4764	56,1%
Outcome measure		
Neonatal mortality within 28 days	766	90‰

The univariate regression analysis (table 2) showed that gestational age and the use of antenatal corticosteroids were the most important antenatal indicators of neonatal mortality. Furthermore, parity, maternal age, hypertensive disorders, a non-cephalic presentation, blood loss in 2nd stage of gestation, SGA and fetal gender were all univariate significant associated with neonatal mortality.

Stepwise backward selection eliminated 6 of the 13 introduced variables including hypertension, previous preterm birth, blood loss, PROM, SES and parity. Our final model consisted of 7 variables: gestational age, antenatal administration of corticosteroids, SGA, level of hospital, ethnicity, maternal age and fetal gender.

Table 3 shows the coefficients of the final model along with the respective odds ratios derived from the multivariate analyses. The predicted probabilities ranged from 0.0035 to 0.675 (IQR 0.11-0.18). The AUC was 0.83 (95% CI 0.83-0.83), demonstrating a good capacity to discriminate between cases with and without neonatal mortality. The accuracy measured by the Brier score was 0.067 (95% CI 0.067-0.067) corresponding to a Brier skill score of 10.4. The p-value for the Hosmer-Lemeshow C-statistic was 0.15, showing no statistically significant evidence of lack of fit. This finding is also visualised in the calibration graph (figure 2).

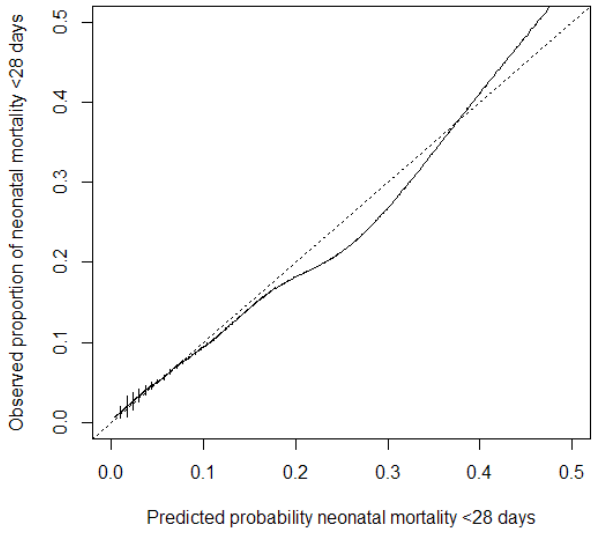

Figure 2. Calibration graph. The vertical bars represented the frequency of the mortality outcomes.To enhance interpretation the axes were adjusted to the scale from 0.0 to 0.5 based on the low observed and predicted outcome incidence after 0.5.

Table 2. Univariate associations between candidate predictors and neonatal mortality in very preterm infants

		Neonatal mortality <28 days (n=8500)			AUC
		Odds ratio	95% CI	p-value	
Maternatal characteristics					
Multiparous		1,33	1,14-1,54	0,002	0,53
Maternal age (years)	< 25	1,02	0,83-1,25	0,04	0,52
	25-34	1,00			
	≥ 35	1,27	1,06-1,53		
Caucasian maternal ethnicity		0,91	0,76-1,08	0,28	0,51
Low SES		0,87	0,75-1,04	0,12	0,51
Pregnancy characteristics					
Hypertension/(pre)eclampsia		0,64	0,54-0,76	<0.0001	0,54
Previous preterm birth		1,09	0,80-1,47	0,59	0,50
Blood loss in 2nd half of pregnancy		1,36	1,04-1,77	0,03	0,51
Prelabour rupture of membranes		0,93	0,73-1,19	0,55	0,50
Labour					
3rd level hospital at birth		0,93	0,79-1,09	0,35	0,51
Antenatal corticosteroids		0,50	0,41-0,60	<0.0001	0,57
Non-cephalic fetal presentation		1,71	1,46-1,99	<0.0001	0,56
Neonatal characteristics					
Gestational age (days)		0,93	0,93-0,94	<0.0001	0,82
Small for gestational age		1,87	1,50-2,32	<0.0001	0,53
Male gender		1,19	1,02-1,39	0,023	0,52

Table 3. Multivariate Logistic Regression Model for predicting neonatal mortality of 8500 very preterm live-born infants

Predictor		Regression coefficient	SE	Odds ratio	95% CI
Intercept		17,9046			
Gestational age (days)		-0,1014	0,0035	0,90	0,90 -0,91
Antenatal corticosteroids		-0,8043	0,1001	0,45	0,37 -0,54
3rd level hospital at birth		-0,2824	0,0913	0,75	0,63 -0,90
Maternal age	< 25	-0,1194	0,1168	0,89	0,71 -1,12
	25-34			1,00	
	≥ 35	0,2083	0,1058	1,23	1,00 -1,52
Caucasian maternal ethnicity		0,2713	0,1039	1,31	1,11 -1,61
Small for gestational age		0,8883	0,1273	2,43	1,89 -3,12
Male gender		0,2133	0,0861	1,24	1,05 -1,47

Performance measures
AUC
0.83
AUC after internal validation
0.83
Hosmer-Lemshow test
c-statistic p-value
0.15
Brier-score (95% CI)
0.065

A prediction model without SGA had similar characteristics. Alternative models leaving out one or more variables had less lack of fit (data not shown).

Finally we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predicted value (NPV) (table 4). At a predicted probability cut-off of 10% the sensitivity is 73.5%, the specificity 78.3%, the PPV 25.4% and the NPV 96.8%. At the different cut-off of 40% the PPV was 58.6% and the NPV was 93.4%.

Table 4. Predicted probabilities of neonatal mortality at different cutt-off points

Predicted probabilities	Sensitivity	Specificity	PPV	NPV
1%	99,1%	11,4%	10,0%	99,2%
5%	83,0%	63,6%	18,4%	97,4%
10%	73,5%	78,6%	25,4%	96,8%
15%	64,0%	86,2%	31,5%	96,0%
20%	55,0%	90,1%	35,4%	95,3%
40%	29,8%	97,9%	58,6%	93,4%
60%	5,1%	99,8%	73,6%	91,4%

PPV=Positive Predictive Value, NPV= Negative Predicted Value

Discussion

Principal findings

We developed and internally validated a prognostic model for antenatal prediction of neonatal mortality after very preterm birth (<32 weeks). The final model consisted of 7 variables and showed a good discrimination capacity. Gestational age, administration of antenatal corticosteroids, level of hospital, SGA, maternal age, maternal ethnicity and fetal gender emerged as independent predictors, which can be known before birth.
In current clinical practice, antenatal counseling of women after the threshold of viability who are likely to deliver before 32 weeks of gestation is often based on general information like gestational age.[11] Instead, our model provides a tool for obstetricians for individual risk assessment for women at risk of spontaneous or iatrogenic very preterm.

Strengths and weaknesses

This model is based on data of the Netherlands Perinatal Registry. This nationwide registry contains data derived in 99% of all hospitals providing obstetrical care in The Netherlands. Using a large population based cohort like the PRN reduces the chances of over- and underestimating effects. Another strength is the extended statistical analysis, including the use of a wide range of model performance measures and correcting for possible optimism in the internal validation using the standard bootstrap procedure. Our statistical analyses meet all quality items for prognostic models suggested in a systematic review on this subject.[11] There are of course also limitations in the current PRN database. In the registry there are obligatory fields and non-obligatory fields.

There is in the registry only information on the use of antenatal corticosteroids provided by the neonatologists and not yet by obstetricians. This information is derived from non-obligatory fields. In the revision of the perinatal registry this information will also be provided by the obstetricians and is obligatory. This lack of data quality could give a bias and an additional prediction model without antenatal corticosteroids showed similar AUC but lower goodness of fit. Other limitations were that there was no information on BMI and smoking status of the pregnant women.

Relation to other studies

To the best of our knowledge this is the first prognostic model for antenatal prediction of neonatal mortality (within 28 days) in (threatening) very preterm births from 25 weeks onwards.[11] Draper et al.[4] and Cole et al.[20] developed prognostic models for this aim but they included birth weight or estimated fetal weight based on actual birth weight in their model. In contrast, we have only included predictors that can be known with more certainty before birth and excluded birth weight, non-cephalic position and Apgar score. Sulkes J et al developed a pre-delivery model in the pre-surfactant time before 1990.[21] Ambalavanan et al. developed two prognostic model for antenatal prediction of neonatal mortality in extreme low birth weight (<1000 gram) infants.[12] In their study population of 8,608 births the median gestational age was 25 weeks.

The first small model included the following predictors: any prenatal steroids given, non-Hispanic black maternal ethnicity and gestational age. The full antenatal model also included: mother had hypertension/eclampsia, mother had vaginal bleeding in first or second trimester, maternal age, center mortality rate, parity, prenatal care, mother's marital status, presence of labor, tocolytic agents used, multiple birth and antibiotics used. These predictors have similarities to the ones used in our model however we developed the model for a broader gestational age group. The full antenatal model had an AUC of 0.80 which is similar to our findings. However, the prediction model developed by Ambalavanan et al. included all introduced potential predictors instead of using stepwise backward selection for selecting the most relevant ones.[17] Furthermore, we used the standard bootstrap methods of Efron[19] a preferred method of internal validation instead of dividing the dataset in a training and test set because it maximizes statistic effiency.[22]

All of the independent predictors gestational age, administration of antenatal corticosteroids, female gender, small for gestational age, non-Caucasian maternal ethnicity, high maternal age and delivery in a 3rd level perinatal centre [3,4,23,24] in our model were identified to be important in the prediction of neonatal mortality after (very) preterm birth in previously published research.[11] We confirmed the finding that, when adjusting for gestational age, Caucasian women are at increased risk for neonatal mortality of infants born preterm.[25]

Meaning of the results and future research

The presented prediction model provides caregivers in obstetrics and neonatology a tool for improved counselling of women presenting with threatening very preterm birth and a viable infant. To assess the model's generalisibility one should aim for external validation of the model in a dataset in other countries than ours like recently was done for the Draper model.[26, 27] Our model solely focuses on singleton births. As multiple pregnancies are at increased risk for (very) preterm birth compared to singleton pregnancies, with a lower neonatal mortality chances, we aim to develop a separate antenatal prediction model for multiple pregnancies based on the national registration.[3,24] Furthermore, future prognostic models should also consider severe neonatal morbidity like infant respiratory distress syndrome, necrotizing enterocolitis[28], bronchopulmonary dysplasia[29] and intraventricular haemorrhages as outcome measures in their analyses. Together with neonatal mortality these future models could further improve antenatal counselling of pregnant women. Adequate counselling of pregnant women and their partners on the possible mortality risk of their threatened very premature born child is important.[8,10] The model is developed to be used during pregnancy and not developed for counseling on end of life decisions around viability neither for hospital benchmarking. To implement current and future validated prognostic models we are working on a web-based or applets application for caregivers for online calculation of the patient's individual risk of neonatal mortality after very preterm birth.

Conclusion

We have developed and internally validated a prognostic model for antenatal prediction of neonatal mortality after very preterm singleton birth in a large nationwide database. The model has a good performance and can be a tool in counselling women at risk for very preterm birth for children as it can help caregivers better quantify this risk.

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CHAPTER 9

Reproductive outcome after early-onset pre-eclampsia

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Abstract

Background *Early-onset pre-eclampsia is an important cause of maternal and neonatal morbidity and mortality and is believed to have a significant impact on future maternal physical and psychological health. However, structured follow-up data of women with a history of early-onset pre-eclampsia are lacking. This study aims to present comprehensive data of a large cohort of women with a history of early-onset pre-eclampsia with respect to future reproductive health, family planning and subsequent pregnancy rates.*

Methods *A tertiary referral cohort of 304 women entered the follow-up study at 6-12 months after their first delivery. Detailed data on maternal and neonatal outcomes, family planning and subsequent pregnancies were recorded. In addition, data on perspectives, major concerns and decision-making of women who had not achieved a second pregnancy were collected by questionnaire and structured interviews. Data were compared with a population of 268 low-risk primiparous women with an uncomplicated delivery.*

Results *At a mean of 5.5 years after first delivery, 65.8% of women with a history of early-onset pre-eclampsia had achieved a second pregnancy compared with 77.6% of healthy controls. At follow-up, 19.1% of women with a history of early-onset pre-eclampsia had an active wish to become pregnant, whereas 15.1% of women did not wish to achieve a future pregnancy. In the latter group, decision-making was most commonly influenced by fear of recurrent disease (33%) and fear to deliver another premature child (33%) among others reasons, e.g. post partum counselling and concerns of the partner.*

Conclusions *The majority of women with a history of early-onset pre-eclampsia achieve or wish to achieve a second pregnancy within the first years after delivery. Nonetheless, first pregnancy early-onset pre-eclampsia appears to have a significant impact on future reproductive health and decision-making of affected patients, that emphasizes the importance of careful post partum counselling.*

Introduction

Pre-eclampsia is a common and potentially life-threatening condition, that affects both the mother and her fetus in about 1% of first pregnancies.[1] Although the ancient Greeks already recognized and described this characteristic pattern of disease in pregnant women, the origins of pre-eclampsia are still largely unknown.[2] At present, the maternal syndrome of pre-eclampsia is defined as the occurrence of hypertension combined with proteinuria after the 20th week of pregnancy in formerly normotensive women.[3,4] However, pre-eclampsia probably develops through multiple pathways and affects vascular function of all major organ systems, including the placenta.[5,6] Common complications of pre-eclampsia include eclampsia, the hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, severe hypertension and pulmonary edema. Pre-eclampsia is a major cause of acute and long-term maternal morbidity and mortality, perinatal deaths, iatrogenic preterm birth, and intrauterine growth restriction.[7,8] Perinatal outcome of infants born to pre-eclamptic mothers is closely related to gestational age at delivery.[9] Mortality is highest in nulliparous women, of whom up to 10% of pre-eclamptic patients have an early onset of disease before 34 weeks of gestation.[10] In addition, early-onset pre-eclampsia is associated with a significantly increased risk for the affected mothers, and maternal mortality is about a 20-fold higher for pre-eclampsia at <32 weeks' gestation in comparison with pre-eclampsia that occurs at term.[11] Early-onset pre-eclampsia may therefore be considered as a different clinical entity with respect to disease severity, maternal and fetal outcome.[4] Also, long-term maternal complications, e.g. an increased risk of subsequent adverse pregnancy outcome, cardiovascular diseases and post traumatic stress, occur more frequently in women with a history of early-onset pre-eclampsia, compared with women with a history of late-onset disease.[7,12]

At present, few studies have systematically acquired reproductive follow-up data of women with a history of early-onset pre-eclampsia, mostly because adequate data on patient and reference groups are hard to retrieve. Furthermore, little is known about the possible traumatic impact of the disease on later physical and mental well-being. Follow-up of 116 women that experienced severe pre-eclampsia and HELLP-syndrome showed that 18% required psychological treatment in the years after delivery. In addition, 34% abstained from further pregnancies because they were afraid of a recurrence of the HELLP syndrome.[12,13] A history of early-onset pre-eclampsia is likely to influence many aspects of women's health and reproduction and may affect the decision whether or not to consider planning a subsequent pregnancy.

In previous studies, we and others have shown that outcome of a subsequent pregnancy after early-onset pre-eclampsia in the first pregnancy is generally favourable.[14-16] However, despite extensive counselling, the number of women who do not attempt to achieve a second pregnancy is expected to be higher than in the general population.

Currently, little is known about the reproductive choices and motives of these former pre-eclamptic women and their partners with respect to a future pregnancies. Here, we aimed to obtain structured reproductive follow-up data of a large tertiary referral cohort of primiparous women with a history of early-onset pre-eclampsia. We investigated subsequent pregnancy rate in comparison with women with an uncomplicated first pregnancy and delivery. In addition, we identified factors that contributed to the reproductive decision-making process and common motives of women with a history of early-onset pre-eclampsia who chose not to attempt a second pregnancy, to aid future counselling of affected individuals and their partners.

Materials and Methods

Study population

All 304 primiparous women with a history of early-onset pre-eclampsia that were referred to the University Medical Centre Utrecht, the Netherlands, between June 1993 and December 2006, entered the follow-up database. Early-onset pre-eclampsia was defined as pre-eclampsia resulting in delivery before 34 completed weeks of gestation. At 6-12 months after delivery, demographic, general medical, family history, and obstetric data were recorded.[16] With a minimum of 1.2 years after their first delivery, reproductive follow-up data were obtained and subsequent pregnancy outcome was recorded and verified from the medical records. All women were routinely tested for cardiovascular risk factors and common hereditary and acquired thrombophilias. Counselling with respect to future reproductive health and subsequent pregnancy outcome was planned after test results were complete and was performed by a senior consultant perinatologist.

Pre-eclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP), as gestational hypertension >140/90 mmHg at two separate occasions and proteinuria >300 mg per 24h.[3] HELLP-syndrome was defined according to previously described criteria, as lactate dehydrogenase >600 U/L and/or haptoglobin ≤0.3 g/L, serum aspartate aminotransferase and/or serum alanine aminotransferase >50 U/L, and platelet count <100 x 10^9/L .[17] Small-for-gestational-age was defined as birthweight below the 10th percentile for gestational age at delivery, based on the Dutch population charts.[18] For all live born infants, with permission of the parents, structured neonatal follow-up data were obtained in a standardized follow-up program performed by specialized neonatologists at our hospital. This includes data concerning cognitive and neuromotor development and known disabilities common to prematurely children, as previously described.[19]

Women who, at follow-up, declared to have no intention to become pregnant again were asked to participate in an additional survey. This survey consisted of a brief questionnaire and an interview concerning their motivations not to attempt a subsequent pregnancy. Finally, we investigated the interval between first delivery and timing of subsequent pregnancy in patients who achieved a second pregnancy. We created a reference group of patients with an uneventful pregnancy that ended in a spontaneous birth of a non-malformed child in vertex position at home in the period of January 1998 to December 2002 (n = 268). The Dutch obstetrical system, where healthy women with uncomplicated pregnancies give birth at home, gives us an opportunity to select patients for the reference group. In 2001–2002, 30% of the deliveries in the Netherlands took place at home.[20]

Statistics

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) 15.0 (SPSS, Inc., Chicago, IL, USA). Study groups were compared by the use of the independent samples T-test for continuous variables and the χ^2 test for non-continuous variables, where appropriate. Statistical significance was assumed if a two-sided p-value was <0.05.

Results

During the study time a total of 304 patients were admitted to the University Medical Centre who met the inclusion criteria of first pregnancy early-onset pre-eclampsia and were eligible for follow-up. Baseline characteristics for these women are shown in table 1. At a mean follow-up time of 5.5 years after first delivery, complete reproductive follow-up data were obtained for 284 women (93.4%). Women who were lost to follow-up had a significantly longer interval between primary delivery and follow-up attempt, but showed no further differences in baseline characteristics compared with women who entered follow-up. Overall pregnancy rate at follow-up was significantly lower (65.8%) in women with a history of early-onset pre-eclampsia, compared with 77.6% in the reference group of 204 patients with an uncomplicated first pregnancy and delivery. As shown in figure 1, ninety-seven women with a history of early-onset pre-eclampsia did not achieve a second pregnancy during follow-up. The majority (55.7%) of these women wished to become pregnant again, but did not succeed as yet. The remaining 43 (44.3%) women wished to have no further pregnancy.

Table 1. Baseline characteristics of 304 primiparous women with a history of early-onset pre-eclampsia at <34 weeks of gestation, in addition to a reference group of 268 low-risk primiparous women with an uncomplicated term delivery.

	Patient group			Reference group
	Total	**Complete Follow-up**	**Lost to follow-up**	
Number of included women	304	284	20	268
Mean age at time of first delivery in years (SD)	30.2 (4.46)	30.2 (4.45)	29.0 (4.51)	29.7 (3.6)
Mean interval between first delivery and follow-up in years (SD)	5.6 (2.76)	5.5 (2.72)	6.8 (3.01)*	5.7 (1.45)
Perinatal deaths	67 (22.0%)	61 (21.5%)	6 (30.0%)	0 (0%)^
HELLP	181 (59.5%)	171 (60.2%)	10 (50.0%)	0 (0%)^
Number of neonates with a birthweight < p10	137 (45.1%)	129 (45.4%)	8 (40.0%)	24 (9.0%)^
Number of neonates with a birthweight < p5	66 (21.7%)	62 (21.8%)	4 (20.0%)	11 (4.1%)^
Neonatal follow-up**				
Mean Griffith (SD)	103.1 (9.8)	102.9 (9.9)	N/A	N/A
Mean Bailey (SD)	96.9 (13.7)	97.0 (13.9)	94.0 (12.7)	N/A

* P<0.05 for the complete follow-up group, as compared with the reference group by Student's T-test analysis
^ P<0.001 for the complete follow-up group, as compared with the reference group by Student's T-test analysis
** data on neonatal follow-up were available for N=45 participants for the Griffith's and for N=65 participants for Bailey's score assessment

We observed a significantly shorter follow-up interval and a significantly lower number of perinatal deaths in patients who wished a second pregnancy in comparison to patients who achieved a second pregnancy (table 2). A similar difference in follow-up interval was observed between with no wish to become pregnant and patients that had become pregnant again. In addition, patients that did not wish to become pregnant were significantly older at the time of the complicated first delivery. No differences were observed between women with or without HELLP-syndrome, or who delivered neonates that were small-for-gestational-age (SGA). Also, reproductive follow-up appeared unrelated to neonatal outcome (table 2). Of all patients with no future pregnancy wish 36 women (83.7%) were willing to participate in our additional survey. The other seven patients refused participation or could not be contacted (table 3). Of interest, in non-participants the number of perinatal deaths was higher compared with the participants (P<0.01), in whom none was observed. Reasons for not attempting a subsequent pregnancy after early-onset pre-eclampsia are summarized in table 4.

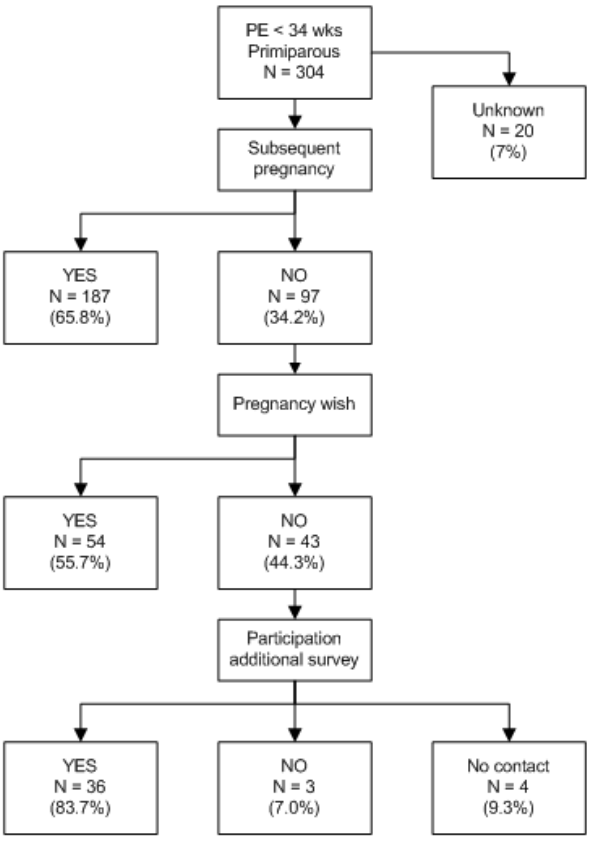

Figure 1. Flow chart of reproductive follow-up of 304 primiparous women with a history of early-onset pre-eclampsia (PE) that required delivery before 34 weeks of gestation.

The most common reason was fear of recurrent maternal hypertensive disease (33.3%) or preterm delivery (33.3%). Other reasons included a completed family, advice against future pregnancy of the patient's partner or her family, intensive parental care required for the first-born child, recurrence risk of hereditary syndromes and a negative advice given by the perinatologist.

The interval between first delivery and subsequent pregnancy (interpregnancy interval) was unknown for 18 women in the patient group and 9 women in the reference group (table 5). Women with a history of early-onset pre-eclampsia had a longer mean interval of 2.2 years, compared with 1.7 years in low-risk controls with an uneventful obstetric history. Figure 2 shows the cumulative ongoing pregnancy rates for each group during follow-up after their first pregnancy, which are generally lower in formerly pre-eclamptic women throughout the first 8 years. This difference was statistically significant (χ^2 test $p<0.001$) after ≥3 or more years after the first complicated delivery. Finally, the relationship between the outcome of the first delivery and the interpregnancy interval was studied.

As shown in table 5, mothers to a living child after a first delivery complicated by early-onset pre-eclampsia, had significantly lower subsequent pregnancy rates and a longer mean interpregnancy interval, when compared with women who lost their child during the first complicated pregnancy.

Table 2. Reproductive outcome of 284 women with a history of early-onset pre-eclampsia, in addition to a reference group of 268 low-risk primiparous women with an uncomplicated term delivery.

	Patient group			Reference group	
	Subsequent pregnancy	**No subsequent pregnancy, positive pregnancy wish**	**No subsequent pregnancy, negative pregnancy wish**	**Subsequent pregnancy**	**No subsequent pregnancy, unknown pregnancy wish**
Number of included women	187	54	43	208	60
Mean age at time of first delivery in years (SD)	29.6 (4.24)	30.2 (5.22)	33.0 (3.27)*	29.7 (3.47)	29.3 (4.10)
Mean interval between first delivery and follow-up in years (SD)	6.1 (2.77)	4.1 (2.26)^	4.4 (2.06)^	5.8 (1.43)	5.5 (1.50)
Perinatal deaths	53 (28.3%)	6 (11.1%)*	2 (4.7%)^	0 (0%)	0 (0%)
HELLP	108 (57.8%)	32 (59.3%)	31 (72.1%)	0 (0%)	0 (0%)
Number of neonates with a birthweight < p10	90 (48.1%)	22 (40.7%)	17 (39.5%)	17 (8.2%)	7 (11.7%)
Number of neonates with a birthweight < p5	46 (24.6%)	10 (18.5%)	6 (14.0%)	8 (3.8%)	3 (5.0%)
Neonatal follow-up**					
Mean Griffith	102.6 (10.7)	102.9 (10.2)	103.4 (9.1)	N/A	N/A
Mean Bailey	96.1 (14.7)	97.8 (14.7)	97.6 (12.5)	N/A	N/A

* P<0.05 as compared with the subsequent pregnancy group by Student's T-test or χ^2 test, where appropriate
^ P<0.001 as compared with the subsequent pregnancy group by Student's T-test or χ^2 test, where appropriate
** data on neonatal follow-up were available for N=44 participants for the Griffith's and for n=63 participants for Bailey's score assessment

Table 3. Characteristics of participants and non-participants in additional survey for women not planning to achieve a subsequent pregnancy after first pregnancy early-onset pre-eclampsia.

	Participation in additional survey	**No participation in additional survey**
Number of included women	36	7
Mean age at time of first delivery in years (SD)	32.7 (3.41)	33.9 (2.39)
Mean interval between first delivery and follow-up in years (SD)	4.2 (1.87)	5.5 (2.78)
Perinatal deaths	0 (0%)	2 (28.6%)*
HELLP	25 (69.4%)	6 (85.7%)
Number of neonates with a birth weight < p10	14 (38.9%)	3 (42.9%)
Number of neonates with a birth weight < p5	4 (11.1%)	2 (28.6%)
Neonatal follow-up		
Mean Griffith	102.8 (10.2)	103.9 (8.8)
Mean Bailey	96.0 (14.5)	99.2 (11.3)

* P<0.001 as compared with the subsequent pregnancy group by χ^2 test
** data on neonatal follow-up were available for N=43 participants for both the Griffith and Bailey score assessment

Table 4. Motivations and main reasons for choosing not to achieve a subsequent pregnancy after a first pregnancy complicated by early-onset pre-eclampsia.

Motivation	Frequency	Main reason
Fear of becoming sick	32	12
Fear of hospital admission	8	--
Fear of admission to intensive care unit	1	--
Poor care by hospital	2	--
Fear of delivering a premature child	10	12
First child demands full attention	13	2
Child wish is fulfilled	6	4
Wish of partner and/or environment	6	3
Fertility related	4	--
Hereditary disease in family	2	1
Doctor's advice	2	2
	Total	36

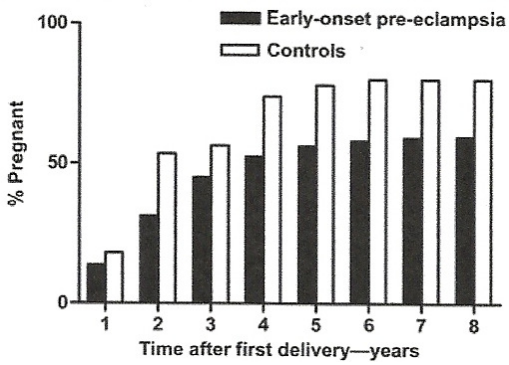

Figure 2. Cumulative proportion of primiparous women who achieved a second ongoing pregnancy (irrespective of pregnancy wish) after a first pregnancy complicated by early-onset pre-eclampsia that required delivery before 34 weeks of gestation, compared with a low-risk reference group of controls with an uncomplicated first pregnancy and term delivery.

Table 5. Relationship between outcome of first delivery and reproductive follow-up.

Outcome of first delivery	Patient group n=284		Reference group n=268	
	Living child n=223	No living child n=61	Living child n=268	No living child n=0
Women who achieved a subsequent pregnancy	134 (60.1%)	52 (85.2%)^	208 (77.6%)^^	-
Women who did not achieve a subsequent pregnancy	89 (39.9%)	8 (13.1%)^	60 (22.4%)^^	-
Women who plan to achieve a subsequent pregnancy	48 (21.5%)	6 (9.8%)§	N/A	-
Women who do not plan to achieve a subsequent pregnancy	41 (18.3%)	2 (3.2%)§§	N/A	-
Interpregnancy interval# (SD)	2.7 (1.49)	1.0 (0.62)†	1.7 (1.07)††	-

interval between first delivery and second pregnancy.
Data represent N=169 cases with a history of early-onset pre-eclampsia and N=208 controls who delivered a second child within the follow-up time.
* versus patient group (p<0.05)
** versus patient group (p=0.001)

§ versus living child patient group (p<0.05)
§§ versus living child patient group (p<0.01)
^ versus living child patient group (p<0.001)
^^ versus living child patient group (p<0.001)
† versus living child patient group (p<0.001)
†† versus living child patient group(p<0.001)

Discussion

This study summarizes comprehensive data on reproductive follow-up of a cohort of 304 patients with a history of early-onset pre-eclampsia. Our findings indicate that the majority of women become or wish to become pregnant within 5 to 8 years after a first pregnancy complicated by a delivery before 34 weeks of gestation due to a severe hypertensive disorder. However, a history of early-onset pre-eclampsia is associated with lower rates of ongoing pregnancies in the first years after delivery, when compared with low-risk women who experienced an uncomplicated first pregnancy. Also, women with a history of early-onset pre-eclampsia have a longer mean interval between their first and subsequent pregnancy and about one in six women do not wish to attempt a second pregnancy at all. The results from our study provide insight into possible reasons why a proportion of women with a history of first pregnancy early-onset pre-eclampsia does not wish to achieve a subsequent pregnancy. From our data, we conclude that different motivational elements play a role in the parents' decision, that may or may not be directly related to obstetrical history. Also, our data show that neonatal outcome after early-onset pre-eclampsia seems likely to have influenced future reproductive decision-making. Women who lost their infant due to perinatal complications or prematurity associated with early-onset pre-eclampsia were more likely to attempt a subsequent pregnancy with a shorter interpregnancy interval, as compared with women whose first child was alive at follow-up. We found no association between the neonatal disability score at follow-up and subsequent reproductive outcome. The presence and degree of disability did not affect the number of women who achieved or wished to achieve a second pregnancy.

Despite a relatively low recurrence rate of approximately 5-6% for early-onset pre-eclampsia,[14,16] the most common reasons to choose against future pregnancies were fear of recurrent maternal disease and fear to deliver preterm . From our data, we are unable to say whether the effect of early-onset pre-eclampsia on future reproductive performance is mostly due to the impact of previous severe maternal disease, previous preterm delivery or both. In a similar study, Van Pampus et al.[12] observed a comparable impact of a history of HELLP-syndrome on subsequent pregnancy rates, which was independent of gestational age at delivery. Conversely, recently published follow-up data from Habli et al.[21] and colleagues demonstrated that women with HELLP-syndrome at <28 weeks had higher rates of posttraumatic anxiety and depression <5 years of delivery, when compared with women with HELLP syndrome and delivery >28 weeks. Of note, in our data, no differences in future reproductive outcome were observed between women with early-onset pre-eclampsia with or without concomitant HELLP syndrome. Nonetheless, our data are consistent with the hypothesis that early-onset pre-eclampsia and HELLP-syndrome are associated with long-term psychological stress in a substantial number of women.

Appropriate counselling and psychological support may therefore be useful to aid women to make confident choices regarding their reproductive future, although the implementation of structured post partum care for formerly pre-eclamptic women has not been fully evaluated at present .[8,22]

This study has a number of strengths and limitations that are worth mentioning. Accomplishing a reproductive follow-up of women with a history of early-onset pre-eclampsia is a lengthy task, as it is a relatively rare condition that affects approximately 1 in 500 first pregnancies. Our study of 304 women with early-onset pre-eclampsia comprises an elaborate and unique effort to prospectively obtain comprehensive follow-up data of a well-described tertiary referral cohort of women affected by this potentially life-threatening disorder. Although the majority of patients recover after delivery and have achieved or wish to achieve a subsequent pregnancy, it is likely that pregnancy rates are lower than in the general population. This study may provide important tools for appropriate post partum counselling of affected women with respect to future reproductive outcome. Although neurological outcome at neonatal follow-up was not associated with reproductive decision-making in our study, these data were not available for all patients and information on certain specific developmental disorders was lacking. Also, we cannot rule out the possibility that women with a severely disabled child were more likely to be non-respondent to our follow-up calls. Unfortunately, data concerning pregnancy wish were not available for our reference group, thus a direct comparison of all motivations for uture reproductive decisions after normal pregnancy could not be analyzed. During our study period the standards and quality of neonatal intensive care has changed profoundly. The women's possibly changing attitude over time toward the improved neonatal care might have influenced our results. Unfortunately, this is an inevitable aspect of our study as the time span of including patients is long in such a rare event in pregnancy. Furthermore, in defining SGA, we used population charts that were developed in 1969. As (at least term born) neonates are probably heavier nowadays, this might have led to an underestimation of the number of SGA infants. Finally, our data do not comprise information on the use of assisted reproductive techniques (ART) in the patient and reference group. Differences between both groups might have led to differences in subsequent pregnancy rate. However, we have no reason to assume that differences in the use of ART have influenced our results to a large degree.

In conclusion, our study shows that a majority of women with a history of early-onset pre-eclampsia achieve or wish to achieve a second pregnancy within the first years after delivery. Nonetheless, first pregnancy early-onset pre-eclampsia appears to have a significant impact on future reproductive health and decision-making of affected patients, which emphasizes the importance of appropriate post partum counselling. Future research should aim at evaluating the need for structured follow-up programs for women who experienced early-onset pre-eclampsia with respect to long-term maternal physical, psychological and reproductive health.

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CHAPTER 10

Summary and general discussion

Preterm birth affects 10% of all newborns worldwide. The related morbidity and mortality exacts not only a high toll on individuals born preterm, but also on their families and the communities in which they live.[1,2] The pathogenesis of preterm birth is complex and largely unknown.[3,4] Despite extensive research, preterm birth remains relatively hard to predict and therefore difficult to prevent and is one of the major clinical and scientific challenges in modern obstetric healthcare.

In this thesis we aimed (1) to study trends and risk factors of preterm birth, (2) to develop prognostic models for preterm birth and its related complications and (3) to explore the impact of preterm birth on the reproductive decision making of the parents.

Part 1. Trends and risk factors

In **chapter 2** we presented an analysis of temporal trends in preterm birth in the Netherlands. The overall risk of preterm birth (<37 weeks) was 7.7% and the risk of very preterm birth was 1.3%. Our study showed a significant decrease in total preterm birth risk (from 6.4 to 6.0% in singleton pregnancies) between 2000 and 2007. For singleton pregnancies this was due to a significant decrease in spontaneous preterm birth without premature prelabour rupture of membranes (pPROM). Risk of total preterm birth and its subtypes were higher in nulliparous women compared to multiparous women. For multiple pregnancies there was no significant trend in total preterm birth risk although the subtype of medically indicated preterm birth did increase significantly. This trend towards increasing iatrogenic preterm birth was most pronounced in the 34-36 weeks subgroup of gestational age. We observed a large contribution of preterm birth (<37 weeks) to overall incidence of perinatal mortality (68% of all perinatal deaths). The reported decreasing trend in total preterm birth risk in singleton pregnancies stands in contrast to observations in many other developed countries where the increase in medically indicated preterm birth led to increasing trend of total preterm birth risk. We conjecture that our deviating findings are due to socio-cultural and organisational factors influencing the doctor's attitude towards interventions.

Chapter 3 presents a systematic review and meta-analysis of ethnic disparities in the risk of preterm birth. We found 45 studies on the association between maternal ethnicity and the risk of preterm birth, of which 41 reported a significant positive association between at least one ethnic group and preterm birth risk. Blacks appear to have a significantly increased (range of adjusted ORs 0.6 to 2.8, pooled odds ratio 2.0 (95% CI 1.8-2.2)) risk of preterm birth when compared to whites (30 included studies). For women of Asian ethnicity there was no significant association, with ORs ranging from 0.6 to 2.3 (17 included studies).

For women of Hispanic ethnicity there was no significant difference in the risk of preterm birth when compared to whites. Currently recognized risk factors do not appear to explain the increased risk of preterm birth among black women. Despite the heterogeneity of the included studies in defining ethnicity and adjustment for possible confounding, ethnic disparities clearly exist. This merits research on the causal pathways of these differences, and on preventative measures to reduce the incidence of preterm birth. As ethnic compositions of societies differ greatly, future prospective research should also focus on ethnic groups living outside the United States.

In **chapter 4** we investigated ethnic disparities in preterm birth and its perinatal complications in the Netherlands. Overall risk of spontaneous preterm birth was 5.4% in a population cohort of 969,491 singleton births in The Netherlands. African women have a significant increased risk of preterm birth (OR 1.33; 95% CI 1.26-1.41), but have a decreased risk of subsequent adverse neonatal outcome (OR 0.51; 95% CI 0.41-0.64). Mediterranean women had a decreased risk of preterm birth when compared to European white women, but also a significant decreased risk of subsequent adverse neonatal outcome (OR 0.84; 95% CI 0.72-0.98).

Compared to European whites, other ethnic groups had a decreased risk of adverse neonatal outcome after preterm birth. For an identical pregnancy length, neonates of African, South-Asian, Mediterranean and East-Asian women seem to be better resistant to the harmful impact of preterm birth. One of the most important risk factors for preterm birth is having a history of previous preterm birth.[3,4] This recurrence risk of preterm birth is well established in the case of succeeding singleton pregnancies.

In **chapter 5** we investigated whether this recurrence risk also occurs in the case of a twin pregnancy followed by a subsequent singleton pregnancy. We found that the risk of subsequent singleton preterm birth is significantly increased after a previous preterm twin delivery when compared to a previous term twin delivery. Twin gestation is thus not only a risk factor for preterm birth in the current pregnancy, but also accounts for an increased risk (5.2% versus 0.8%) in a subsequent singleton pregnancy. We showed that the increased risk of subsequent singleton preterm birth is even higher after a spontaneous preterm twin delivery (aOR 9.9; 95% CI 4.4-22.4) in comparison to an iatrogenic preterm twin delivery. The risk of preterm birth increases as the pregnancy length at the preterm twin delivery is shorter.

In **chapter 6** the opposite direction was under investigation: The risk of spontaneous preterm twin birth in women with a history of singleton delivery. We found that the risk of subsequent twin preterm birth is significantly increased after a previous preterm singleton delivery when compared to a previous term singleton delivery. Of the 232 women who had a preterm singleton delivery, 132 women (56.9%) had a spontaneous preterm birth in the subsequent twin pregnancy. The spontaneous singleton preterm birth risk in the 3,839 women who delivered their singleton at term was 20.9% (n=804).

Part 2. Prognostic models

In the second part of this thesis we aimed at developing prognostic models for the prediction of (spontaneous) preterm birth and its related complications.

In **chapter 7** we developed and internally validated a prognostic model for predicting the adverse pregnancy outcome of spontaneous preterm birth (<37 weeks). Our model consisted of 13 variables, had an AUC of 0.63 (95% CI 0.63-0.63), and exhibited over-prediction at high predicted probabilities. The strongest predictors were a history of previous preterm birth (OR 9.53, 95% CI 9.03-10.06), drug abuse (OR 4.23, 95% CI 3.54-5.06), and vaginal bleeding in the first half of pregnancy (OR 4.10, 95% CI 3.65-4.61). Our prognostic model, which combines all mentioned predictors, has the potential to facilitate the process of indentifying individual women at higher risk for preterm birth after spontaneous onset of birth. Although the development and validation of our prognostic model is an important next step towards individual risk assessment for spontaneous preterm birth, the moderate performance of the model limits its clinical usefulness. We expect, however, that the inclusion of various other variables such as cervical length, which were not available in the PRN registry, would boost the model's performance.

Chapter 8 describes the development and internal validation of a prognostic model for antenatal prediction of neonatal mortality after very preterm birth (<32 weeks). The final model consisted of 7 variables and showed a large range of predicted probabilities (0.0035-0.675) and a good discrimination capability (AUC 0.84). Gestational age, administration of antenatal corticosteroids, level of hospital, small for gestational age, maternal age, maternal ethnicity and fetal gender emerged as independent predictors, which can be known before birth.

In current clinical practice, antenatal counseling of women after the threshold of viability who are likely to deliver before 32 weeks of gestation is often based on general information like gestational age.[5] Instead, our model consists of a tool for obstetricians to provide individual risk assessment for women at risk of spontaneous or iatrogenic very preterm birth.

Part 3. Impact of preterm birth

Chapter 9 summarizes comprehensive data on reproductive follow-up of a cohort of 304 patients with a history of iatrogenic preterm birth due to early-onset pre-eclampsia. Our findings indicate that the majority of women become or wish to become pregnant within 5 to 8 years after a first pregnancy that was complicated by a delivery before 34 weeks of gestation due to a severe hypertensive disorder. However, a history of early-onset pre-eclampsia is associated with lower rates of ongoing pregnancies in the first years after delivery, when compared with low-risk women who experienced an uncomplicated first pregnancy. The results from our study provide insight into possible reasons why some women with a history of first pregnancy with an early-onset pre-eclampsia do not wish to achieve a subsequent pregnancy.

From our results, we conclude that different motivational elements play a role in the parents' decision, which may or may not be directly related to obstetrical history. Improved counselling and psychosocial treatment of women with a history of iatrogenic preterm birth due to early-onset pre-eclampsia might positively influence reproductive decision-making.

Implications for clinical practice and future research

The work presented in this thesis introduces some directions for future research and clinical practice. In this thesis several risk factors for preterm birth were further explored. The results may help clinicians in improving their risk assessment of preterm birth, for instance for specific ethnic groups or for women with a history of preterm birth. Furthermore this thesis provides tools for more accurate counselling of women with respect to their risk of preterm birth and/or related complications. On the other hand we must conclude that spontaneous preterm birth is still a difficult event to predict. Despite the population based dataset of the Netherlands Perinatal Registry (PRN) and the robust methodological approach, we were still not able to develop a prognostic model for spontaneous preterm birth that can be applied in clinical practice yet. This is partly due to absence of some relevant variables in the PRN dataset, but is moreover a result of the complexity of the pathogenesis of preterm birth, which makes it still hard to predict.

Preterm obstetric interventions

The relatively low risk of medically indicated preterm birth among singletons reported in this thesis in combination with the higher risk of perinatal mortality in the Netherlands seems to be paradoxical. Perhaps the more expectant treatment strategies in The Netherlands play a role in this matter. On the other hand, the scientific evidence for a more proactive intervening approach is limited. At present, major randomized controlled trials investigate the best treatment regime for women with premature prelabour rupture of membranes (PPROMEXIL study[6], PROMPT study[7]) and hypertensive disorders (HYPITAT II study[8]) between 34 and 37 weeks of gestation. The outcome of these studies might influence doctor's behaviour in the future.

Defining optimal gestational age

We presented not only data on ethnic disparities in spontaneous preterm birth risk, but also on the impact of preterm birth and how this differs between the main ethnic groups. We have shown that for African and South-Asian women the risk of preterm birth is significantly increased, whereas the actual impact of preterm birth on neonatal outcome is reduced for infants born preterm from these mothers. This apparent varying impact of preterm birth by ethnic group raises the question about defining the optimal pregnancy duration. The optimal pregnancy length of 40 weeks was based on a simple frequency distribution of gestational age at the time of spontaneous onset of labour in white women. In daily practice, these definitions are generalized for all women.[9]

Our results suggest an ethnic variation in optimal gestational age, with children born from African, Mediterranean and East-Asian women having better outcomes at earlier gestation age than their European white counterparts. In other words, these fetuses appear to be mature at an earlier gestational age.

Therefore, future research should focus on defining ethnic-specific optimal gestational age. Optimal gestational age, in this context, is defined as the gestational age at which risk of perinatal morbidity or mortality is the lowest. This has implication on redefining thresholds for preterm and postterm pregnancies and thus impacting daily obstetric practice. For instance in the Netherlands this might concern the referral pattern for women delivering before 37 weeks of gestation, but it might also imply a less expectant approach for specific ethnic groups who are having an ongoing pregnancy beyond 40 weeks of gestation.

Recurrence risk of preterm birth

The increased risk of preterm birth in twin pregnancies, which are often a result of artificial reproductive technology, also impacts subsequent singleton pregnancies. These findings can help clinicians to counsel their patients with a history of spontaneous or iatrogenic preterm delivery of twins and quantify their recurrence risks for spontaneous preterm birth.

Previous singleton preterm birth is often an indication for the use of progestagens in the next singleton pregnancy as a preventive measure for recurrence of preterm birth.[10] With these and previous findings, one should investigate the effectiveness of preventive measures like progestagens in singleton pregnancies following preterm twin deliveries as well.

Individual risk assessment for preterm birth

The development and internal validation of our prognostic model for preterm birth is an important next step towards individual risk assessment for spontaneous preterm birth, but the moderate performance of the model limits at present its clinical usefulness and emphasizes the difficulty of predicting preterm birth. In the future, our model and its successors with additional predictors should help clinicians indentify women at high risk for preterm birth. The improved counselling of women should focus on the modifiable predictors during pregnancy and should help patients recognize the early symptoms of threatening preterm labour. Another application of our model is the selection of women at higher risk for trials on preventive treatments strategies. Progestagens[10] and Cerclage procedure[11] have been shown to significantly reduce the risk of preterm birth in women with a history of preterm birth. Using our prognostic model we can investigate whether these treatments are beneficial for a broader group of pregnant women as well. For such an application prediction models should be better calibrated. To assess the model's generalisability one should aim for external validation of the model in a dataset in other populations.

Although the difficulties in individual preterm birth risk assessment are evident, we should still focus on expanding the development, validation and implementation of prognostic models. To this end, we need the inclusion of more potentially relevant variables and the standardization of the collection of well-defined variables. In particular the combination of maternal demographic and pregnancy characteristics, ultrasound and laboratory results, and other biomarkers merits more research. For this purpose we are currently setting up a prospective cohort in the region of the Academic Medical Center of Amsterdam (ZonMw grant number 50-50200-98-054). In this cohort we aim to study risk factors - in the field of public health and occupation as well as medical technical factors - to enable early detection of pregnant women at increased risk of preterm birth. In the end, integration of these risk factors in a risk prediction model should enable the identification of pregnant women at increased risk for preterm birth. The main challenge is to collect data on not only a large number of pregnant women in an unselected population, but also on their offspring, both short term (neonatal and paediatric care) and long term (child health centers). This will provide a much more complete understanding of the complex pathogenesis and adverse consequences of preterm birth and will in the end lead to a reduction of the harm that is caused by it.

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Curriculum vitae

Jelle Matthijs Schaaf was born on August 16th 1983 in Tilburg, The Netherlands. After graduating secondary school at the Theresialyceum in Tilburg in 2001 he moved to Utrecht. After one year of studying psychology at the University of Utrecht he was drawn a place in the school of medicine at the same university. During his study he completed internships in rural Nepal as well as on the island of Aruba. In December 2008 he graduated medical school and started working as a resident on the department of Obstetrics & Gynaecology of the St. Antonius Ziekenhuis in Nieuwegein and Utrecht. In February 2010 Prof. A. Abu-Hanna, Prof. B.W.J. Mol and dr. A.C.J. Ravelli gave him the opportunity to start a PhD project on the risk assessment and prediction of preterm birth in the Academic Medical Center (AMC) of Amsterdam. He started his residency in Obstetrics and Gynaecology in October 2012 in the Flevoziekenhuis in Almere.

List of publications

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Wereldwijd wordt 10% van alle neonaten geboren vóór de 37 weken zwangerschap en is er volgens de internationale richtlijnen dus sprake van vroeggeboorte. De hieraan gerelateerde morbiditeit en mortaliteit hebben niet alleen grote gevolgen voor de pasgeborene en diens familie, maar ook voor de samenleving. De pathogenese van vroeggeboorte is complex en is nog altijd grotendeels onbekend. Ondanks uitgebreid wetenschappelijk onderzoek is vroeggeboorte nog steeds moeilijk te voorspellen en dus evenmin te voorkomen. Derhalve vormt vroeggeboorte één van de grootste klinische en wetenschappelijke uitdagingen in de moderne verloskundige zorg. In dit proefschrift richten wij ons op (1) het bestuderen van trends en risicofactoren voor vroeggeboorte, (2) het ontwikkelen van prognostische modellen voor vroeggeboorte en de daaraan gerelateerde complicaties en (3) het exploreren van de impact van (iatrogene) vroeggeboorte op de reproductieve besluitvorming van de ouders.

Deel 1. Trends en risicofactoren

In **hoofdstuk 2** presenteren wij een analyse van de temporele trends in de vroeggeboorten in Nederland. Het risico op vroeggeboorte (<37 weken) is 7.7% en het risico op ernstige vroeggeboorte (<32 weken) is 1.3%. Onze studie laat zien dat er tussen de jaren 2000 en 2007 een significante afname heeft plaats gevonden van zowel het risico op vroeggeboorte (van 6.4% naar 6.0% in eenling-zwangerschappen), als van het risico op perinatale sterfte. Voor eenling- zwangerschappen is dit een gevolg van een significante afname in het aantal spontane vroeggeboorten zonder langdurig gebroken vliezen. Het risico op vroeggeboorte is voor nullipara vrouwen hoger dan voor multipara vrouwen. Voor meerlingzwangerschappen worden geen significante trends gevonden in het totale risico op vroeggeboorte, hoewel bij de subverdeling wel een significante toename van iatrogene vroeggeboorten wordt gezien. Deze trend richting meer iatrogene vroeggeboorten wordt voornamelijk gezien bij een zwangerschapsduur van 34 tot en met 36 weken. We zien tevens dat vroeggeboorte een grote bijdrage levert aan de totale incidentie van perinatale mortaliteit (68% van alle perinatale sterfte). De gerapporteerde afnemende trend van vroeggeboorten in eenlingzwangerschappen staat in contrast met studies in andere Westerse landen. Daarin wordt vaak beschreven dat het aantal vroeggeboorten juist is toegenomen. Dit wordt toegeschreven aan het grotere aantal obstetrische interventies in de preterme zwangerschap. Wij vermoeden dat onze afwijkende bevindingen worden veroorzaakt door sociaal-culturele en organisatorische verschillen welke de attitude van de artsen jegens interventies beïnvloeden.

Hoofdstuk 3 omvat een systematische review en meta-analyse inzake de etnische verschillen in het risico op vroeggeboorte. We hebben 45 studies gevonden die de relatie beschrijven tussen maternale etniciteit en het risico op vroeggeboorte.

Hiervan beschrijven 41 studies een significant positief verband tussen tenminste één etnische groep en het risico op vroeggeboorte. Vergeleken met blanke vrouwen blijken donkere vrouwen van (oorspronkelijk) Afrikaanse afkomst een significant verhoogd risico op vroeggeboorte te hebben. De bestudeerde artikelen laten een spreiding van gecorrigeerde odds ratios zien van 0.6 tot 2.3 (gepoolde odds ratio 2.0; 95% BI 1.8-2.2). Voor vrouwen met een Aziatische achtergrond is geen significant verband gevonden. Algemeen erkende confounders blijken de gevonden verschillen niet te verklaren. Ondanks de heterogeniteit in het definiëren van maternale etniciteit en het omgaan met confounders tussen de geïncludeerde studies, zijn etnische verschillen in het risico op vroeggeboorte duidelijk aanwezig. Deze bevinding vraagt om aanvullende studies naar de oorzaken van deze verschillen en naar preventieve maatregelen om de incidentie van vroeggeboorte te verlagen. Daarnaast dient onderzoek gedaan te worden naar etnische groepen buiten de Verenigde Staten, aangezien het merendeel van de bestaande studies daar is uitgevoerd.

In **hoofdstuk 4** hebben we in de Nederlandse populatie de etnische verschillen in het risico op vroeggeboorte en de daaraan gerelateerde perinatale complicaties onderzocht. In het totale cohort van 969.491 vrouwen is het overall risico op spontane vroeggeboorte 5.4%. Afrikaanse vrouwen hebben een significant verhoogd risico op vroeggeboorte, maar hebben een verlaagd risico op aansluitende neonatale complicaties (odds ratio 0.51; 95% BI 0.41-0.64). Mediterrane vrouwen hebben een verlaagd risico op vroeggeboorte, maar ook een verlaagd risico op neonatale complicaties (odds ratio 0.84; 95% BI 0.72-0.98). Vergeleken met Europese blanke vrouwen, hebben de overige etnische groepen een verlaagd risico op neonatale complicaties na vroeggeboorte. Bij een identieke zwangerschapsduur lijken pasgeborenen van Afrikaanse, Zuid-Aziatische, Mediterrane en Oost-Aziatische moeders beter bestand te zijn tegen de schadelijke impact van vroeggeboorte. Een met vroeggeboorte belaste obstetrische voorgeschiedenis vormt één van de belangrijkste risicofactoren voor (opnieuw) een vroeggeboorte. Dit herhaalrisico is uitgebreid beschreven in wetenschappelijke literatuur als het gaat om opvolgende eenlingzwangerschappen.

In **hoofdstuk 5** hebben we onderzocht of dit herhaalrisico ook geldt in het geval van een opvolgende eenlingzwangerschap na een eerdere vroeggeboorte van een tweeling. Onze bevinding is dat het risico op een vroeggeboorte in een opvolgende eenlingzwangerschap significant is verhoogd na een vroeggeboorte van een tweeling (vergeleken met eerdere a terme geboorte van een tweeling). Tweelingzwangerschappen vormen dus niet alleen een risico voor vroeggeboorte in de huidige zwangerschap, maar verhogen ook het risico op vroeggeboorte in een eerstvolgende eenling-zwangerschap (5.2% versus 0.8%). Wij tonen aan dat het risico op vroeggeboorte in de eerstvolgende eenlingzwangerschap hoger is na een spontane vroeggeboorte van een tweeling (gecorrigeerde odds ratio 9.9; 95% BI 4.4-22.4) dan na een eerdere iatrogene vroeggeboorte van een tweeling.

Het herhaalrisico op vroeggeboorte neemt toe naarmate de zwangerschapsduur in de voorgaande tweelingzwangerschap korter is geweest.

In **hoofdstuk 6** hebben we de tegenovergestelde vraag onderzocht: wat is het risico op spontane vroeggeboorte in een tweelingzwangerschap bij vrouwen met een voorgaande eenlingzwangerschap? Onze resultaten tonen aan dat het risico op een spontane vroeggeboorte in een aansluitende tweelingzwangerschap significant verhoogd is als de voorgaande eenlingzwangerschap ook in een vroeggeboorte heeft geresulteerd. Van de 232 vrouwen met een vroeggeboorte in de eenlingzwangerschap hebben 132 vrouwen (56.9%) in de aansluitende tweelingzwangerschap een spontane vroeggeboorte gehad. Het risico op spontane vroeggeboorte bij de 3839 vrouwen die in hun voorgaande eenlingzwangerschap in de a terme periode zijn bevallen, is 20.9% (n=804).

Deel 2. Prognostische modellen

In het tweede deel van dit proefschrift stellen we ons tot doel om prognostische modellen te ontwikkelen voor het voorspellen van vroeggeboorte en de daaraan gerelateerde complicaties.

In **hoofdstuk 7** wordt de ontwikkeling en interne validatie beschreven van een prognostisch model voor het voorspellen van vroeggeboorte (<37 weken). Het ontwikkelde model bestaat uit 13 variabelen, heeft een AUC van 0.63 (95% BI 0.63-0.63) en laat overpredictie zien bij hogere waarden van voorspelde kansen. De sterkst voorspellende variabelen zijn een vroeggeboorte in de voorgeschiedenis (odds ratio 9.53; 95% CI 9.03-10.06), drugs misbruik (odds ratio 4.23; 95% BI 3.54-5.06) en vaginaal bloedverlies in de eerste helft van de zwangerschap (odds ratio 4.10; 95% BI 3.65-4.61). Het prognostisch model heeft de potentie om vrouwen met een verhoogd risico op spontane vroeggeboorte te identificeren en daarmee om de zorgverlener te ondersteunen bij het maken van een individuele risicoselectie. Hoewel de ontwikkeling en validatie van dit prognostisch model een belangrijke volgende stap is in het proces van individuele risicoselectie, is het huidige model nog niet geschikt om geïmplementeerd te worden in de moderne obstetrische zorg. We verwachten echter dat toevoeging van extra variabelen die (nog) niet beschikbaar zijn in de PRN (Perinatale Registratie Nederland), zoals cervixlengte, de bruikbaarheid van het prognostisch model sterk zal verbeteren.

Hoofdstuk 8 beschrijft de ontwikkeling en interne validatie van een prognostisch model voor het antenataal voorspellen van neonatale sterfte in het geval van (dreigende) ernstige vroeggeboorte (<32 weken). Het model bestaat uit 7 variabelen en laat een brede spreiding zien van de voorspelde kansen (0.0035-0.675). Het discriminatieve vermogen van het model is goed (AUC 0.84). De variabelen zwangerschapsduur, het gebruik van antenatale corticosteroïden, het niveau van het ziekenhuis, maternale leeftijd, maternale etniciteit en intra-uteriene groeirestrictie zijn opgenomen in het uiteindelijke model. Al deze gegevens kunnen bekend zijn vóór de geboorte.

In de huidige klinische praktijk is de antenatale counseling van vrouwen (en hun partners) met een dreigende ernstige vroeggeboorte vaak gebaseerd op algemene informatie; niet specifiek voor het individu. Ons model kan als een hulpmiddel dienen voor zorgverleners bij het voorlichten van vrouwen met een dreigende ernstige spontane of iatrogene vroeggeboorte.

Deel 3. Impact van vroeggeboorte

In **Hoofdstuk 9** worden de resultaten gepresenteerd van een follow-up onderzoek van 304 vrouwen met een voorgeschiedenis van een iatrogene vroeggeboorte na het doormaken van vroege pre-eclampsie. Onze resultaten laten zien dat, bij follow-up na 5 tot 8 jaar na die eerste gecompliceerde zwangerschap, de meerderheid van de vrouwen weer zwanger is geworden, of in elk geval de wens daartoe heeft. Echter, wanneer deze groep wordt vergeleken met vrouwen die een ongecompliceerde eerste zwangerschap hebben doorgemaakt, is een voorgeschiedenis van vroege pre-eclampsie (leidend tot iatrogene vroeggeboorte) geassocieerd met lagere percentages van opvolgende zwangerschappen in de eerste jaren na de vroege pre-eclampsie. Verder laten we zien wat bij een voorgeschiedenis van vroege pre-eclampsie de mogelijke redenen zijn om af te zien van een volgende zwangerschap. Verbeterde counseling en psychosociale begeleiding na het doormaken van een dergelijke gecompliceerde zwangerschap zou de reproductieve besluitvorming van koppels positief kunnen beïnvloeden.


Joaa
zeee - tie!!
CONCLUSIE

Dankwoord

Prof. dr. A. Abu-Hanna, beste Ameen. Dank voor je begeleiding en ondersteuning. Onze wetenschappelijke interessegebieden komen soms niet geheel overeen, maar des te meer waardering heb ik voor het geduld waarmee je mij hebt laten kennismaken met de Medische Informatiekunde.

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