Neonatal Respiratory Morbidity

The effects of timing of elective caesarean sections and hypertensive disorders during pregnancy

Freke Anna Wilmink

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Neonatale Respiratoire Morbiditeit

De effecten van timing van electieve sectio caesarea en hypertensieve ziektes tijdens de zwangerschap

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'We're Alright' - Ilse DeLange

Voor Ronald

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General Introduction

Fetal lung development and maturity

Lungs develop in different stages throughout pregnancy and after being born. Fetal lung development starts at 5 weeks gestation with creation of a diverticulum from the ventral foregut.[1-3] At 12 to 14 weeks of gestation, the primordial system differentiates into the future bronchial and respiratory system.[1] Around a gestational age of 40 weeks, 17-70 million alveoli are present. After birth, the number of alveoli will continue to increase during the first 5 to 8 years of life. Thereafter the present alveoli will grow and increase their surface for diffusion and gas exchange.[1]

From 24 weeks onwards the production of surfactant starts and increases every week.[1,3] Surfactant is synthesized by type II pneumocytes and prevents atelectasis in the neonatal lungs by decreasing alveolar surface tension.

Neonatal respiratory morbidity

Short-term neonatal respiratory morbidity is usually defined as respiratory distress syndrome (RDS) or Transient Tachypnea of the Newborn (TTN)/ Wet lung syndrome. Overall, the incidence of respiratory morbidity at term (from 37^{+0} weeks of gestation onwards) is low (< 5%). However, after a caesarean section the incidence of respiratory morbidity is higher than after vaginal birth. The incidence of RDS and TTN is 7.4- 10.0%, 4.2- 5.5% and 1.8- 3.5% at 37^{+0-6}, 38^{+0-6} and 39^{+0-6} weeks of gestation, respectively.[4,5]

Elective caesarean sections

The incidence of caesarean sections (CSs) continues to increase worldwide. Although low in comparison worldwide, in the Netherlands the incidence of a caesarean section (CS) has increased from 7.4% in 1990 to 16.6% in 2015.[6,7] In 2011, the CS rates in the United Kingdom and the United States were 23.4% and 32.3%, respectively.[8] Explanations for the increase in CS rates worldwide include the increase in elective CS for breech presentations and an increase of elective repeat caesarean deliveries.[8] Two types of CSs are either elective (or planned) CSs and emergency (or unplanned) CSs. An elective CS is defined as a planned CS before spontaneous start of labour, without strict medical indication.

The risks for neonatal respiratory morbidity and subsequently transfer rates to the Neonatal Intensive Care Unit (NICU) are significantly higher after a planned caesarean delivery compared to a planned or spontaneous vaginal delivery, also at term.[9-11] As the risks

diminish significantly with increasing gestational age until 39^{+0} weeks of gestation, optimal timing of planning and performing a CS is important to prevent unnecessary iatrogenic neonatal morbidity.[4,5,11,12] However, postponing a planned CS beyond 39^{+0} weeks of gestation increases the chance of a spontaneous start of labour and the need (at that moment) to perform a CS in an unplanned or emergency setting.

Hypertensive disorders during pregnancy and respiratory morbidity in short and long term

A common complication during pregnancy are hypertensive disorders, which comprise pre-existent hypertension (PEH), gestational hypertension (GH), preeclampsia (PE), superimposed preeclampsia and Haemolysis Elevated Liver Enzymes Low Platelets (HELLP) syndrome. All these hypertensive disorders are associated with adverse neonatal outcomes such as fetal growth restriction and (iatrogenic) preterm birth.[13-15] Preterm birth and low birth weight are independently associated with a higher risk for lower lung function and asthma in later life.[16-20] It is hypothesized that hypertensive disorders also have a direct effect on neonatal respiratory morbidity, through disturbed placental function and an altered fetal angiogenic status, hereby affecting fetal lung development and lung maturation.[21-24] Animal studies have shown that dysregulation of angiogenesis during fetal development, resulting in an anti-angiogenic status, may be implicated in the development of bronchopulmonary dysplasia (BPD).[25] BPD is a severe complication of the newborn, associated with chronic respiratory morbidity and impaired neurodevelopment.[19,26] Several cohort studies in humans observed a higher risk for BPD of the neonate in women with preeclampsia, although some studies were inconclusive.[21,27-31] Besides short-term respiratory morbidity, it can be hypothesized that an anti-angiogenic status during pregnancy also has long-term effects on respiratory health in the offspring of women with hypertensive disorders during pregnancy (e.g. wheezing and asthma).

Aims of this thesis

Against this background, the aims of this thesis can be summarized as follows:

Part 1

1. To evaluate the incidence and timing of elective caesarean sections at term, and to assess neonatal outcome associated with the specific timing.

2. To determine the number of associated emergency (unplanned) CS as compared to early planned (37^{+0}-38^{+6}) elective CSs to prevent one neonate with respiratory complications, in a policy of elective CSs from 39^{+0} weeks onwards.
3. To assess neonatal morbidity and mortality of elective CSs from 35^{+0} weeks onwards of uncomplicated twin pregnancies.

Part 2

4. To assess preeclampsia is associated with development of bronchopulmonary dysplasia in very preterm neonates (<32^{+0} weeks gestation).
5. To examine associations of maternal blood pressure at multiple time points during pregnancy and gestational hypertensive disorders with the risk of lower lung function, wheezing and asthma in late childhood.

Setting

For the studies described in chapter 2, 3 and 5 we used data of 'The Netherlands Perinatal Registry', currently called Perined. Perined is a national registry comprising data of all midwifery and obstetric care. In addition, it also contains neonatal care and outcome measurements for a large part of the Netherlands. For chapter 4, a decision analysis, we used data from existing literature. The study described in chapter 6 is a retrospective cohort of very preterm births <32^{+0} weeks of gestation of the Sophia Children's Hospital-Erasmus Medical Centre, with follow up data from the Neonatal Intensive Care Unit, as well as from the peripheral hospitals organized in the Research Consortium Neonatology South-West of the Netherlands. The study described in chapter 7 is embedded in The Generation R Study, an ongoing population-based cohort study from the Sophia Children's Hospital-Erasmus Medical Centre, designed to identify early environmental, biological, and social determinants of growth, development, and future health.[32]

Outline of this thesis

Part 1 of this thesis focuses on timing of elective CSs to prevent iatrogenic neonatal morbidity, especially respiratory morbidity. Chapter 2 and 3 focus on incidence and timing of elective CSs of singleton pregnancies and associated adverse neonatal outcome. Chapter 5 focuses on incidence and timing of elective CSs of uncomplicated twin pregnancies and associated adverse neonatal outcome. Chapter 4 highlights the importance of maintaining vigilance with respect to elective timing of delivery, and presents a discussion analysis calculating the number of associated emergency (unplanned) CS as compared to early

planned (37^{+0}-38^{+6}) elective CSs to prevent one neonate with respiratory distress or wet lung syndrome, in a policy of elective CSs from 39^{+0} weeks onwards.

Part 2 focuses on the associations of hypertensive disorders during pregnancy, and respiratory morbidity of the offspring in short (Chapter 6) and in long term (Chapter 7). In the general discussion in chapter 8 the relevance and implications of the main findings are being discussed for clinical practice. Additionally, the possibility of prenatally prediction of fetal lung maturity is addressed and recommendations for future research are proposed. Finally, chapter 9 presents a summary of the findings of this thesis.

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PART 1

Timing of elective caesarean sections

2

Neonatal outcome following elective caesarean section beyond 37 weeks of gestation; a 7-year retrospective analysis of a national registry

F.A. Wilmink

C.W.P.M. Hukkelhoven

S. Lunshof

B.W.J. Mol

J.A.M. van der Post

D.N.M. Papatsonis

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Abstract

Background

To evaluate number and timing of elective caesarean sections at term and to assess perinatal outcome associated with this timing.

Methods

A recent retrospective cohort study including all elective caesarean sections of singleton pregnancies at term (n = 20.973) with neonatal follow-up. Primary outcome was defined as a composite of neonatal mortality and morbidity.

Results

More than half of the neonates were born before 39 weeks of gestation, and they were at significantly higher risk for the composite primary outcome than neonates born thereafter. The absolute risks were 20.6% and 12.5% for birth before 38 and 39 weeks respectively, as compared to 9.5% for neonates born at or after 39 weeks. The corresponding adjusted odds ratios (95% confidence interval) were 2.4 (2.1 to 2.8) and 1.4 (1.2 to 1.5), respectively.

Conclusion

More than 50% of the elective caesarean sections are applied before 39^{+0} weeks, thus jeopardizing neonatal outcome.

Introduction

In the Netherlands the incidence of a caesarean section has been increased from 8.5% in 1993[1] to 15.1% in 2007[2]. The risk for pulmonary disorders and subsequent transfer rates to the neonatal intensive care unit (NICU) are significantly higher after a planned caesarean delivery compared to planned vaginal delivery[3-7]. It is known that, even in term pregnancies, the risk for neonatal respiratory morbidity after a planned caesarean section diminishes significantly with an increase of gestational age until week 39^{+0} [8-12]. Because of the rising incidence of caesarean sections, correct timing of the elective caesarean section is of the utmost importance to prevent unnecessary neonatal (respiratory) morbidity.

Tita et al.[12] recently showed that neonatal morbidity is still significantly higher in neonates born after an elective repeat caesarean section between 38^{+4} to 38^{+6} weeks as compared to neonates born thereafter. The aims of our study were to evaluate the number and timing of elective caesarean sections at term in the Netherlands and to assess perinatal outcome associated with this timing.

Methods

The Netherlands Perinatal Registry (PRN) is a national database which includes 96% of all approximately 190,000 deliveries per year after 16 completed weeks of gestation in the Netherlands, that are under supervision of a midwife or an obstetrician[13]. After every delivery and after every admitted neonate, standardized digital forms are entered in this nationwide database. The neonatal follow-up in the PRN is registered for around 68% of all hospitals in the Netherlands. All items recorded in the Perinatal Registry are recorded by the caregiver, who can use a standard manual with additional information on the definitions. The data are annually sent to the national registry office, where a number of range and consistency checks (routine audit) are conducted. False records are sent back to the caregiver, who is given ample opportunity to correct them. In an earlier study, we have compared outcome measures – such as perinatal mortality - in our PRN registry with civil registration data, and it appeared that the quality of the outcome measurements was high.[14]

For this study, data from the PRN concerning 1,300,099 births between January 1, 2000 to December 31, 2006 were analyzed for perinatal outcome after elective caesarean section at term. The study was limited to those hospitals that systematically registered neonatal follow-up. In addition, pregnancies complicated by intra-uterine fetal deaths, emergency caesarean sections, multiple pregnancies, fetus with congenital anomalies, elective caesarean sections after spontaneous rupture of membranes or signs of labour and mothers with an adverse medical or obstetric history and/ or complications of pregnancy that could

influence the risk for neonatal morbidity were excluded. Indications for an elective caesarean section included repeat caesarean section, breech presentation, traumatic first pregnancy or maternal request.

According to national guidelines[15] calculation of gestational age was based on the first day of the last menstrual period and verified by a first trimester ultrasound. In case of discrepancy between the two measurements (error margin 7 days), gestational age was determined by the results of the first trimester ultrasound.

Outcome measures

We defined our primary outcome as a composite measure of neonatal mortality until the 28th day after birth, and/ or neonatal morbidity which includes any of the following adverse events: severe resuscitation (defined as 'endotracheal artificial respiration and/ or administration of buffers and/ or other'), sepsis (including both clinically suspected patients as well as proven infections with positive cultures), respiratory complications (registered as Respiratory Distress Syndrome (RDS), wet lung syndrome or Transient Tachypnea of the Newborn (TTN), pneumothorax or air leakage), respiratory support (Oxygen (O2), Intermittent Positive Pressure Ventilation (IPPV), Continuous Positive Airway Pressure (CPAP)), hypoglycaemia (defined as a serum or plasma glucose level of less than 2,5mmol/l), neurologic morbidity (described as convulsions or intracranial haemorrhage), admission to the Neonatal Intensive Care Unit (NICU), admission to any neonatal ward ≥ 5 days and a 5-minute Apgar score ≤ 3. In addition to our primary outcome measure we also analyzed the incidence and odds ratio's for any of the above individual outcome measures and for: a 5-minute Apgar score ≤ 7, necrotizing enterocolitis, meconium aspiration and hyperbilirubinaemia. To be able to compare our results with the literature we also defined a combined respiratory outcome measure, including both respiratory complications (RDS, TTN, pneumothorax, air leakage) and respiratory support (O2, IPPV, CPAP). The follow-up of neonates stopped at discharge from the hospital. If they were transferred to another hospital (for example a university hospital), follow-up was continued.

Socio-economic status was based on the mean household income level of the neighbourhood, which was determined by the first four digits of the woman's postal code. Small for gestational age was defined as a birth weight less than the 10th percentile, derived from sex-, parity- and race-specific growth curves[16].

Statistical analysis

We calculated the incidence of neonatal outcomes for each completed week of gestation at the time of caesarean section. The Cochran-Armitage test for trend was used to test the presence of trends. Logistic regression analyses were used to study the association between

neonatal outcomes and gestational age at delivery relative to 39 completed weeks of gestation. For each outcome we calculated the odds ratio (OR) and 95% confidence interval (95% CI) and adjusted for potential confounders known to be associated with these outcomes: maternal age[4;12], ethnicity[12], parity[4], socio-economic status[4;12], fetal gender[9;17] and fetal position[9]. The robustness of our findings was tested by performing four sensitivity analyses and repeating the regression analyses in which: 1) births with uncertain gestational age (2.6%) were excluded, 2) infants with a birth weight less than the 10th percentile were excluded, 3) infants in non-vertex position were excluded, 4) additional adjustments for study centre were performed to correct for potential variation in clinical decision making. Missing values occurred for only 0.007% of all confounders and were imputed once[18;19], using R software[20]. All other analyses were performed using SAS software, version 9.1 (SAS Institute, Cary NC).

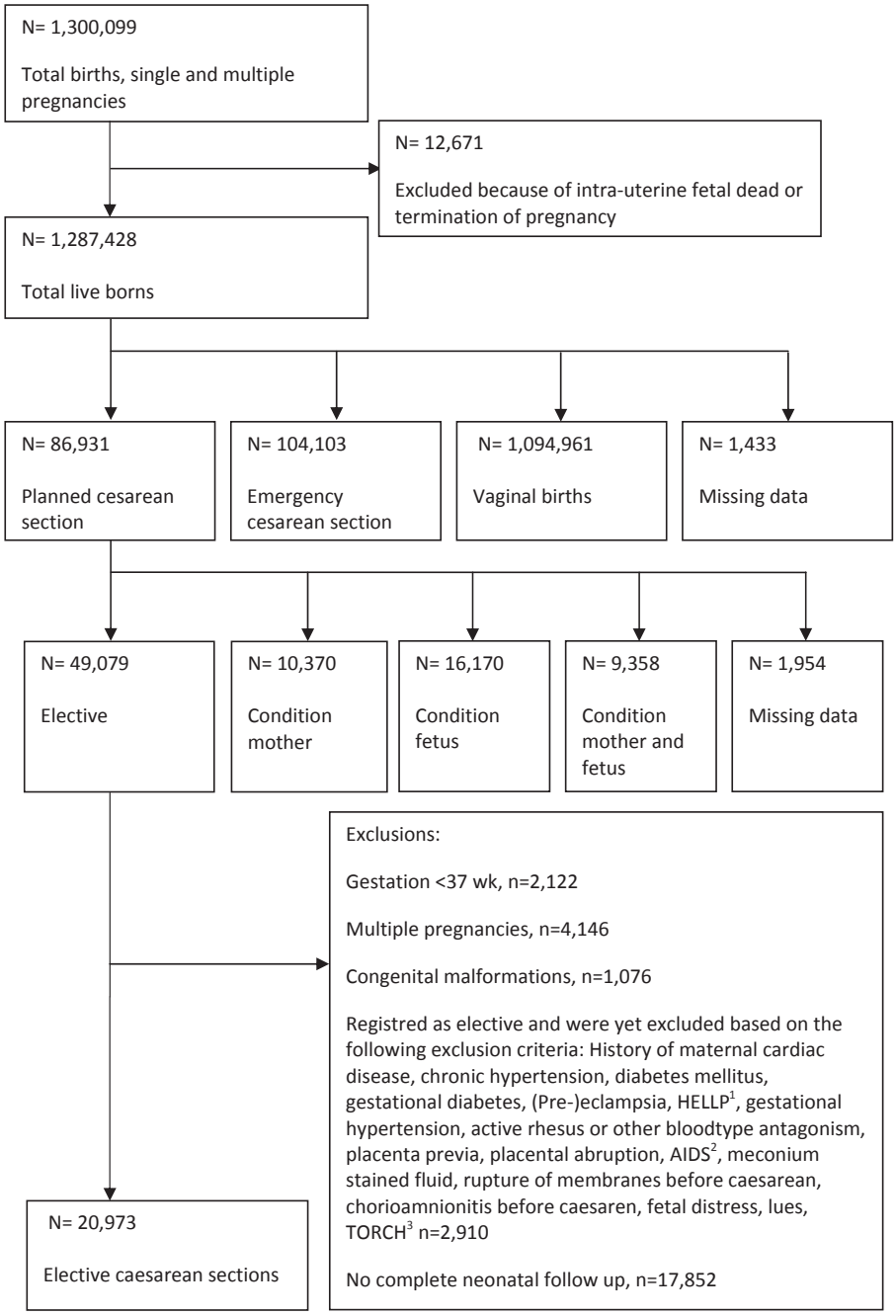
Results

Figure 1 shows the study profile. In the study period, 1,300,099 births of single and multiple pregnancies were registered by the PRN. We excluded 12,671 births because of intra-uterine fetal deaths or termination of pregnancy. We also excluded 1,094,961 vaginal births, 104,103 emergency caesarean sections, and 1,433 births because of missing data. Among 86,931 planned caesarean sections, 49,079 (56.5%) deliveries were registered as elective. Initially we excluded all births before 37^{+0} weeks of gestation (n=2,122), secondly 4,146 multiple pregnancies, thirdly 1,076 fetuses with congenital malformations, and subsequently 2,910 mothers with an adverse medical or obstetric history and/ or complications of pregnancy that could influence the risk of neonatal morbidity. Finally, 17,852 cases were excluded because of incomplete follow-up. We therefore report on 20,973 elective caesarean sections.

In total 11,873 (56.6%) elective caesarean sections were performed before 39^{+0} weeks of gestation, 1,734 (8.3%) at 37^{+0-6} and 10,139 (48.3%) at 38^{+0-6} weeks. At 39^{+0-6} weeks of gestation 6,647 (31.7%) elective caesarean sections were performed and 2,453 (11.7%) at 40^{+0} weeks or later (Table 1).

Maternal and infant characteristics differed among the different categories for gestational age (Table 1). Compared to women who delivered at 39^{+0} weeks or later, women who delivered before 39^{+0} weeks of gestation tended to be slightly older, from Western origin and multiparous. The mean birth weight increased with an increasing gestational age at delivery. Neonates born after 39^{+0} weeks of gestation were significantly more often small (<10th percentile) or large (>90th percentile) for gestational age.

Figure 1. Flow chart



[1]Hemolysis, elevated liver-enzymes, and low platelet count; [2]acquired immunodeficiency syndrome; [3]toxoplasmosis, German measles, cytomegalovirus, herpes simplex.

Table 1. Maternal and neonatal characteristics shown per week of gestation at delivery

Week of gestation	37^{+0-6}	38^{+0-6}	39^{+0-6}	40^{+0-6}	41^{+0-6}	≥ 42
Proportion of deliveries	**n=1,734 (8.3%)**	**n=10,139 (48.3%)**	**n=6,647 (31.7%)**	**n=1,274 (6.1%)**	**n=782 (3.7%)**	**n=397 (1.9%)**
Maternal characteristics						
Age at delivery (years)[1]						
Mean[2]	32.1 ± 4.6	31.9 ± 4.4	32.0 ± 4.5	31.9 ± 4.7	31.7 ± 4.5	31.7 ± 4.5
< 20	17 (1.0)	54 (0.5)	33 (0.5)	3 (0.2)	6 (0.8)	2 (0.5)
20 - < 25	85 (4.9)	482 (4.8)	340 (5.1)	77 (6.0)	37 (4.7)	24 (6.1)
25 - < 30	355 (20.5)	2,325 (22.9)	1,428 (21.5)	299 (23.5)	195 (24.9)	96 (24.2)
30 - < 35	742 (42.8)	4,464 (44.0)	2,959 (44.5)	542 (42.5)	341 (43.6)	164 (41.3)
35 - < 40	457 (26.4)	2,413 (23.8)	1,585 (23.9)	292 (22.9)	172 (22.0)	95 (23.9)
≥40	78 (4.5)	401 (4.0)	302 (4.5)	61 (4.8)	31 (4.0)	16 (4.0)
Race or ethnic group[1]						
Western	1,557 (91.5)	9,103 (91.7)	5,878 (91.2)	1,069 (87.2)	688 (89.4)	342 (88.4)
Asian	28 (1.7)	146 (1.5)	109 (1.7)	33 (2.7)	10 (1.3)	3 (0.8)
Other	116 (6.8)	677 (6.8)	459 (7.1)	124 (8.3)	72 (9.4)	42 (10.9)
Parity[1]						
Primipara	594 (34.3)	3,714 (36.6)	2,745 (41.3)	419 (32.9)	295 (37.7)	156 (39.3)
Multipara	1,140 (65.7)	6,425 (63.4)	3,902 (58.7)	855 (67.1)	487 (62.3)	241 (60.7)
Socio-economic status[1]						
Very high	359 (21.0)	2,009 (20.2)	1,442 (22.0)	237 (18.8)	153 (19.8)	71 (17.9)
High	362 (21.2)	2,156 (21.7)	1,336 (20.4)	268 (21.3)	184 (23.8)	92 (23.2)
Normal	331 (19.4)	1,901 (19.1)	1,190 (18.2)	224 (17.8)	135 (17.5)	81 (20.5)
Low	336 (19.7)	1,856 (18.6)	1,170 (17.9)	221 (17.6)	128 (16.6)	65 (16.4)
Very low	318 (18.6)	2,034 (20.4)	1,414 (21.6)	308 (24.5)	173 (22.4)	87 (22.0)
Child characteristics						
Gender[1]						
Male	855 (49.3)	4,941 (48.7)	3,172 (47.7)	663 (52.0)	402 (51.4)	202 (50.9)
Female	878 (50.7)	5,197 (51.3)	3,475 (52.3)	611 (48.0)	380 (48.6)	195 (49.1)
Position[1]						
Vertex	957 (55.2)	4,746 (46.9)	2,943 (44.3)	754 (59.3)	475 (60.9)	285 (71.8)
Breech	688 (39.7)	5,029 (49.6)	3,434 (51.7)	458 (36.0)	279 (35.8)	99 (24.9)
Other	88 (5.1)	355 (3.5)	266 (4.0)	59 (4.6)	26 (3.3)	13 (3.3)
Birth weight (grams)[1]						
Mean[2]	3183 ± 484	3358 ± 459	3495 ± 463	3739 ± 515	3868 ± 512	3908 ± 528
< 2500	118 (6.8)	208 (2.1)	70 (1.1)	4 (0.3)	0	3 (0.8)
Small for gestational age[1,3]	113 (6.5)	581 (5.7)	487 (7.3)	101 (7.9)	61 (7.8)	36 (9.0)
Large for gestational age[1,4]	233 (13.4)	1,246 (12.3)	917 (13.8)	250 (19.6)	146 (18.7)	63 (15.9)

[1]P-value < 0.05. Values are absolute numbers (%) or [2]means ±SD. [3] < p10, [4] > p90.

The overall and separate incidence rates of the study outcomes are shown per week of gestation in Table 2. Neonates born at 37^{+0-6} or 38^{+0-6} weeks of gestation were, compared to neonates born after 39^{+0} weeks of gestation, at significantly higher risk for the composite primary outcome. The absolute risks were 20.6% at 37^{+0-6} and 12.5% at 38^{+0-6} weeks compared with 9.5% at 39^{+0-6} weeks of gestation (p for trend < 0.0001). Most separate neonatal outcomes showed significant trends (p for trend < 0.05) towards an increased incidence for delivery below 39^{+0} weeks (Table 2). During our study period three neonates died within 24 hours after delivery (one at 37, one at 39 and one at 42 weeks of gestation), and one neonate died between day 2 and 7 at 38 weeks of gestation.

The analyses adjusted for potential confounders confirmed the observed trends towards the decreasing incidence of outcome measures with increasing gestational age up to 39^{+0} weeks of gestation (Table 3). Adjusted odds ratios (95% confidence interval) for the primary outcome at 37^{+0-6} and 38^{+0-6} weeks were 2.4 (2.1 to 2.8) and 1.4 (1.2 to 1.5) respectively. When exclusively considering the combined respiratory outcome absolute risks were 6.8% at 37^{+0-6} and 3.5% at 38^{+0-6} weeks compared with 2.1% at 39^{+0-6} weeks of gestation, with odds ratio's (95% confidence interval) at 37^{+0-6} and 38^{+0-6} weeks of 3.2 (2.5 to 4.2) and 1.7 (1.4 to 2.1) respectively.

Just like Tita et al[12] we did a subgroup analysis for all births between 38^{+4-6} weeks (n= 5046). Compared to neonates borne after 39^{+0} weeks, neonates born between 38^{+4-6} weeks still had a significantly higher risk for an adverse neonatal outcome, odds ratios (95% confidence interval) for primary outcome and for our combined respiratory morbidity were 1.3 (1.1 to 1.4) and 1.4 (1.1 to 1.8) respectively. All performed sensitivity analyses showed robustness of our findings (results not shown).

There were no cases of necrotizing enterocolitis or hypoxic-ischemic encephalopathy, and only three cases of intracranial bleeding between 38^{+0-6} weeks.

Comment

We analyzed the neonatal outcome of 20,973 electively performed caesarean sections at term in the Netherlands. More than half of all elective caesarean sections at term were performed before 39^{+0} weeks gestation. As compared with caesarean sections at 39^{+0-6} weeks, these early planned caesareans had a significantly higher overall risk of various poor neonatal outcome measures, including resuscitation, sepsis, respiratory morbidity and support, admission to the NICU and prolonged hospitalization. This composite primary outcome occurred in 1 in 5 neonates born between 37^{+0} and 37^{+6} and in 1 in 8 neonates born

Table 2. Incidence of neonatal morbidity after elective caesarean section per week of gestation at delivery

Week of gestation	37^{+0-6}	38^{+0-6}	39^{+0-6}	40^{+0-6}	41^{+0-6}	≥ 42	
Proportion of deliveries	**(n = 1,734)**	**(n = 10,139)**	**(n = 6,647)**	**(n = 1,274)**	**(n = 782)**	**(n = 397)**	**P for trend[1]**
Primary outcome (including neonatal death)[2]	358 (20.6)	1,265 (12.5)	634 (9.5)	120 (9.4)	79 (10.1)	39 (9.8)	< 0.0001
Resuscitation							
Oxygen	68 (3.9)	275 (2.7)	161 (2.4)	33 (2.6)	23 (2.9)	9 (2.3)	
Mask-balloon ventilation	34 (2.0)	127 (1.3)	70 (1.1)	11 (0.9)	5 (0.6)	1 (0.3)	
Severe resuscitation	1 (0.1)	8 (0.1)	6 (0.1)	0	0	0	0.3349
Sepsis	14 (0.8)	37 (0.4)	14 (0.2)	5 (0.4)	3 (0.4)	1 (0.3)	0.0003
Combined respiratory outcome[3]	118 (6.8)	356 (3.5)	136 (2.1)	25 (2.0)	14 (1.8)	3 (0.8)	< 0.0001
Respiratory distress syndrome	8 (0.5)	21 (0.2)	7 (0.1)	0	0	0	0.0022
Transient tachypnea of the newborn	72 (4.2)	256 (2.5)	91 (1.4)	19 (1.5)	8 (1.0)	0	< 0.0001
Intermittent positive pressure ventilation	10 (0.6)	15 (0.2)	5 (0.1)	1 (0.1)	1 (0.1)	0	< 0.0001
Continuous positive airway pressure	34 (2.0)	54 (0.5)	15 (0.2)	1 (0.1)	2 (0.3)	0	< 0.0001
Hypoglycaemia	56 (3.2)	207 (2.0)	102 (1.5)	25 (2.0)	14 (1.8)	7 (1.8)	< 0.0001
Convulsions	1 (0.1)	9 (0.1)	3 (0.05)	1 (0.1)	0	0	0.2578
Admission							
Neonatal Intensive Care Unit	13 (0.8)	32 (0.3)	16 (0.2)	2 (0.2)	1 (0.1)	0	0.0031
To any neonatal ward ≥5 days	214 (12.3)	629 (6.2)	290 (4.4)	51 (4.0)	43 (5.5)	22 (5.5)	< 0.0001
Apgarscore[4]							
≤3	1 (0.1)	3 (0.03)	1 (0.02)	0	1 (0.1)	0	0.1687
≤6	11 (0.6)	29 (0.3)	11 (0.2)	3 (0.2)	5 (0.6)	0	0.0011
Meconium aspiration	1 (0.1)	0	4 (0.1)	0	0	0	0.1130
Hyperbilirubinaemia	30 (1.7)	61 (0.6)	35 (0.5)	3 (0.2)	6 (0.8)	1 (0.3)	< 0.0001

[1]P-value was calculated by the Cochrane-Armitage test for trend for the period from 37 to 39 weeks. [2]Primary outcome is defined as a composite measure of: neonatal mortality until the 28th day after birth, and/ or neonatal morbidity which can exist of any of the following adverse events: severe resuscitation, sepsis, respiratory complications (registered as Respiratory distress syndrome (RDS), Transient tachypnea of the newborn (TTN), pneumothorax or air leakage, respiratory support (oxygen, intermittent positive pressure ventilation (IPPV), Continuous positive airway pressure (CPAP)), hypoglycaemia, convulsions, intracranial haemorrhage, admission to the neonatal intensive care unit, admission to any neonatal ward ≥ 5 days and a 5-minute Apgar score ≤ 3. [3]Combined respiratory outcome is defined as a composite measure of: RDS, TTN, pneumothorax, air leakage, oxygen, IPPV and CPAP. [4]5-minute Apgar score.

Table 3. Multivariate analysis of neonatal morbidity after elective caesarean section

Week of gestation	37^{+0-6}	38^{+0-6}	39^{+0-6}	40^{+0-6}	41^{+0-6}	≥ 42
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Primary outcome (including neonatal death)[1]	2.4 (2.1-2.8)	1.4 (1.2-1.5)	Reference	0.9 (0.8-1.2)	1.01 (0.8-1.3)	0.9 (0.7-1.3)
Sepsis	3.6 (1.7-7.7)	1.7 (0.9-3.1)	Reference	1.8 (0.6-5.0)	1.7 (0.5-6.1)	1.1 (0.1-8.3)
Combined respiratory outcome[2]	3.2 (2.5-4.2)	1.7 (1.4-2.1)	Reference	0.9 (0.6-1.3)	0.8 (0.4-1.4)	0.3 (0.1-1.0)
Respiratory distress syndrome	3.8 (1.4-10.5)	1.9 (0.8-4.5)	Reference	NA	NA	NA
Transient tachypnea of the newborn	2.9 (2.1-3.9)	1.8 (1.4-2.3)	Reference	1.0 (0.6-1.6)	0.7 (0.3-1.4)	NA
Intermittent positive pressure ventilation	6.8 (2.3-20.0)	1.9 (0.7-5.3)	Reference	0.9 (0.1-7.6)	1.5 (0.2-12.8)	NA
Continuous positive airway pressure	7.8 (4.3-14.5)	2.3 (1.3-4.0)	Reference	0.3 (0.0-2.3)	0.99 (0.2-4.4)	NA
Hypoglycaemia	2.1 (1.5-2.9)	1.3 (1.1-1.7)	Reference	1.2 (0.8-1.8)	1.1 (0.6-1.9)	0.98 (0.5-2.1)
Convulsions	1.2 (0.1-11.9)	2.0 (0.5-7.4)	Reference	0.8 (0.1-7.8)	NA	NA
Admission						
Neonatal intensive care unit	2.8 (1.3-5.8)	1.3 (0.7-2.3)	Reference	0.5 (0.1-2.4)	0.5 (0.1-3.5)	NA
To any neonatal ward >5 days	3.1 (2.6-3.7)	1.5 (1.3-1.7)	Reference	0.9 (0.7-1.2)	1.3 (0.9-1.7)	1.2 (0.8-1.9)
Apgar score[3]						
≤3	3.3 (0.2-53.5)	2.2 (0.2-21.6)	Reference	1.9 (0.1-30.6)	NA	NA
≤6	3.8 (1.6-8.8)	1.7 (0.9-3.5)	Reference	1.3 (0.4-4.6)	3.6 (1.3-10.5)	NA
Hyperbilirubinaemia	3.1 (1.9-5.1)	1.1 (0.7-1.7)	Reference	0.4 (0.1-1.3)	1.3 (0.5-3.1)	0.4 (0.1-3.0)

Values are Odds ratios (95% confidence interval) from logistic regression models. Models were adjusted for possible confounders: maternal age (as categorical variable), race or ethnic group, socio-economic status, gender of neonate, fetal position and parity. NA = Not applicable, odds ratio's not available due to low incidence. [1]Primary outcome is defined as a composite measure of: neonatal mortality until the 28th day after birth, and/ or neonatal morbidity which can exist of any of the following adverse events: severe resuscitation, sepsis, respiratory complications (registered as Respiratory distress syndrome (RDS), Transient tachypnea of the newborn (TTN), pneumothorax or air leakage), respiratory support (oxygen, Intermittent positive pressure ventilation (IPPV), Continuous positive airway pressure (CPAP)), hypoglycaemia, convulsions, intracranial haemorrhage, admission to the Neonatal Intensive Care Unit, admission to any neonatal ward ≥ 5 days and a 5-minute Apgar score ≤ 3. [2]Combined respiratory outcome is defined as a composite measure of: RDS, TTN, pneumothorax, air leakage, Oxygen, IPPV and CPAP. [3]5-minute Apgar score.

between 38^{+0} and 38^{+6} weeks which was significantly higher compared to 1 in 10 neonates at 39^{+0-6} weeks of gestation. The risks of separate adverse neonatal outcomes for delivery at 37 weeks and at 38 weeks were also higher. Adjustment for potential confounding variables confirmed the significant trends toward decreasing incidence of neonatal complications with increasing gestational age up to 39 weeks.

The strength of our study is that it comprises recently collected data of almost all deliveries of our country, which results in a large sample size and is therefore a broad reflection of current clinical decision making. Our study has some limitations. First, the reliability of our data depends on the preciseness of registration of obstetricians and paediatricians in the past 7 years. The registration of a planned caesarean section is subdivided into 'elective', 'condition mother', 'condition fetus' and 'condition mother and fetus'. After selecting the 'elective' caesarean cohort we applied strict exclusion criteria (Figure 1). However, it is possible that we did not include the complete population of elective caesareans as, for example, obstetricians can register repeat caesarean section under 'condition mother' instead of as 'elective' due to the risk of a uterine rupture during a trial of labour. This might have affected our results, but it is unlikely that those cases would have shown a totally different association between timing of section and outcome than the deliveries investigated in this study. Reliability of the gestational age at birth is also of great importance. The basic care provided in the Netherlands as is stated in our national guideline regarding prenatal care is that all women will receive a first trimester ultrasound to establish/ confirm the at term date. Prenatal care with ultrasound scanning in the first trimester is well available for low risk and high risk patients. The PRN database contains a separate question about certainty of the term data. In 97.4% of the births gestational age was registered as certain. If the analysis was restricted to these 97.4%, we observed similar results. The neonatal follow up in the PRN is not registered for around 32% of all hospitals. We assume that the incidence of neonatal morbidity in these hospitals is not different from those with good neonatal follow up because both types of hospitals are equally distributed across the country, use the same – national - clinical guidelines and are financed similarly. Furthermore, analyses demonstrated that for both hospitals with good and hospitals with no follow up timing of caesarean section rate was similar (results not shown). Socio-economic status was based on the mean household income level of the neighbourhood, which was determined by the first four digits of the woman's postal code. Using this proxy measure may have led to some misclassification. However, studies on perinatal mortality in relation to socio-economic status and neighbourhood which were recently carried out in the Netherlands showed neighbourhood as a strong indicator for both perinatal outcome and socio-economic status[21].

One could question our decision to exclude all stillbirths. In this large database there have been instances where a woman booked for an elective caesarean section at a particular gestation presented with unexplained stillbirth at or after 37^{+0} weeks. Unfortunately, the exact date of stillbirth is not stated in our database, thus leaving no possibility to perform an 'intention to treat' analysis from 37 weeks onwards. Moreover, many women with a stillbirth will have had a vaginal delivery after their tragic event, thus making it impossible to distinguish between women that had a stillbirth while waiting for a caesarean section, and women with a planned vaginal delivery who had a stillbirth. However, the effect will be minimal as we are studying low risk pregnancies. The association between increasing gestational age and diminishing risk of neonatal morbidity until 39^{+0} weeks of gestation is not new[4;8-10;12], but except for Tita et al[12], these studies had a limited sample size, focused on respiratory morbidity and analyzed their results in completed weeks of gestation. Compared to previous studies we found lower absolute numbers of respiratory morbidity in all gestational age weeks, although there was a significant increase of respiratory morbidity with decreasing gestational age. Some authors might have used broader definitions for respiratory distress or did not exclude mothers with risk factors for an adverse neonatal outcome[4;8;10]. To be able to compare our results with these studies we also defined a combined respiratory outcome measure which shows more similar results. Recently, a large prospective study of 13,258 electively performed caesarean sections was published by Tita et al.[12] which did not only focus on respiratory morbidity but on a composite outcome measure of neonatal mortality and morbidity. To be able to compare our results we defined a similar composite outcome measure of neonatal morbidity. The results of our primary composite outcome are comparable. In contrast with Tita et al[12], our data did not show a significantly higher risk for neonatal morbidity by postponing the caesarean section until after 40^{+0} weeks.

Before publication of the analysis of Tita et al. [12] the significant difference in neonatal morbidity between 38^{+4-6} weeks and 39^{+0} weeks was not known. We hope that the results of our study, which are in line with those found by Tita et al, will convince more gynaecologists to postpone planned caesarean sections until after 39^{+0} weeks.

The fear of an increasing number of intrapartum caesarean sections can influence timing and hamper implementation of postponing caesarean sections. Morrison et al.[8] showed that by altering the planning of elective caesarean sections from 38^{+0-6} to 39^{+0-6} only 10% of patients will be in labour before the planned date. Hansen et al.[4] reported that 25% of intended vaginal deliveries started before 39^{+0} weeks of gestation. In the Netherlands 13.6% of singleton births without congenital malformations started spontaneously between 37^{+0} and 38^{+6} weeks gestation, of which 93.2% ended in a vaginal delivery and 6.8% ended in a secondary caesarean section. It is difficult to compare maternal risks versus benefits of the

newborn. Intrapartum caesarean sections may have an increased risk for maternal morbidity and mortality compared with elective caesarean sections[22;23]. Compared to vaginal delivery, caesarean section is associated with almost 4 times increase in maternal mortality[23], a longer time to recover and the risk of complication of the operation[24]. On the other hand the start of labour or rupture of the membranes could be a benefit for the infants born because of stimulation of surfactant in the fetal lungs[25].

We will undertake further studies to analyze factors that can possibly influence neonatal morbidity and therefore must be considered in timing and decision making. Prospective designs will also facilitate exact registration of the number of intrapartum caesarean sections and intra-uterine deaths by postponing every planned caesarean section after 39^{+0} weeks of gestation, and to evaluate the maternal morbidity associated with these intrapartum caesareans which will enable us to consider maternal risks in timing of elective caesarean sections as well.

Conclusion

Performing elective caesarean sections before 39^{+0} weeks of gestation jeopardizes neonatal outcome and should be avoided whenever possible.

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3

Timing of elective term caesarean sections; trends in the Netherlands

F.A. Wilmink

C.W.P.M. Hukkelhoven

J.A.M. van der Post

E.A.P. Steegers

B.W.J. Mol

D.N.M. Papatsonis

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Abstract

Background

To evaluate whether the percentage of elective caesarean sections (CSs) before a gestational age of 39^{+0} weeks, relative to the total number of elective CSs, has decreased between 2000 and 2010 and what factors are associated with this decrease.

Methods

Retrospective cohort study with data from the Netherlands Perinatal Registry. All full-term elective CSs between 2000 and 2010 were selected (n=59,653).

Results

The percentage of elective CSs before 39^{+0} weeks decreased from 56% in 2000 to 43% in 2010 ($p<0.0001$). In peripheral teaching and non-teaching hospitals, elective CSs were performed more often before 39^{+0} weeks than in university hospitals; percentages were 53%, 57% and 46%, respectively. Adjusted odds ratios (95%CI) were 1.38 (1.30-1.47) for peripheral teaching hospitals and 1.55 (1.46-1.65) for peripheral non-teaching hospitals. In hospitals where the number of deliveries per year is in the lower quartile, an elective CS before 39^{+0} weeks was performed more often than in hospitals in the upper quartile, 60% versus 52% ($p<0.0001$).

Conclusion

From 2000 to 2009, the timing of elective CS before 39^{+0} weeks has marginally improved, while in 2010 a declining trend is starting; although 43% of elective CS was still performed before 39^{+0} weeks. This results in an increased risk of neonatal morbidity.

Introduction

The percentage of caesarean sections (CSs) in the Netherlands increased from 8.3% in 1993[1] to 16.8% in 2010[2]. Part of these CSs is carried out electively, for example because of a breech presentation or a previous caesarean section (CS). Between 1995 and 2001, several articles were published which showed that the risk of neonatal morbidity after a CS decreases significantly with increasing gestational age. This effect can no longer be demonstrated from 39^{+0} weeks onwards.[3-5] Two recent publications have shown that even in the period from 38^{+4} to 38^{+6} weeks compared to 39^{+0-6} weeks, the risk of neonatal morbidity is significantly increased by a factor of 1.2-1.3.[6,7] The guideline: 'Indications for caesarean sections', published by the Dutch Association for Obstetrics & Gynaecology in 2011, recommends performing an elective CS from 39^{+0} weeks.[8]

The increasing number of elective CS[9] makes a correct timing of this intervention important to prevent iatrogenic neonatal morbidity in both the short and long term. Previous research showed that between 2000 and 2006, more than 56% of elective CSs in the Netherlands were carried out before a gestational age of 39^{+0} weeks.[7] However, this study did not look at the course of events over the years. We therefore evaluated whether the percentage of elective CSs before a gestational age of 39^{+0} weeks has decreased between 2000 and 2010 and what factors were associated with this decrease.

Material and Method

From the database of the Netherlands Perinatal Registry, all full-term elective CSs from January 1st, 2000 until December 31st, 2010 were selected. About 96% of the approximately 180,000 births per year in the Netherlands with a gestational age > 16^{+0} weeks are recorded in this national database. [2] A CS was defined as elective if it was recorded as a 'primary caesarean section' with the indication 'elective'. Subsequently, fetuses with a congenital abnormality, women with a complicated medical history or obstetric complication that could affect the outcome of the neonate, and women with spontaneously ruptured membranes were excluded (specified in Figure 1). We analyzed the incidence of elective CSs per year and in addition per week of gestational age from 37^{+0-6}, up to and including 42^{+0-6} weeks.

Factors that were possibly related to performing an elective CS before 39^{+0} weeks consisted of patient characteristics, namely: age, parity, ethnicity, position of the fetus, socio-economic status (SES) and hospital characteristics, namely: type of hospital (academic, versus peripheral teaching hospital, versus peripheral non-teaching hospital), size of hospital (based on the number of deliveries per year in percentile values) and day of the week on which the elective CS was performed.[10-12] The number of deliveries <p25, between p25-p75

and >p75 corresponded to numbers of <720,720-1400 and >1400 deliveries per year, respectively.

Statistical analysis

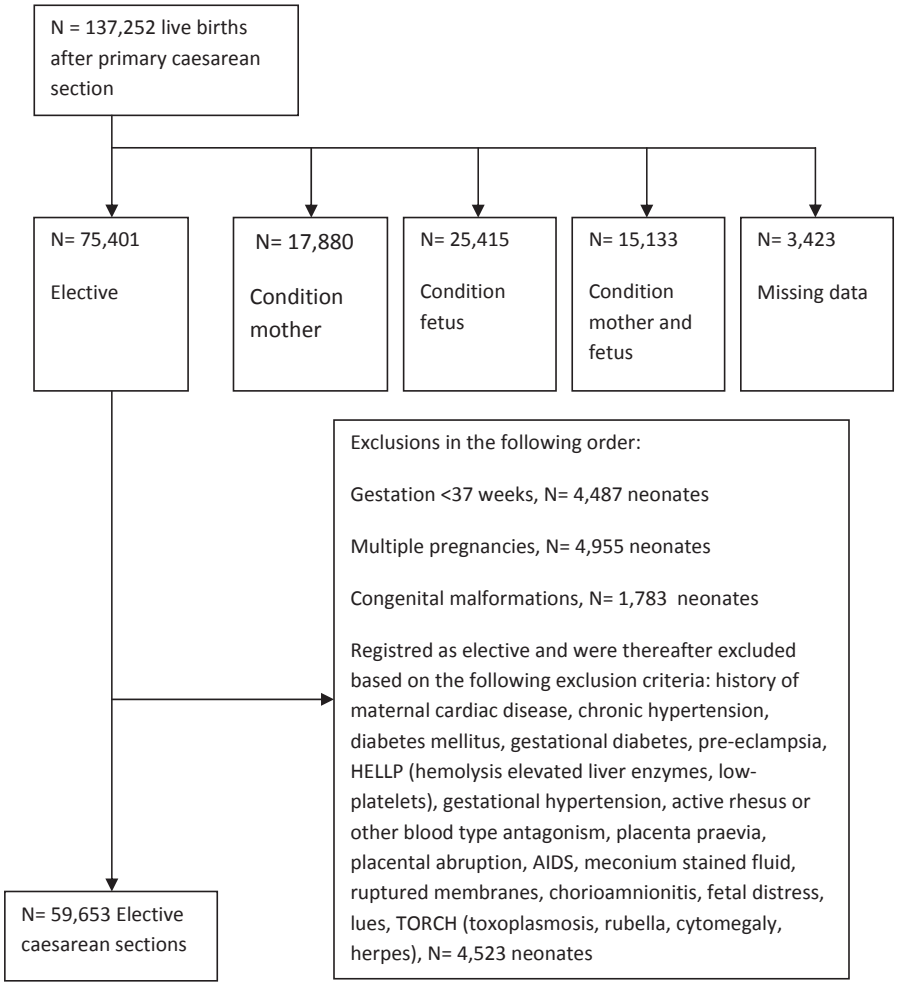
Trends in patient characteristics, hospital characteristics and the incidence of elective CSs before a gestational age of 39^{+0} weeks were studied through linear regression, logistic regression and Poisson regression analysis. The differences in the performance of an elective CS before 39^{+0} weeks in the hospitals, broken down by type of hospital and number of deliveries per year (in percentile values), were assessed with the χ^2 test. Through multivariate logistic regression analysis, it was investigated which factors were significantly related to the performance of an elective CS before 39^{+0} weeks. Wednesday was chosen in advance as a reference day, because there are still two plannable days before and after Wednesday. Therefore we had no need to correct for multiple testing. Because there is probably a strong correlation between the type of hospital and the number of deliveries per year in a hospital (multicollinearity), we have omitted this latter factor from our multivariate model. Results of the multiple regression analysis are presented in odds ratios (OR), adjusted for all factors from the multivariate analysis and also for year, with a 95% confidence interval (95% CI). Two-sided tests were performed and a p-value < 0.05 was considered statistically significant. All analyses were performed with the statistical package SAS (version 9.3; SAS Institute Inc., Cary NC, USA).

Results

Between 2000 and 2010, a total of 1,331,749 live births were registered. Of these, 137,252 neonates were delivered by means of a primary CS, which in 75,401 cases was classified as elective (Figure 1). Exclusions were made because of a gestational age $<37^{+0}$ weeks (n=4,487), multiple pregnancy (n=4,955), neonates with congenital abnormalities (n=1,783) and mothers with a complicated medical history, obstetric complication or spontaneously ruptured membranes (n=4,523). A total of 59,653 elective CSs in the full-term period were available for further analysis.

Table 1 shows the course of maternal and neonatal characteristics over time. The mean age of the mother increased over the years from 31.9 to 32.4 years and the percentage of women over 35 years of age at the time of birth from 26.9% to 33.3%. From 2001 onwards, the percentage of women of Western ethnicity decreased slightly, as did the number of nullipara. The number of neonates in cephalic presentation has increased since 2001. The sex and birth weight distribution did not show any clinically relevant differences over the

Figure 1. Flow chart



years. The percentage of children with a birth weight <p10[13] was 5.6% before and 6.7% after 39^{+0} weeks of gestation.

Figure 2 shows the percentages of elective CSs per week of gestational age and per year from 2000 to 2010 inclusive. The percentage of elective CSs performed before a gestational age of 39^{+0} weeks decreases significantly from 56.3% in 2000 to 43.2% in 2010 ($p < 0.0001$). This holds especially for the number of elective CS between 38^{+0-6} weeks, in favour of the

number of elective CS between 39^{+0-6}. In university hospitals, 5,271 elective CSs were performed, of which 46% before 39^{+0} weeks. In peripheral teaching and non-teaching hospitals, these numbers and percentages were n=27,798 (53% before 39^{+0} weeks) and n=26,584 (57% before 39^{+0} weeks), respectively, Figure 3. These percentages are significantly higher compared to the elective CS rate before 39^{+0} weeks in university hospitals (p<0.0001) and also significantly higher in peripheral non-teaching hospitals compared to peripheral teaching hospitals (p<0.0001). When analyzing the number of deliveries per year, hospitals in the lower quartile and between p25-p75 had significantly higher percentages of elective CSs before 39^{+0} weeks than hospitals in the upper quartile (respectively 60%, 56% and 52%, p<0,0001), Figure 4. We also observed a significant difference between hospitals in the lower quartile and hospitals between the p25-p75 (p<0.0001).

In trend analysis by type of hospital and by number of deliveries per year (in percentile values), the differences between the two remained approximately the same over the years (Figures 5 and 6).

Multivariate logistic regression analysis (Table 2) showed a significant relationship between an elective CS before a gestational age of 39^{+0} weeks and nulliparity, women of non-Western ethnicity and women with the highest socio-economic status. We also saw that in a peripheral teaching hospital and in a peripheral non-teaching hospital an elective CS was performed more often before 39^{+0} weeks than in a university hospital (with adjusted OR (95%CI) of 1.38 (1.30-1.47) and 1.55 (1.46-1.65) respectively). An elective CS was performed less often before 39 0/7 weeks on Fridays and more often on Sundays, compared to the reference day Wednesday.

Figure 2. Distribution of the incidence of elective CSs according to week of gestation in the period 2000-2010.

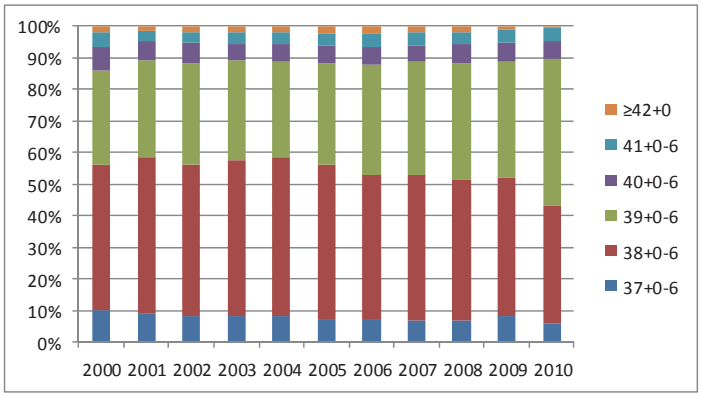
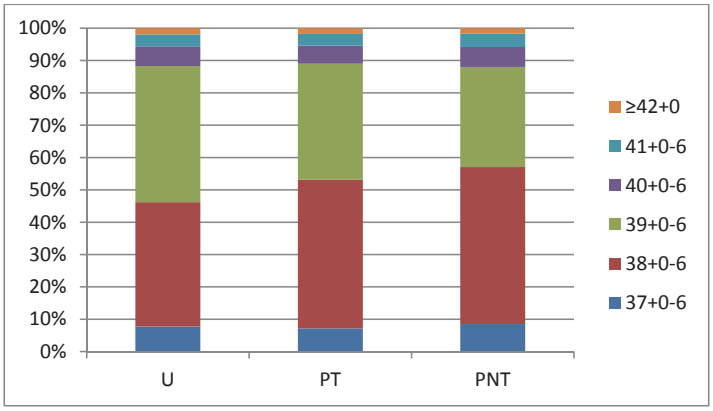
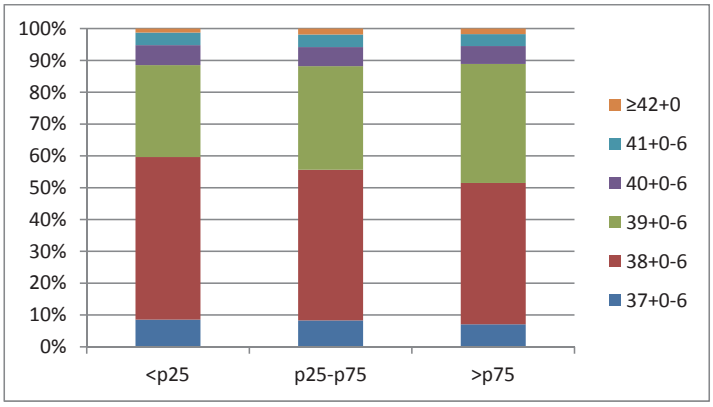


Figure 3. Total incidence of elective CSs in the period 2000-2010, shown per week of gestation, broken down by type of hospital.



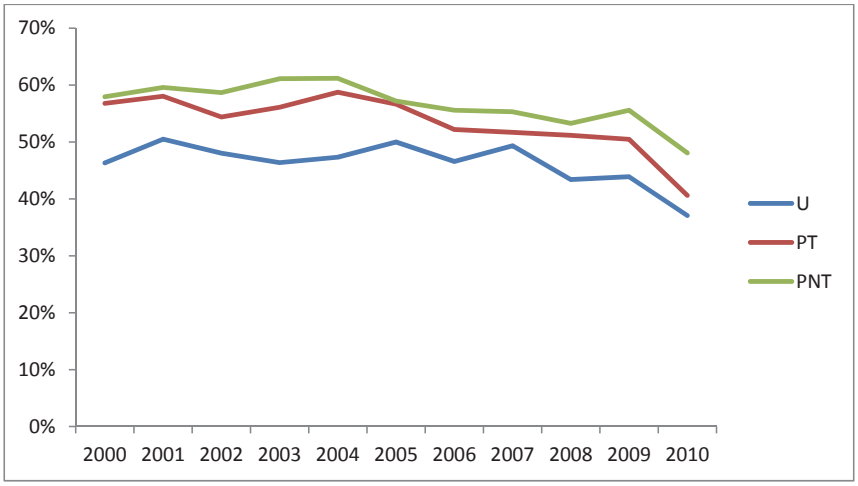
U = university hospital
PT = peripheral teaching hospital
PNT = peripheral non-teaching hospital

Figure 4. Total incidence of elective CSs in the period 2000-2010, shown per week of gestation, broken down by the number of births in a hospital.



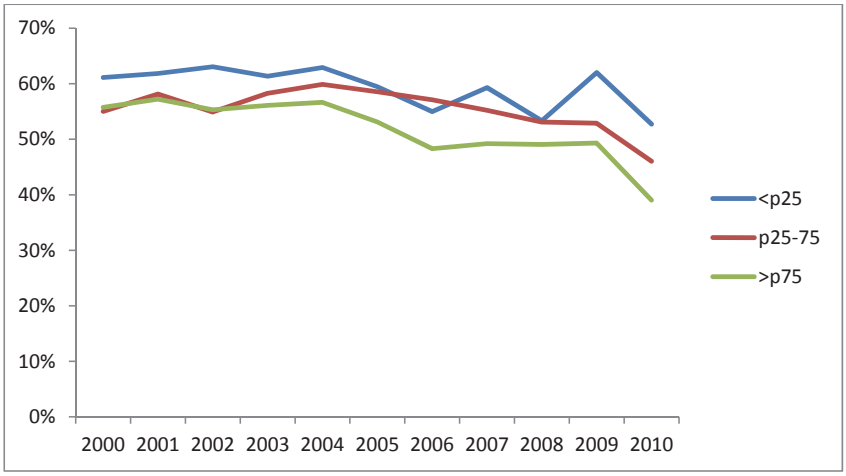
<P25 corresponds to <720 births/year
P25-75 corresponds to 720-1400 births/year
>P75 corresponds to >1400 births/year

Figure 5. Incidence of elective CSs performed before 39^{+0} weeks of gestation, in the period 2000-2010, broken down by type of hospital.



U = university hospital
PT = peripheral teaching hospital
PNT = peripheral non-teaching hospital

Figure 6. Incidence of elective CSs performed before 39^{+0} weeks of gestation, in the period 2000-2010, broken down by the number of births in a hospital.



<P25 corresponds to <720 births/year
P25-75 to 720-1400 births/year
>P75 to >1400 births/year

Table 1. Review of the timing of elective caesarean sections in the Netherlands; percentage distribution of maternal and neonatal characteristics over time

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Proportion of deliveries	n= 3,994	n= 6,082	n= 6,043	n= 6,108	n= 5,616	n= 5,646	n= 5,336	n= 5,083	n= 5,043	n= 5,283	n= 5,419	
Maternal characteristics*												**p-value†**
Age at CS												
Mean (SD)	31.9 (4.3)	31.7 (4.4)	31.6 (4.4)	31.8 (4.5)	32.0 (4.4)	32.1 (4.6)	32.3 (4.5)	32.2 (4.6)	32.4 (4.6)	32.3 (4.6)	32.4 (4.7)	**<0.0001**
< 35 years	73.1	74.1	75.5	72.8	71.1	69.5	68.7	66.7	65.8	67.5	66.7	
≥ 35 years	26.9	25.9	24.5	27.2	28.9	30.5	31.3	33.3	34.2	32.5	33.3	**<0.0001**
Ethnicity												
Western	91.5	92.1	91.4	91.2	90.6	89.6	89.9	88.4	89.3	87.3	88.3	**0.0004**
Non-Western	8.5	7.9	8.6	8.8	9.4	10.4	10.1	11.6	10.7	12.7	11.7	
Missing (n)	*81*	*129*	*126*	*122*	*115*	*167*	*148*	*152*	*176*	*195*	*245*	
Parity												**<0.0001**
Nullipara	31.2	40.9	40.2	39.4	38.1	38.0	35.7	35.8	34.9	33.0	34.9	
Multipara	68.8	59.1	59.8	60.6	61.9	62.0	64.3	64.2	65.1	67.0	65.1	
Missing (n)	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2*	*0*	
Socio-economic status‡												0.28
Very high	21.0	21.8	20.0	21.2	22.0	21.3	22.4	22.1	21.2	22.1	21.4	
High	20.3	19.8	19.7	20.5	20.1	20.8	18.7	19.6	20.8	20.1	19.6	
Normal	18.1	19.2	18.9	19.3	18.5	17.9	18.8	18.2	18.3	16.5	17.6	
Low	19.8	19.5	19.3	18.4	17.8	18.4	19.0	18.7	17.1	18.0	18.2	
Very low	20.8	19.6	22.2	20.6	21.6	21.5	21.2	21.4	22.5	23.3	23.2	
Missing (n)	*20*	*39*	*49*	*68*	*102*	*137*	*125*	*135*	*119*	*154*	*164*	

Table 1. Continued

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Proportion of deliveries	n= 3,994	n= 6,082	n= 6,043	n= 6,108	n= 5,616	n= 5,646	n= 5,336	n= 5,083	n= 5,043	n= 5,283	n= 5,419	
Child characteristics												**p-value†**
Gender												0.6
Male	49.1	49.0	48.5	48.4	48.6	48.3	48.8	49.3	49.5	49.7	48.3	
Female	50.9	51.0	51.5	51.6	51.4	51.7	51.2	50.7	50.5	50.3	51.7	
Missing (n)	*1*	*3*	*1*	*0*	*0*	*0*	*2*	*0*	*0*	*0*	*0*	
Fetal position												
Cephalic	57.9	42.8	45.1	45.3	47.1	48.1	50.5	51.1	52.8	55.9	57.1	**<0.0001**
Breech	37.1	53.7	51.1	50.7	49.6	48.8	45.9	45.4	44.0	41.1	40.3	**<0.0001**
Other	5.0	3.5	3.8	4.0	3.3	3.1	3.6	3.5	3.2	3.0	2.6	**<0.0001**
Missing (n)	*10*	*1*	*3*	*4*	*1*	*3*	*1*	*2*	*3*	*9*	*9*	
Birth weight (grams)												
Mean (SD)	3473 (492)	3414 (478)	3427 (501)	3430 (500)	3455 (497)	3440 (503)	3465 (492)	3479 (493)	3495 (497)	3486 (501)	3488 (485)	**<0.0001**
< 2500	1.7	1.7	2.0	2.0	2.0	1.8	1.7	1.4	1.7	1.7	1.4	**0.0221**
< P10[§]	5.9	6.8	6.9	6.5	5.8	6.7	5.8	5.5	5.5	5.5	5.5	**<0.0001**

*In percentages, unless otherwise indicated. †P-value calculated with linear regression analysis (average age, average birth weight and socio-economic status), logistic regression analysis (age ≥ 35 years, parity, gender and presentation) and with Poisson-regression analysis (ethnicity, birth weight < 2500 g and birth weight < P_{10}). ‡Based on the average income per household in the neighbourhood based on the first 4 digits of the zip code. §Birth weight < 10^{th} percentile according to growth curves adjusted for gender, parity and ethnicity.

Table 2 Probability of performing an elective caesarean section before 39^{+0} weeks of gestation; results of multivariate logistic regression analysis

Factors	Categories	Odds ratio*	95% CI
Age (years)			
	< 20	1.01	0.80-1.27
	20-24	0.99	0.91-1.07
	25-29	1.03	0.98-1.07
	30-34	reference	
	35-39	1.04	1.00-1.08
	≥ 40	1.07	0.98-1.16
Parity			
	nullipara	**0.82**	**0.78-0.85**
	multipara	reference	
Ethnicity			
	Western	reference	
	non-Western	**0.9**	**0.85-0.94**
Fetal position			
	cephalic	reference	
	breech	**1.09**	**1.05-1.13**
	other	0.99	0.90-1.08
Socio-economic status			
	very high	**0.92**	**0.88-0.95**
	average	reference	
	very low	0.99	0.95-1.04
Hospital type			
	non-teaching hospital	**1.55**	**1.46-1.65**
	teaching hospital	**1.38**	**1.30-1.47**
	university hospital	reference	
Day of the week			
	Monday	1.02	0.97-1.08
	Tuesday	1.01	0.96-1.06
	Wednesday	reference	
	Thursday	0.96	0.91-1.01
	Friday	**0.93**	**0.88-0.98**
	Saturday	0.93	0.81-1.07
	Sunday	**1.21**	**1.03-1.42**

*Odds ratios, apart from being adjusted for all factors in the model, also adjusted for year.

Discussion

We investigated trends in the timing of elective caesarean sections before 39^{+0} weeks and found a limited decrease in the period 2000-2009, and a stronger decrease in 2010. At the moment there are no more recent data available. However, also in 2010 the percentage of elective CSs before 39^{+0} weeks is still high (43%). In addition, elective CSs were more often performed before 39^{+0} weeks in peripheral hospitals with a smaller number of deliveries per year.

The relationship between an increased risk of neonatal morbidity and an elective CS carried out before 39^{+0} weeks has already been demonstrated in previous research, in the same population in the period 2000-2006. [7] In this study, we have therefore limited ourselves to trends in timing. However, if we extrapolate the risk of neonatal respiratory morbidity which was reported earlier to this cohort, 6.8% and 3.5% of neonates born between 37^{+0-6} and 38^{+0-6} weeks, respectively, would be exposed to an increased risk of respiratory morbidity compared to 0.8-2.1% if all elective CSs would be performed from 39^{+0} weeks onwards. In absolute numbers this corresponds to 1,836 neonates with an increased risk of respiratory morbidity compared to 1,229 neonates when all elective CS would only be performed from 39^{+0} weeks onwards, which is an average of 55 additional neonates with respiratory morbidity per year.

In 2010, the definition of 'term' was already questioned by proposing new subcategories for term pregnancy (early-term 37^{+0}- 38^{+6} weeks versus full-term 39^{+0} - 40^{+6} weeks).[14] Studies into the long-term effects of gestational age at birth show that children born at 37 and 38 weeks, as opposed to children born after 39^{+0} weeks, have a higher risk of health problems such as asthma and more often need special education.[15,16] Because the absolute number of children born early-term is so high, their share in the total group of children with health problems and in the group using special education is relatively high.[15,16]

Recently, a randomized study was published that showed no statistically significant difference in NICU admissions between a planned CS at 38^{+3} (13.9%) and 39^{+3} weeks (11.9%).[17] Nevertheless, trends in NICU admission and respiratory morbidity are all in favour of the group born >39^{+0} weeks.

Our data provide a good reflection of clinical practice throughout the Netherlands. Although the reliability of the data depends on the submission of the data from the Netherlands Perinatal Registry by all clinical practices; this research mainly concerns parameters that are registered as mandatory items. In addition, we have strictly selected our cohort and it concerns large numbers. Because the percentage of neonates with a birth weight <p10[13] after 39+0 weeks (6.7%) is higher than that before 39^{+0} weeks (5.6%), it is not likely that a

large proportion of CSs <39^{+0} weeks was performed on indication of intrauterine growth restriction, but were registered as' elective'. However, elective sections that could not be postponed, for example due to preeclampsia or spontaneous contractions, may have been registered as elective. This could be a possible explanation for the increased risk of an elective CS <39^{+0} weeks on Sunday. The optimum percentage of elective CS before 39^{+0} weeks depends on the number of women who spontaneously come into labour and on the registration; 0% seems not feasible in this respect. Also, elective CSs may have been missed because they are registered with the indication 'maternal condition' for example. However, it is unlikely that the timing of these CS would be different from that in our studied population. We have opted for a weekly analysis instead of a daily analysis because earlier research showed a clear turning point with regard to the increased risk of neonatal morbidity at 39^{+0} weeks.[6,7] This is possibly a limitation of the present study.

The fact that there is still a lot of room for improvement in the Netherlands is probably multifactorial. Firstly, until March 2011, there was no Dutch guideline that gave advice on the timing of a caesarean section.[8] However, a national guideline is often insufficient and adaptation of the local protocols in particular leads to an improvement in the quality of care. In Utah, USA, it was previously found that the obstetric clinics did not comply with the guideline of The American College of Obstetricians and Gynecologists (ACOG), which recommended that elective induction and elective CS should not be carried out before a gestational age of 39^{+0} weeks to avoid neonatal complications. After the introduction of a quality assurance program on nine obstetric departments, the percentage of elective CSs and inductions <39^{+0} weeks dropped from 28% to 10% in six months, and after six years the percentage remained stable at around 3%.[11] The Ohio Perinatal Quality Collaborative Writing Committee (2010) also succeeded to significantly decrease the number of elective inductions before 39^{+0} weeks by increasing knowledge, quality control and awareness.[18] In 2010, the effect of the implementation of a local protocol was presented in this journal, showing that the percentage of elective CS <39^{+0} weeks had decreased significantly from 84% to 38%, resulting in less neonatal respiratory morbidity.[19]

A second, probable cause of the fact that one has continued to perform elective CSs < 39^{+0} weeks is that the absolute numbers of neonatal morbidity and mortality per hospital are low, which means that one is (too) little confronted with the iatrogenic neonatal morbidity.[10,11] Thirdly, patient characteristics and logistic factors such as the desire for a certain birth date, overexertion, performing of CS by their own gynaecologist, available OR-time, and the pregnant woman's fear for a prelabour CS, probably play a role.[11]

A previous publication showed that when shifting an elective CS from 38^{+0-6} to 39^{+0-6} weeks, only 10% would come into labour before the planned date.[5] It is also difficult to weigh up the logistical problems and maternal risks of an intrapartum section against the neonatal

benefits of spontaneous starting of the delivery by contractions or ruptured membranes whereby production of catecholamine's and stimulation of surfactant in the fetal lungs ensure a better respiratory starting point for the newborn.[20,21]

A recent analysis showed that when performing an elective CS between 37^{+0} and 38^{+6} weeks compared to an elective CS from 39^{+0} weeks, maternal morbidity did not decrease (OR (95%CI) 1.16 (1.00-1.34)) and a longer maternal hospitalization duration (≥ 5 days) occurred even more often (95%CI) 1.96 (1.54-2,49)).[22] The latter was, however, possibly related to the longer duration of admission of the neonate.[22] In addition to a decrease in neonatal morbidity, it has recently been shown that it is cost-effective not to perform an elective CS before 39^{+0} weeks.[23]

Conclusion

In the period 2000-2009, the number of elective CSs carried out before 39^{+0} weeks was marginally reduced. In 2010, a downward trend is starting, although 43% of elective CSs were still performed before a gestational age of 39^{+0} weeks. This results in an increased risk of neonatal morbidity and long-term health problems for the child.

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4

Timing of elective pre-labour caesarean section: a decision analysis

F.A. Wilmink

C.T. Pham

N. Edge

C.W.P.M. Hukkelhoven

E.A.P. Steegers

B.W.J. Mol

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Abstract

Background

Since caesarean sections (CSs) before 39^{+0} weeks gestation are associated with higher rates of neonatal respiratory morbidity, it is recommended to delay elective CSs until 39^{+0} weeks. However, this bears the risk of earlier spontaneous labour resulting in unplanned CSs, which has workforce and resource implications, specifically in smaller obstetric units. We aimed to assess, in a policy of elective CSs from 39^{+0} weeks onwards, the number of unplanned CSs to prevent one neonate with respiratory complications, as compared to early elective CS.

Methods

We performed a decision analysis comparing early term elective CS at 37^{+0-6} or 38^{+0-6} weeks to elective prelabour CS, without strict medical indication, at 39^{+0-6} weeks, with earlier unplanned CS, in women with uncomplicated singleton pregnancies. We used literature data to calculate the number of unplanned CSs necessary to prevent one neonate with respiratory morbidity.

Results

Planning all elective CSs at 39^{+0-6} weeks required 10.9 unplanned CSs to prevent one neonate with respiratory morbidity, compared to planning all elective CS at 38^{+0-6} weeks. Compared to planning all elective CSs at 37^{+0-6} weeks we needed to perform 3.3 unplanned CSs to prevent one neonate with respiratory morbidity.

Conclusion

In a policy of planning all elective pre-labour CSs from 39^{+0} weeks of gestation onwards, between 3 and 11 unplanned CSs have to be performed to prevent one neonate with respiratory morbidity. Therefore, in our opinion, fear of early term labour and workforce disutility is no argument for scheduling elective CSs $<39^{+0}$ weeks.

Introduction

Rates of caesarean sections (CSs) are increasing in Australia with 33.4% of women birthing by CS in 2015, compared to 28.5% in 2003.[1,2] Of all birthing women in 2015, 21% underwent CS prior to labour.[2] This has significant health implications for infants, as elective CSs are associated with higher rates of neonatal respiratory morbidity compared to intended vaginal delivery.[3-5] As this discrepancy reduces with increasing gestational age until 39^{+0} weeks of gestation, clinical guidelines in Australia and New Zealand, the United Kingdom and the United States recommend to delay elective pre-labour CS until 39^{+0} weeks' gestation.[5-13] Alternative recommendations are verification of lung maturity or to administer corticosteroids in advance for those CS planned prior to 39^{+0} weeks.[7,11,14]

In 2012 still 51.6% of pre-labour CS occurred before 39^{+0} weeks in Australia.[2] This percentage seems even higher in private hospitals (66.8%).[15] On the one hand, delay of elective CSs until 39 weeks bears the risk of earlier spontaneous labour resulting in an unplanned CS. Given that in Australia more than 25% of women give birth in regional or remote areas, this may have resource and workforce implications as in these locations staff are often not on-site continuously and an unplanned CS may require initiation of 'call-backs'.[1] On the other hand, these locations are more likely to have limited access to neonatal facilities and thus reducing the potential for neonatal complications is crucially important.

Use of a decision analysis tree is a quantitative approach to clinical problem solving that utilizes local, national and international data to estimate the probabilities of a certain outcome. In this decision analysis we assessed, in a policy of elective CSs from 39^{+0} weeks onward, the number of unplanned CS that would be required to prevent one infant with respiratory complications.

Materials and Methods

Definitions of CS

An elective (pre-labour) CS is defined as a planned CS without strict medical indication and performed before the start of labour. An unplanned CS is defined as a CS performed before the scheduled date after start of labour.

Decision tree model

Decision tree modelling enables the comparison of the outcomes of alternative clinical strategies in the absence of clinical trials.[16,17] A decision tree with a 3-week time horizon was constructed to model possible clinical strategies for timing of birth for women requiring

elective CS (Figure 1). The decision tree begins with three main branches stemming from a decision node, which represents the choice of a clinical strategy. A series of branches from each of the clinical strategies represent the different paths and outcomes for particular combinations of events. Each path on the decision tree has a probability of being taken and an outcome (neonate with or without respiratory morbidity). The sum of the main outcome from the series of branches for each strategy were then calculated and compared. We assumed that elective CSs are not planned before 37^{+0} weeks of gestation. *The three main strategies, without the administration of antenatal corticosteroids, were:*

1) Elective CS planned at 39^{+0-6} weeks of gestation, with risk of an unplanned CS at 37^{+0} until 38^{+6} weeks of gestation
2) Elective CS booked at 38^{+0-6} weeks of gestation, with risk of an unplanned CS between 37^{+0-6} weeks of gestation
3) Elective CS booked at 37^{+0-6} weeks of gestation.

Alternative strategies, with the administration of antenatal corticosteroids, were:

1) Elective CS booked at 38^{+0-6} weeks of gestation, with risk of an unplanned CS at 37^{+0-6} weeks of gestation
2) Elective CS booked at 37^{+0-6} weeks of gestation.

A second decision tree was constructed to include the possibility of lung maturity testing, using probabilities based on the sensitivity and specificity of the Lecithin-Sphingomyelin (L/S)ratio test (figure not shown).

Alternative strategies with performing an L/S ratio test were:

1) Elective CS booked at 37^{+0-6} weeks of gestation after performing an L/S ratio test.

Our main outcome measure was the number of unplanned CSs needed to perform to prevent one neonate with respiratory morbidity defined as Respiratory Distress Syndrome (RDS) or Transient Tachypnoea of the Newborn (TTN).

Data sources

The probabilities that were used as inputs for the decision tree model were based on previous literature and pregnancy outcome data from state-based and national government publications.[2,18] To obtain relevant data we searched PubMed: "Caesarean Section"[Mesh] in combination with the following free search terms: “elective”, or “respiratory morbidity” or “corticosteroids”. In addition our search was filtered by ‘English’ and ‘last 10 years’. The definitive search was performed on the 9th of July, 2017 and produced 1,786 hits. After scanning titles, abstracts and cross references we identified 5 cohort studies and 1 Cochrane

Figure 1. Decision Tree Model

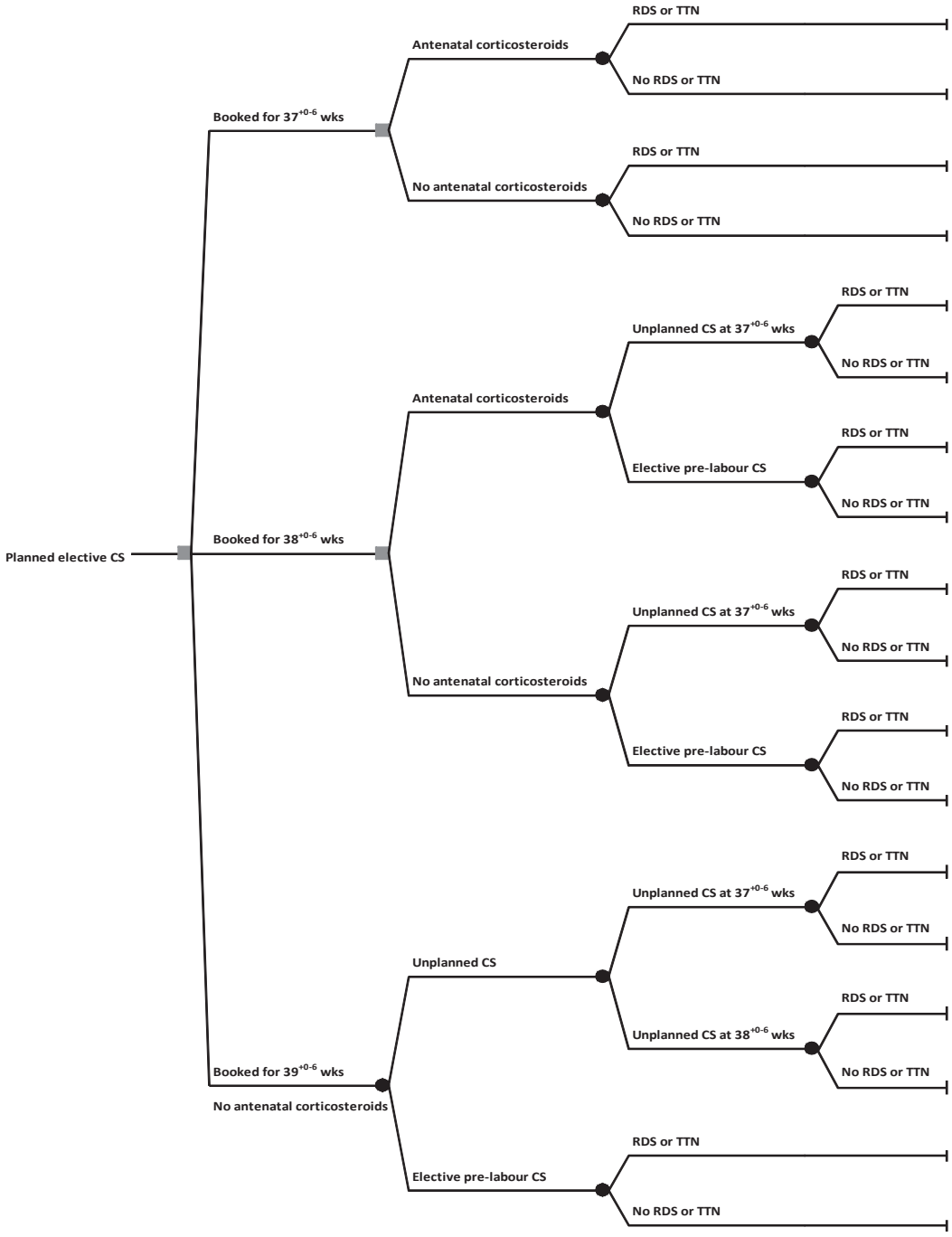

Table 1. Neonatal respiratory morbidity associated with elective Caesarean Section

Reference	n	Respiratory outcome	Weeks		
			37^{+0-6}	38^{+0-6}	39^{+0-6}
			% (n/n_{total})	% (n/n_{total})	% (n/n_{total})
Morrison et al.[10]	2,341	NICU admission with RDS or TTN	7.4 (27/366)	4.2 (45/1,063)	1.8 (9/505)
Hansen et al.[5]	32,580	Combined respiratory morbidity†	10.0 (20/191)	5.1 (55/1,083)	2.1 (22/1,051)
Tita et al.[9]	13,258	RDS or TTN	8.2 (68/833)	5.5 (213/3,904)	3.5 (221/6,510)
		RDS	3.7 (31/833)	1.9 (75/3,904)	0.9 (58/6,510)
		TTN	4.8 (40/833)	3.9 (153/3,904)	2.7 (178/6,510)
Wilmink et al.[8]	20,973	Combined respiratory morbidity‡	6.8 (118/1,734)	3.5 (356/10,139)	2.1 (136/6,647)
		RDS or TTN	4.6 (80/1,734)	2.7 (277/10,139)	1.5 (98/6,647)
		RDS	0.5 (8/1,734)	0.2 (21/10,139)	0.1 (7/6,647)
		TTN	4.3 (74/1,734)	2.5 (256/10.139)	1.4 (91/6,647)
Chiossi et al.[19]	23,749	RDS or TTN	9.1 (118/1,296)	6.4 (294/4,601)	4.0 (274/6,941)
		RDS	3.8 (49/1,296)	2.1 (98/4,601)	1.0 (71/6,941)
		TTN	5.3 (69/1,296)	4.3 (196/4,601)	2.9 (203/6,941)

Abbreviations: Neonatal Intensive Care Unit (NICU), Respiratory Distress Syndrome (RDS), Transient Tachypnea of the Newborn (TTN). †ICD-10 codes including any respiratory distress, TTN, or persistent pulmonary hypertension ‡RDS, TTN, pneumothorax, oxygen supplementation, intermittent positive pressure ventilation, or continuous positive airway pressure

review which presented data about neonatal respiratory morbidity following term elective CS stratified by week of gestation from 37^{+0} weeks of gestation onwards (Table 1).[5,8-10,19,20]

The rate of unplanned CSs is based on the rate of singleton live births with spontaneous start of labour, with all women still having to deliver as the denominator, in 2012 until 2014. This was 3.75% between 37^{+0} and 37^{+6} weeks and 12.39% between 37^{+0} and 39^{+0} weeks of gestation, which corresponds with data from international literature.[8,10,20]

Analysis

Following the decision tree the number of unplanned CSs needed to perform to prevent one neonate with respiratory morbidity were calculated, based on the obtained data. The risks of delivering earlier with an unplanned CS were taken into account. We assumed incidence rates of respiratory morbidity in neonates born after unplanned CS to be equivalent to the incidence rates of respiratory morbidity after elective CS.

Sensitivity analyses

One-way sensitivity analyses were performed to address the uncertainty and examine the impact of the probabilities, at 37^{+0-6}, 38^{+0-6} and 39^{+0-6} weeks of gestation, of respiratory morbidity and unplanned CS on the cost to prevent 1 neonate with respiratory morbidity for our four main strategies. The lower and upper 95% limits were tested for the following parameters:

Probability of respiratory morbidity with:

- Elective CS at 37^{+0-6} weeks with and without antenatal corticosteroids
- Unplanned CS at 37^{+0-6} weeks with and without antenatal corticosteroids
- Elective CS section at 38^{+0-6} weeks with and without antenatal corticosteroids
- Unplanned CS at 38^{+0-6} weeks without antenatal corticosteroids
- Elective CS at 39^{+0-6} weeks without antenatal corticosteroids

Probability of having an unplanned CS at:

- 37^{+0-6} weeks with a planned elective CS at 38^{+0-6} weeks
- 37^{+0-6} or 38^{+0-6} weeks with a planned elective CS at 39^{+0-6} weeks

This study was exempt from institutional review board ethical approval.

Results

Number of unplanned CSs needed to perform.

Pooled incidences of RDS and TTN were calculated per week of gestation with separate outcome data from 3 large cohort studies.[8,9,19] Pooled incidences of RDS and TTN together were 6.9%, 4.2% and 2.9% for neonates born at 37^{+0-6}, 38^{+0-6} or 39^{+0-6} weeks of gestation respectively (Table 2). This corresponds with a risk reduction of 39.1% by planning at 39^{+0-6} weeks compared to 38^{+0-6} weeks and of 58.0% by planning at 39^{+0-6} weeks compared to 37^{+0-6} weeks of gestation. We used data from the Cochrane review to calculate the risk reduction

of respiratory morbidity after elective CS *with* the administration of antenatal corticosteroids. These relative risks, 95% confidence interval were 0.49 (0.16-1.57) and 0.44 (0.17-1.14) at 37^{+0-6} and 38^{+0-6} weeks, respectively.[20]

In Table 3 we present the results of our decision analysis.

Main strategies <u>without</u> the administration of antenatal corticosteroids:

1) When planning all elective CSs at 39^{+0-6} weeks, to prevent one neonate with respiratory morbidity we needed to perform:
    a. 10.9 unplanned CSs, compared to planning all elective CSs at 38^{+0-6} weeks.
    b. 3.3 unplanned CSs, compared to planning all elective CSs at 37^{+0-6} weeks.
2) When planning all elective CSs at 38^{+0-6} weeks, to prevent one neonate with respiratory morbidity we needed to perform 1.4 unplanned CSs, compared to planning all elective CS at 37^{+0-6}.

Strategies <u>with</u> the administration of antenatal corticosteroids:

1) When planning all elective CSs at 38^{+0-6} weeks *with* antenatal corticosteroids, to prevent one neonate with respiratory morbidity we needed to perform:
    a. 2.5 unplanned CSs, compared to planning all elective CS at 37^{+0-6} *with* antenatal corticosteroids.
    b. 3.0 unplanned CSs, compared to planning all elective CS at 39^{+0} weeks *without* antenatal corticosteroids.

Strategy with performing an L/S ratio test:

1) When planning all elective CSs at 39 weeks, to prevent one neonate with respiratory morbidity we needed to perform 3.9 unplanned CSs compared to planning all elective CSs at 37+0-6 weeks after a positive L/S ratio test (and therefore assuming sufficient lung maturity).

Table 2. Pooled incidences of RDS and TTN associated with elective Caesarean Section

Reference	n	Respiratory outcome	Weeks		
			37^{+0-6}	**38^{+0-6}**	**39^{+0-6}**
			%	%	%
Pooled incidences†	44,539	RDS or TTN	6.9	4.2	2.9
		RDS	2.3	1.0	0.7
		TTN	4.7	3.3	2.4

Abbreviations: Respiratory Distress Syndrome (RDS), Transient Tachypnea of the Newborn (TTN).
†Pooled incidences with separate outcome data from Tita et al.[9], Wilmink et al.[8], and Choissi et al.[19]

Table 3. Number of emergency CSs needed to perform to prevent one neonate with RDS or TTN

Elective CS booked (weeks)	Number of emergency CS needed to perform†
Strategy without administration of antenatal corticosteroids	
For 39^{+0-6} compared to 38^{+0-6}	10.9
For 39^{+0-6} compared to 37^{+0-6}	3.3
For 38^{+0-6} compared to 37^{+0-6}	1.4
Strategy with administration of antenatal corticosteroids	
For 38^{+0-6} *with* AC compared to 37^{+0-6} *with* AC	2.5
For 38^{+0-6} *with* AC compared to 39^{+0-6} *without* AC	3.0
Strategy without administration of antenatal corticosteroids after a positive L/S ratio	
For 39^{+0-6} compared to 37^{+0-6}	3.9

Abbreviations: Caesarean Section (CS), Respiratory Distress Syndrome (RDS), Transient Tachypnea of the Newborn (TTN), Antenatal Corticosteroids (AC). †Number of emergency CS needed to perform to prevent one neonate with RDS or TTN

Discussion

Main findings

With a policy change of booking all elective CSs at 39^{+0-6} weeks of gestation, depending on prior booking policy at 37^{+0-6} or at 38^{+0-6} weeks of gestation, between 3 and 11unplanned CSs are necessary to prevent one neonate with respiratory morbidity, respectively. Correspondingly, this will reduce the risk of a neonate with respiratory morbidity with approximately 50%. If delaying until 39^{+0} weeks is absolutely not possible because of fetal or maternal complications, a strategy with the administration of antenatal corticosteroids and booking an elective CS at 38^{+0-6} weeks compared to booking an elective CS at 37^{+0-6} weeks of gestation, 2.5 unplanned CSs need to be performed to prevent one neonate with respiratory morbidity. To prevent one neonate with respiratory morbidity, 3.9 unplanned CSs need to be performed if delaying until 39^{+0} weeks of gestation, compared to delivery at 37^{+0-6} weeks after a positive L/S ratio test (indicates fetal lung immaturity).

Strength and limitations

Our decision analysis shows valid and clear results and can assist in common practice and informed clinical decision-making. Large randomized trials are lacking and absolute numbers of severe respiratory morbidity at term are low. Therefore we used data of large observational studies, published in peer reviewed journals. All showed the same decreasing

trend of respiratory morbidity with an increase of gestational age from 37^{+0} to 39^{+0} weeks onwards, assuming validity. There were some uncertainties. We had no data on the incidence of respiratory morbidity in neonates born with unplanned CS after onset of labour; therefore we assumed these incidences to be equal, in agreement with recent literature.[21] If this assumption is not correct (literature shows conflicting results),[10] and neonatal respiratory outcome after an intrapartum CS would be better compared to neonatal respiratory outcome after a prelabour CS, the number of CS needed to perform to prevent 1 sick neonate would be even lower. If the incidences of neonatal respiratory morbidity in CSs after the onset of labour were lower than after a planned elective CS, the numbers of unplanned CS to perform to prevent one neonate with respiratory complications would be even lower. As numbers were too small to have valid data on the incidence of RDS and TTN, risk reduction of respiratory morbidity after administration of antenatal corticosteroids was calculated based on 'admission to a special baby care unit with respiratory morbidity'.[20] Although there are several adverse neonatal outcome measures associated with early term elective CSs (hypoglycaemia, hyperbilirubinaemia, sepsis, longer hospitalisation and neonatal intensive care admission)[8], we only assessed respiratory morbidity as neonatal outcome measure, as this is the most important cause of neonatal morbidity in early term births.

Interpretation

The number of unplanned CSs needing to perform will be translated in increased unplanned workforce and will have resource implication, but not necessarily only out of office hours. In a recent trial only 34% with a planning strategy at 39^{+3} and 36% with a planning strategy at 38^{+3} weeks of unplanned CSs was out of hours.[22] One could argue that besides resource implications, unplanned CSs might have higher maternal risks compared with elective CSs. However, a large analysis did not show this.[23] In addition to respiratory morbidity, in CSs before 39^{+0} weeks the risk for hypoglycaemia and longer neonatal admission is also significantly higher, causing maternal-neonatal separation which is associated with reduced rates of breast-feeding initiation.[8,9,24] Also postnatal transfer to a more equipped neonatal unit can be necessary. In addition, a growing body of evidence suggests that children born early term have a greater risk for developmental delay in the first two years of life, have higher chances of respiratory morbidity like wheezing and asthma and more often have special educational needs.[25,26 27-29]

Antenatal corticosteroids

A commonly used alternative strategy is administration of antenatal corticosteroids to all women with a planned CS before 39^{+0} weeks. A randomized clinical trial comparing all women undergoing a CS at term with and without prior administration of antenatal

corticosteroids did show a decrease of admittance to special baby care units, RR, 95% confidence interval: 0.46 (0.23-0.93), however this decrease was not significant for TTN or RDS separately.[14,20] Follow-up in childhood did not show less asthma in the treated group and school assessment showed children in the treated group to be significantly more often in the lowest quartile of academic ability.[30] Furthermore, a recent trial showed an increase of neonatal hypoglycaemia in late preterm infants in the treated group (24.0% vs. 15.0%) which has been associated with impaired neurologic outcome in childhood.[31,32] As the incidence of respiratory morbidity at term is low, following a strategy with administration of antenatal corticosteroids to all mothers, more than 95% of mothers and their neonates will be unnecessary exposed to possible long-term risks.

Lung maturity tests as the L/S ratio (sensitivity 74.6% and specificity of 82.5%) and only performing a CS when the result indicates mature lungs, as alternative is questionable. Bates et al. reported that early term born infants, despite adequate fetal lung maturity with L/S ratio test, still had a significant higher risk of TTN compared to infants born at 39-40 weeks' gestation.[33] Quantus, a new non-invasive lung maturity test, unfortunately has no better test performances (sensitivity 62.1%, specificity 91.3%) between 34^{+0} and 38^{+6} weeks.[34]

Future research

We recommend a large prospective cohort study planning all elective CS at or beyond 39^{+0} weeks of gestation, to assess both neonatal and maternal outcome of elective and all necessary unplanned CS in short and long term.

Conclusion

In a policy of planning all elective pre-labour CSs from 39^{+0} weeks of gestation onwards, between 3 and 11 unplanned CSs have to be performed to prevent one neonate with respiratory morbidity. Therefore, in our opinion, fear of early term labour and workforce disutility is no argument for scheduling elective CSs <39 weeks. Further justification might be provided by conducting a comprehensive economic evaluation. Administration of corticosteroids instead of postponing an elective CS until after 39^{+0} weeks is no good alternative until more data about long-term consequences is available.

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5

Neonatal outcome following elective caesarean section of twin pregnancies beyond 35 weeks of gestation

F.A. Wilmink

C.W.P.M. Hukkelhoven

B.W.J. Mol

J.A.M. van der Post

E.A.P. Steegers

D.N.M. Papatsonis

Based on: American Journal of Obstetrics and Gynecology, 2012 Dec;207(6):480.e1-7

Abstract

Objective

To assess neonatal morbidity and mortality of elective caesarean sections of uncomplicated twin pregnancies per week of gestation beyond 35^{+0} weeks.

Methods

We performed a retrospective cohort study in our nationwide database including all elective caesarean sections of twin pregnancies. Two main composite outcome measures were defined i.e. severe adverse neonatal outcome and mild neonatal morbidity.

Results

We report on 2,228 neonates. More than 17% were born before 37^{+0} weeks of gestation. Adjusted odds ratios (95% confidence interval) for severe adverse neonatal outcome at 35^{+0-6} , 36^{+0-6} and 37^{+0-6} weeks were 9.4 (3.2-27.6), 1.7 (0.5-5.3) and 0.7 (0.2-2.0) respectively; and for mild neonatal morbidity 4.7 (2.6-8.7), 4.9 (3.1-7.9) and 1.4 (0.9-2.1) respectively, compared to neonates born ≥38^{+0} weeks of gestation.

Conclusion

In uncomplicated twin pregnancies elective caesarean sections can best be performed between 37^{+0} and 39^{+6} weeks of gestation.

Introduction

The incidence of twin pregnancies has increased worldwide, especially in western countries.[1-3] The main cause is the use of assisted reproductive technology (ART).[4] Secondly there is an increase in spontaneous twin pregnancies associated with increasing maternal age and ethnicity. [5,6] In the Netherlands the incidence of caesarean sections (CS) with twin pregnancies rose from 26.1% in 1993[7] to 36.9% in 2007[8].

In singleton pregnancies it is known that the risk for respiratory morbidity is significantly higher after an elective (planned) caesarean delivery compared to a planned vaginal delivery [9-12] and that this risk diminishes significantly with advancing gestational age until week 39^{+0}.[13-18] The definition of term pregnancy is being debated, suggesting introduction of new subcategories of term births (early term versus full term).[19] In twin pregnancies, however, this discussion is more complicated. Most literature with regard to timing of twin deliveries is focused on the risk of intrauterine fetal demise with an increase of gestational age. However, no consensus is found on when this risk starts increasing, from 36 to 39 weeks onwards.[20-25] The risks for neonatal mortality and morbidity caused by iatrogenic preterm birth by elective CS of twin pregnancies are unclear as well. The aim of our study was to assess neonatal morbidity and mortality of elective CS for uncomplicated twin pregnancies per week of gestation beyond 35^{+0} weeks.

Methods

Data were extracted from our nationwide database, The Netherlands Perinatal Registry (PRN), that includes 96% of approximately 180,000 deliveries per year at ≥ 16 completed weeks of gestation. The neonatal follow-up is registered in the PRN for approximately 68% of all hospitals. For more details with regard to content, process and quality control of the data collection we refer to a previous article on singleton pregnancies.[18] The current study was approved by the board of the PRN.

For this study, data from the PRN concerning 54,082 live born neonates from twin pregnancies between January 1, 2000 and December 31, 2007 were analyzed. We only included neonates born by an elective CS beyond 35^{+0} weeks of gestation and excluded neonates born by a planned CS registered with a maternal and/ or fetal indication or born by an emergency CS. Also all twins of which one fetus was missing in the registration were excluded. Eventually we excluded all twins of which at least one fetus had a congenital anomaly, and twins of mothers with an adverse medical or obstetric history and/ or a complication of pregnancy which could influence the risk for neonatal morbidity (specified in

Figure 1). The study was limited to hospitals that systematically registered neonatal follow-up.

Calculation of gestational age was, according to national guidelines[26], based on the date matching with ART or based on the first day of the last menstrual period and verified by a first trimester ultrasound, in case of discrepancy, gestational age was determined by the results of the first-trimester ultrasound. A first-trimester ultrasound is part of routine obstetric care, which is available for everyone in the Netherlands. Socioeconomic status was based on the mean household income level of the neighbourhood, which was determined by the first 4 digits of the woman's postal code.[27] Light for gestational age was defined as a birth weight < 10^{th} percentile, heavy for gestational age was defined as a birth weight > 90^{th} percentile. In absence of validated growth curves specific for multiple pregnancies this was based on sex-, parity- and race-specific growth curves developed for singleton pregnancies.[28]

Outcome measures

We studied two main composite outcome measures and two additional outcome measures. Our first main outcome was severe adverse neonatal outcome, defined as a composite measure of neonatal mortality until the 28^{th} day, or neonatal morbidity: a 5 minute Apgar score < 4 , convulsions, intracranial haemorrhage, respiratory morbidity registered as pneumothorax or respiratory distress syndrome, respiratory support by intermittent positive pressure ventilation (IPPV), severe resuscitation (defined as endotracheal artificial ventilation and/ or administration of buffers), and/ or sepsis, including both clinically suspected patients as well as proven infections with positive cultures.

Secondly, we studied mild neonatal morbidity, a composite of: respiratory morbidity registered as transient tachypnea of the newborn, respiratory support (continuous positive airway pressure (CPAP) or O_2) or hypoglycaemia (defined as a serum or plasma glucose level of <2.5mmol/l). We also analyzed the parts of these composite outcome measures separately.

Our two additional outcome measures were admission to the neonatal intensive care unit (NICU) and admission to any neonatal ward for ≥ 5 days. Follow-up of neonates stopped at discharge from the hospital. If they were transferred to another hospital (e.g. a university hospital), follow-up was continued.

Statistical analysis

All analyses were performed using SAS software (Version 9.1; SAS Institute, Cary NC). To evaluate differences in the baseline characteristics we used analysis of variance for continuous variables and the Chi-square test for categorical variables. Because several

categorical variables have small numbers in the gestational age categories we also approximated the exact p-value, using Monte Carlo simulations (n=100,000). Probability values lower than 0.05 were considered statistically significant. The incidence of neonatal outcome was calculated for each week of gestation. The presence of trends in our outcome data was studied with an exact trend analysis (Cochran-Armitage). As we expected a decreasing morbidity with an increasing gestational age we used one-sided p-values with a statistical significance level of 0.025. Missing values occurred for 0.5% of all confounders and were imputed once [29] for the regression analysis using R software (The R Foundation, Vienna, Austria).[30]Uni- and multivariate logistic regression analyses were used to study the association between gestational age at delivery and neonatal outcomes with all elective CS performed after 38^{+0} weeks of gestation as a reference group. The odds ratio (OR) with 95% confidence interval (95% CI) was determined using generalized estimation equations (GEE) for marginal models.[31] The GEE were used to account for the dependency of the twin children from the same pregnancy by using the mothers as a cluster variable. We adjusted the association for maternal age, ethnicity, parity, socioeconomic status and fetal gender.[25,32]

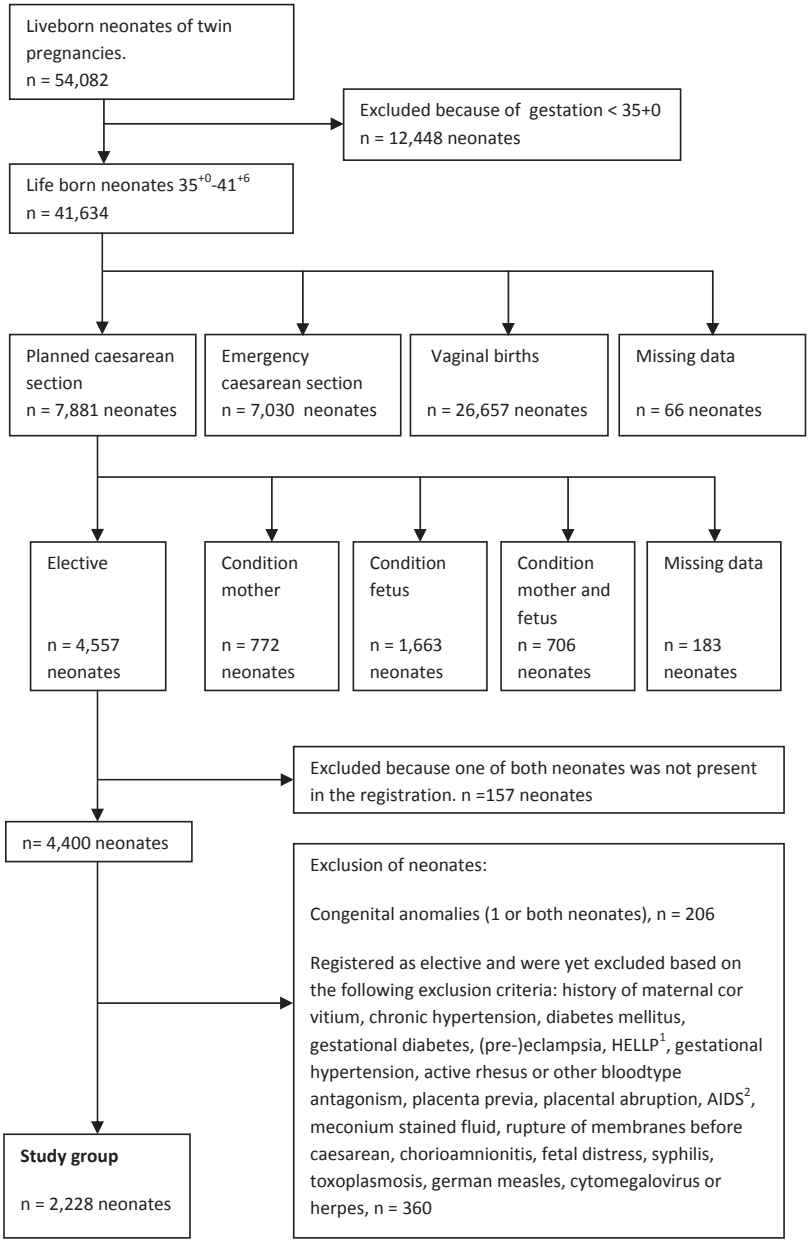
Two sensitivity analyses were performed. Since chorionicity is not registered in our database, we analysed all twins with an unequal gender to validate the results for dichorionic twins. Secondly we repeated the regression analyses in which births with an uncertain gestational age (2.8%) were excluded.

To analyze the incidence of intrauterine fetal demise we selected a separate cohort of all twin pregnancies between 2000 and 2007 with a gestational age beyond 35^{+0} weeks, without congenital anomalies, independent of the (intended) mode of delivery. As the incidence per week of gestation is not measuring the risk of intrauterine fetal demise, also the incidence per 1,000 fetus still in utero was calculated as presented by Yudkin et al.[33]

Results

In the study period, 54,082 live born neonates of twin pregnancies were registered in the PRN. From this population, a study cohort was comprised as shown in Figure 1. We excluded 12,448 neonates which were born before 35^{+0} weeks of gestation. We also excluded neonates born with a vaginal birth (n=26,657), an emergency CS (n=7,030), or a missing mode of delivery (n=66). In total 7,881 live born neonates between 35^{+0}-41^{+6} weeks of gestation were born by a planned CS of whom 4,577 electively. Furthermore we excluded 157 neonates because one neonate of the twin was not completely present in the registration. We also excluded all twins of which at least one neonate had a congenital

Figure 1. Flowchart showing the study profile



[1]Hemolysis, elevated liver-enzymes, and low platelet count; [2]acquired immunodeficiency syndrome

anomaly (n = 103 twins, 206 neonates) and all twins with a mother with an adverse medical history or complication of pregnancy which could have affected the risk for neonatal morbidity specified in figure 1 (n = 180 twins, 360 neonates). Finally, 1,606 neonates had no registered neonatal follow-up. We therefore report on 2,228 neonates of twin pregnancies born by an elective CS after 35^{+0} weeks of gestation.

Between 35^{+0} and 35^{+6} weeks of gestation 104 (4.7%) of these neonates were born, between 36^{+0} and 36^{+6} weeks 290 (13.0%), between 37^{+0} and 37^{+6} weeks 984 (44.2%) and between 38^{+0} and 41^{+6} weeks of gestation 850 (38.1%) of these neonates were born. Maternal and neonatal characteristics are presented in Table 1a and 1b, respectively. Primiparous women tended to deliver more premature than multiparous women. As can be expected the mean birth weight increased with an increasing gestational age at delivery. However, contrary, neonates below the 10th percentile tended to be delivered later.

Table 1a. Maternal characteristics shown per week of gestation at delivery

Week of gestation	**35^{+0-6}**	**36^{+0-6}**	**37^{+0-6}**	**38^{+0}-41^{+6}**	
Number of mothers	**n = 52 (4.7%)**	**n = 145 (13.0%)**	**n = 492 (44.2%)**	**n = 425 (38.1%)**	**P-value[2]**
Age at delivery (years)					
Mean[1]	31.4 ± 5.0	32.2 ± 4.1	32.0 ± 4.4	32.4 ± 4.7	0.09
0-35	38 (73.1)	98 (67.6)	347 (70.5)	272 (64.0)	0.02
> 35	14 (26.9)	47 (32.4)	145 (29.5)	153 (36.0)	
Race or ethnic group					
Western	48 (92.3)	132 (91.7)	429 (87.6)	366 (86.7)	0.12
Other	4 (7.7)	12 (8.3)	61 (12.4)	56 (13.3)	
Missing	*0*	*1*	*2*	*3*	
Parity					
Primipara	30 (57.7)	65 (44.8)	228 (46.3)	201 (47.3)	0.14
Multipara	22 (42.3)	80 (55.2)	264 (53.7)	224 (52.7)	
Socio-economic status					
Very high	10 (19.2)	23 (16.3)	91 (19.0)	83 (19.8)	0.58
High	11 (21.2)	33 (23.4)	105 (21.9)	84 (20.0)	
Normal	7 (13.5)	28 (19.9)	90 (18.8)	76 (18.1)	
Low	13 (25.0)	26 (18.4)	82 (17.1)	69 (16.5)	
Very low	11 (21.1)	31 (22.0)	112 (23.3)	107 (25.5)	
Missing	*0*	*4*	*12*	*6*	

Values are absolute numbers (valid percentages) or [1]mean ±SD . [2]P-values are calculated with analysis of variance (maternal age) or the chi-square test.

Table 1b. Neonatal characteristics shown per week of gestation at delivery

Week of gestation	35^{+0-6}	36^{+0-6}	37^{+0-6}	38^{+0}-41^{+6}	
Number of neonates	**n = 104 (4.7%)**	**n = 290 (13.0%)**	**n = 984 (44.2%)**	**n = 850 (38.1%)**	**P-value[2]**
Gender					
Male	51 (49.0)	140 (48.3)	484 (49.2)	392 (46.1)	0.61
Female	53 (51.0)	150 (51.7)	500 (50.8)	458 (53.9)	
Position					
Vertex	51 (49.0)	104 (35.9)	300 (30.6)	298 (35.1)	0.003
Breech	48 (46.2)	164 (56.6)	570 (58.2)	471 (55.4)	
Other	5 (4.8)	22 (7.6)	110 (11.2)	81 (9.5)	
Missing	*0*	*0*	*4*	*0*	
Birth weight (grams)					
Mean[1]	2304 ± 334	2521 ± 379	2700 ± 375	2878 ± 401	<0.0001
<2500	69 (66.4)	141 (48.6)	281 (28.6)	139 (16.4)	<0.0001
Small for gestational age (<p10)[3]	20 (19.2)	57 (19.7)	241 (24.5)	286 (33.7)	<0.0001
Large for gestational age (>p90)[3]	0 (0.0)	4 (1.4)	8 (0.8)	6 (0.7)	0.57

Values are absolute numbers (valid percentages) or [1]mean ±SD. [2]P-values are calculated with analysis of variance (mean birth weight), the chi-square test or approximated with Monte Carlo simulations (Large for gestational age). [3]Derived from sex-, parity- and race-specific growth curves.

Incidence rates for all outcome measures are presented per week of gestation in Table 2. The absolute risks for severe adverse neonatal outcome were 8.7% between 35^{+0} and 35^{+6}weeks, 1.7% between 36^{+0} and 36^{+6} and 0.7% between 37^{+0} and 37^{+6} weeks compared with 1.1% at a gestational age between 38^{+0} and 41^{+6} weeks of gestation (P for trend exact <0.0001). For mild neonatal morbidity the absolute risks were 22.1% between 35^{+0} and 35^{+6}, 22.1% between 36^{+0} and 36^{+6} and 7.6% between 37^{+0} and 37^{+6} weeks compared to 5.5% between 38^{+0} and 41^{+6} weeks of gestation (P for trend exact <0.0001). Admission to the NICU demonstrated risks of 4.8% between 35^{+0} and 35^{+6}, 1.0% between 36^{+0} and 36^{+6} and 0.5% between 37^{+0} and 37^{+6} weeks compared with 0.2% between 38^{+0} and 41^{+6} weeks of gestation (P for trend exact <0.0001). Admission to any neonatal ward demonstrated risks of 60.6% between 35^{+0} and 35^{+6}, 36.9% between 36^{+0} and 36^{+6} and 19.2% between 37^{+0} and 37^{+6} weeks compared with 15.3% between 38^{+0} and 41^{+6} weeks of gestation (P for trend exact <0.0001). Compared to neonates born between 38^{+0} and 41^{+6} weeks of gestation, neonates born between $35^{+0}$and 35^{+6} are at significantly higher risk for all our outcome measures and between 36^{+0} and 36^{+6} weeks at significantly higher risk for mild neonatal morbidity and hospitalization ≥ 5 days. Between 37^{+0} and 37^{+6} weeks of gestation there are no significantly

higher risks (Table 3). After excluding all neonates with equal gender (n = 1,278), similar results were found (results not shown).

Table 2. The incidence of neonatal morbidity after elective caesarean section of twin pregnancies shown per week of gestation at delivery

Week of gestation	**35^{+0-6}**	**36^{+0-6}**	**37^{+0-6}**	**38^{+0}-41^{+6}**	
Number of neonates	**n = 104**	**n = 290**	**n = 984**	**n = 850**	
	(4.7%)	**(13.0%)**	**(44.2%)**	**(38.1%)**	**P-value[1]**
Severe adverse neonatal outcome[2]	**9 (8.7)**	**5 (1.7)**	**7 (0.7)**	**9 (1.1)**	**<0.0001**
Neonatal death <24h	0 (0.0)	0 (0.0)	1 (0.10)	2 (0.24)	0.25
Neonatal death day 2-7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Neonatal death day 8-28	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Apgar score < 4[3]	1 (1.0)	0 (0.0)	1 (0.1)	1 (0.1)	0.23
Convulsions	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0.52
Intracranial haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Pneumothorax	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0.07
Respiratory distress syndrome	4 (3.9)	4 (1.4)	1 (0.1)	1 (0.1)	0.002
IPPV	1 (1.0)	1 (0.3)	2 (0.2)	0 (0.0)	0.04
Severe resuscitation[4]	1 (1.0)	1 (0.3)	2 (0.2)	2 (0.2)	0.23
Sepsis	4 (3.9)	0 (0.0)	3 (0.3)	3 (0.4)	0.01
Mild neonatal morbidity[5]	**23 (22.1)**	**64 (22.1)**	**75 (7.6)**	**47 (5.5)**	**<0.0001**
Transient tachypnea of the newborn	4 (3.9)	12 (4.1)	21 (2.1)	10 (1.2)	0.002
CPAP	4 (3.9)	5 (1.7)	3 (0.3)	1 (0.1)	<0.0001
O2	10 (9.6)	14 (4.8)	15 (1.5)	11 (1.3)	<0.0001
Hypoglycaemia	13 (12.5)	45 (15.5)	48 (4.9)	30 (3.5)	<0.0001
Admission					
Neonatal intensive care unit	5 (4.8)	3 (1.0)	5 (0.5)	2 (0.2)	<.0001
To any neonatal ward ≥ 5days	63 (60.6)	107 (36.9)	189 (19.2)	130 (15.3)	<.0001

Values are absolute numbers (percentages). [1]P-values are calculated with the Cochran-Armitage test for exact trend analysis. [2]Severe adverse neonatal outcome is defined as a composite measure of: neonatal mortality until the 28th day, or neonatal morbidity defined as: a 5-minute Apgar score < 4, convulsions, intracranial haemorrhage, pneumothorax, respiratory distress syndrome, intermittent positive pressure ventilation, severe resuscitation and/ or sepsis. [3]5-minute Apgar score. [4]Severe resuscitation is defined as endotracheal artificial respiration and/ or administration of buffers. [5]Mild neonatal morbidity is defined as a composite measure of: transient tachypnea of the newborn, respiratory support (O2 or CPAP) and/ or hypoglycaemia.

Table 3. Multivariate analysis of neonatal mortality and morbidity after an elective caesarean section of twin pregnancies

Week of gestation	35^{+0-6}	36^{+0-6}	37^{+0-6}	38^{+0}-41^{+6}
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Severe adverse neonatal outcome[1]	9.4 (3.2-27.6)	1.7 (0.5-5.3)	0.7 (0.2-2.0)	Reference
Mild neonatal morbidity[2]	4.7 (2.6-8.7)	4.9 (3.1-7.9)	1.4 (0.9-2.1)	Reference
Admission				
Neonatal intensive care unit	24.2 (4.5-130.2)	4.4 (0.7-26.7)	2.2 (0.4-11.3)	Reference
To any neonatal ward >= 5days	8.6 (4.9-15.2)	3.4 (2.3-5.1)	1.4 (0.98-1.9)	Reference

Values are Odds ratios (95% confidence interval) from logistic regression models. Models were adjusted for possible confounders: maternal age, ethnicity, parity, socioeconomic status and fetal gender. [1]Severe adverse neonatal outcome is defined as a composite measure of: neonatal mortality until the 28th day, or neonatal morbidity defined as: a 5-minute Apgar score < 4, convulsions, intracranial haemorrhage, pneumothorax, respiratory distress syndrome, intermittent positive pressure ventilation, severe resuscitation and/ or sepsis. [2]Mild neonatal morbidity is defined as a composite measure of: transient tachypnea of the newborn, respiratory support (CPAP or O2) and/ or hypoglycaemia.

The incidence of intrauterine fetal demise is presented in Table 4. Between 36^{+0} and 39^{+6} weeks of gestation this risk seems stable around 1.0 to 2.0 per 1,000 fetus. Thereafter this risk increases to 5.1 and 8.9 per 1,000 fetus at 40^{+0-6} and ≥ 41^{+0} weeks of gestation respectively.

Table 4. Incidence of intrauterine fetal demise in neonates of twin pregnancies between 2000 and 2007

Week of gestation	35^{+0-6}	36^{+0-6}	37^{+0-6}	38^{+0-6}	39^{+0-6}	40^{+0-6}	$\geq 41^{+0}$
Number of neonates	**n = 4,830**	**n = 7,442**	**n = 12,558**	**n = 9,420**	**n = 3,886**	**n = 1,341**	**n = 224**
Absolute incidence (n)	39	51	30	29	7	8	2
Incidence/ 1000 neonates per gestational age at delivery	8.1	6.9	2.4	3.1	1.8	6.0	8.9
Incidence/ 1000 fetus at risk[1]	1.0	1.5	1.1	2.0	1.3	5.1	8.9

[1]Fetus at risk for intrauterine fetal demise are the fetus that are still in utero.

Comment

We analyzed neonatal outcome of 2,228 neonates of twin pregnancies, born by an elective CS from 35^{+0} weeks onwards. More than 17% of these CS were performed before 37^{+0} weeks of gestation. Neonates born between $35^{+0}$and 35^{+6} had a significantly higher risk for all our outcome measures and neonates born between 36^{+0} and 36^{+6} weeks were at significantly higher risk for mild neonatal morbidity and hospitalization ≥ 5 days. Results of our analyses on dichorionic twins, based on unequal gender, appeared to be similar. Until 39^{+6} weeks of gestation the risk of intrauterine demise is stable, thereafter this risk increases.

The strength of our study is that it comprises recently collected data, from an extensive perinatal registry, of a great number of elective CS on all twin pregnancies, as well as on dichorionic twin pregnancies, from the whole country. This results in a large sample size and also is a broad reflection of current clinical decision making and neonatal outcome in the Netherlands. This study has some limitations similar to our study in singletons.[18] Initially the reliability of our data depends on the preciseness of registration of obstetricians and paediatricians. As we applied very stringent criteria when selecting our cohort (Figure 1), it is unlikely that we analyzed results of neonates which were prone to have an adverse outcome. In addition the incidence of neonates light for gestational age (birth weight below the 10^{th} percentile) is significantly increasing with an increase of gestational age. Therefore it is unlikely that neonates prone to an adverse outcome are disproportionately represented before 38^{+0} weeks of gestation. Secondly, reliability of the gestational age at birth is important and this is registered separately. If analyses were restricted to births with a certain gestational age (97.2%), results were similar (not shown). Thirdly, the neonatal follow up in the PRN is not registered for around 30% of all hospitals. However, this is a decision on hospital level rather than on patient level. Either the population in a hospital has complete follow-up or no follow-up at all. We assume that the incidence of neonatal morbidity in these hospitals is not different from those with good neonatal follow up because both types of hospitals are equally distributed across the country, use the same national clinical guidelines and are financed similarly. Finally before 37 weeks of gestation our sample size and the number of cases with a severe adverse neonatal outcome or admission to the NICU are limited.

Comparing our results to current literature there is limited data on timing of elective CS in twin pregnancies. Chasen et al.[35] recommended to avoid an elective CS before the onset of labour or until after 38 weeks of gestation, since the risk of respiratory morbidity was significantly higher before this term. Suzuki et al.[36] could not confirm these results, they didn't show a significant difference in the incidence of respiratory disorders between twins delivered by an elective CS before labour onset at 37 or 38 weeks of gestation. Both

contained small sample sizes. Our data from a much larger cohort show that in absence of fetal or maternal indications an elective CS should not be performed before 37^{+0} weeks of gestation. Thereafter we did not find a significantly higher risk for any of our outcome measures. Furthermore, Hartley et al.[23] demonstrated that without induction of labour, most twins with a vaginal delivery were born at 37 weeks of gestation and had the lowest perinatal mortality rate. Although subsequent results showed nadirs of perinatal mortality, respiratory distress syndrome and long hospital stay at respectively 39, 40 and 38 weeks of gestation, they concluded that induction of labour should be routinely considered for twins between 37 and 38 weeks of gestation.

We found that the risk for intrauterine demise started increasing from 40^{+0} weeks onwards. A large retrospective cohort study of Soucie et al.[25] demonstrated an increased risk of neonatal mortality of neonates of twin pregnancies after 40 weeks of gestation, the risk for fetal deaths was not significantly increased. Sairam et al.[20] showed that already at 39 weeks of gestation the risk of intrauterine demise in multiple gestations exceeded that of post term singleton pregnancies. Minakami et al. found that the incidence of intrauterine fetal demise and early neonatal deaths in twin pregnancies starts increasing from 37 to 38 weeks onwards.[24] However, in these studies they didn't exclude complicated pregnancies or fetus with congenital anomalies which are likely to be at greater risk than uncomplicated twin pregnancies.

Since there is little evidence in timing of elective caesarean sections of twin pregnancies, further studies should focus on the risk for intrauterine fetal demise while waiting, as well as on the risk for iatrogenic neonatal morbidity and mortality while performing a CS too early.

Conclusion

Gestational age related differences in neonatal outcome should be considered in planning elective CS of twin pregnancies. Based on our data elective caesarean sections in uncomplicated twin pregnancies can best be performed between 37^{+0} and 39^{+6} weeks of gestation.

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PART 2

Hypertensive disorders during pregnancy and neonatal respiratory morbidity

6

Preeclampsia and risk of developing bronchopulmonary dysplasia in very preterm neonates

F.A. Wilmink

J. Reijnierse

I.K.M. Reiss

E.A.P. Steegers

R.C.J. de Jonge

Submitted for publication, under revision

Abstract

Objective

Bronchopulmonary dysplasia (BPD) is a severe common complication of preterm birth with considerable short and long-term consequences. As more evidence is emerging that dysregulation of angiogenesis is implicated not only in fetal lung development but also in the pathogenesis of preeclampsia, we assessed if preeclampsia is associated with development of BPD in very preterm neonates.

Methods

A retrospective cohort study of 308 infants born between 24^{+0} and 31^{+6} weeks of gestation in 2011 and 2012. We performed association analysis with univariable and multivariable logistic regression, adjusting for confounders. Secondly models were additionally adjusted for intermediates, to show how an association can be disguised by over adjusting. BPD was diagnosed at 36^{+0} weeks postmenstrual age and defined as the need for oxygen (FiO2>0.21) for at least 12 hours per day, for more than 28 days before or at 36^{+0} weeks postmenstrual age, and classified as mild, moderate or severe.

Results

After applying our exclusion criteria, we report our primary outcome on 247 mother-neonate pairs. Fifty-nine neonates developed BPD (23.9%) which was moderate to severe in 27 of them (10.9%). Preeclampsia was associated with BPD, adjusted odds ratio, 95% confidence interval: 4.79 (1.98, 11.54). However, after adjusting for additional intermediates no statistical significance remained, adjusted odds ratio, 95% confidence interval: 2.12 (0.58, 7.69).

Conclusion

This study shows that early-onset preeclampsia is associated with development of BPD in the very preterm neonate, and that adjusting for intermediates disguises this clinically relevant association.

Introduction

Bronchopulmonary dysplasia (BPD) is a severe complication of preterm birth associated with respiratory morbidity and impaired neurodevelopment in later life.[1,2] Its prevalence is still high, with 25% in neonates born <32 weeks of gestation, in part because more extreme preterm neonates from 24^{+0} weeks post-menstrual age (pma) onwards survive.[3] The pathogenesis of BPD is multifactorial and still not completely understood. What is known, however, is that preterm birth disturbs early lung development and consequently is a risk factor. Gestational age at birth has indeed been found inversely related with the risk for BPD.[4-6] Furthermore, dysregulation of angiogenesis may be implicated in the development of BPD. In animal studies, inhibiting of vascular endothelial growth factor resulted in reduced alveolarization and persistent abnormalities of pulmonary vascular structures.[7,8] A high concentration of endostatin (an anti-angiogenic growth factor) in human cord plasma predicts the development of BPD in very low birth weight infants.[9] Next to BPD, more evidence is emerging for an important role of an anti-angiogenic status in the pathogenesis of preeclampsia.[10,11] It has been hypothesized, therefore, that neonates of mothers with preeclampsia have a higher risk for developing BPD. Tsao et al. showed that an anti-angiogenic status of the mother did reflect in the neonate, as neonates of mothers with preeclampsia had higher cord blood soluble fms-like thyrosine kinase 1(sFlt-1) but lower placental growth factor and vascular endothelial growth factor (VEGF) levels. As a result these infants had lower platelet levels.[12] Tang et al. administered sFlt into the amnion sac of pregnant rats at a stage of lung development parallel to human lung development in preterm infants at 24 to 26 weeks of gestation. This excess of sFlt-1 decreased VEGF signalling and increased apoptosis; reduced alveolarization and pulmonary vascular growth was then observed during infancy of the offspring.[13]

Results of several epidemiologic studies assessing the association between preeclampsia and BPD are inconclusive.[4,6,14-20] This can at least partly be explained by imprecise definitions of BPD, the use of data from national registration systems with risk for false positive or false negative diagnosis, and most importantly by adjusting outcome data for intermediates rather than for confounders alone. It is still very difficult to predict who of these neonates will develop BPD. More insight in associations could lead to earlier detection, improve counselling and support hypotheses for future research, eventually leading to better preventive or therapeutic measures.[21] Therefore we addressed the question whether early onset preeclampsia in the mother is associated with development of BPD in the neonate.

Methods

Design and procedures

We performed a retrospective cohort study of infants born between 24^{+0} and 31^{+6} weeks of gestation in 2011 and 2012 in a large academic level III perinatal centre in the Netherlands. Two investigators (FW, maternal data & JR, neonatal data) systematically extracted medical information from digital records of the department of Obstetrics and Gynaecology, the division of neonatology and the registration system of the Neonatal Intensive Care Unit). At this stage they were blinded to the neonatal outcome and maternal outcome, respectively. Almost all included neonates had been transferred to a non-academic hospital before 36 weeks pma. As registration of the diagnosis BPD in a national database in a referral-based health care system may not be accurate[22], JR visited the hospitals involved to extract the follow-up information until 36 weeks pma, including all days of ventilation and oxygen administration and results of the oxygen reduction test if performed. Any ambiguities were solved in consensus meetings. This concerned six children who had an intercurrent disease or operation for which they briefly needed mechanical ventilation at 36 weeks pma. In these cases, receiving respiratory support just before onset of the intercurrent disease determined the classification of BPD. The study protocol was approved by the local institutional review board, (MEC-2014-013).

Main determinant

Preeclampsia was defined as new onset hypertension (systolic blood pressure ≥140mmHg or a diastolic blood pressure ≥90mmHg, measured twice), after 20 weeks of gestation with the coexistence of one or more of the following new-onset conditions: 1) proteinuria (≥0.3g/24h or a protein-creatinine-ratio ≥30mg/mmol), 2) other maternal organ dysfunction or 3) foetal growth restriction, according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria.[23] Superimposed preeclampsia was defined as preeclampsia in patients with chronic hypertension; total preeclampsia was defined as preeclampsia and superimposed preeclampsia combined. All cases concerned early onset preeclampsia (<32 weeks of gestation).[24] HELLP syndrome was defined as thrombocytes less than 100×10^9/L, both aspartate aminotransferase and alanine aminotransferase more than 70 U/L, and lactate dehydrogenase more than 600 U/L.[25]

Outcome measures

BPD as primary outcome was defined as the need for oxygen (Fraction of inspired Oxygen (FiO2)>0.21) for at least 12 hours per day, for more than 28 days before or at 36 weeks PMA. BPD was classified as mild if FiO_2=0.21, or $0.21<FiO_2\leq0.30$ without any incidents during phase out of oxygen in an oxygen-reduction test. BPD was classified as moderate if $0.21<FiO_2<0.30$

and an oxygen reduction test with incidents during phase out, or an oxygen reduction test was indicated but not performed. BPD was classified as severe if FiO2≥0.30, or if admission of continuous positive airway pressure or mechanical ventilation was required (Table S1).
Secondary we analysed the association of preeclampsia with the combined outcome measure 'deceased or BPD', and with 'uneventful survival', defined as: no BPD, no retinopathy of prematurity (ROP), no sepsis, no necrotizing enterocolitis with Bell's criteria 1-3 and no interventricular haemorrhage (IVH) at 36^{+0} weeks pma.

Covariates

Gestational age was calculated based on a first trimester ultrasound. Prolonged preterm prelabour rupture of membranes (prolonged pPROM) was defined as delivery >24 hours after pPROM. Chorioamnionitis was clinically diagnosed if there was maternal fever (≥38^0C), maternal or foetal tachycardia, or increased levels of C - reactive protein or white blood cell/leukocyte count without any other cause, justifying adaptation of clinical management. A pathological diagnosis of chorioamnionitis was made if microscopic invasion of neutrophilic granulocytes was major. We choose prolonged pPROM as a substitute for chorioamnionitis as this is a more objective measure and had a good correlation with clinical chorioamnionitis as well as with the diagnosis based on pathology results.[26] A completed course of antenatal corticosteroids was rated as "yes" if delivery of the neonate was at least 24 or 12 hours after the last dose of twice betamethasone 12mg every 24h, or the last dose of four times dexamethasone every 12h, respectively.

Respiratory distress syndrome of the neonate (RDS) was defined as respiratory distress early postpartum with the need of surfactant therapy. The number of surfactant doses was registered. Admission of postnatal steroids, dexamethasone or hydrocortisone, were registered. Sepsis was registered as early onset (< 72h after birth) or late onset (> 72h after birth) and registered as 'proven' with a positive blood culture and as 'clinical' upon clinical signs and / or a high C-reactive protein level followed by treatment with antibiotics for 5 days or more. Patent ductus arteriosus was registered if confirmed by ultrasound, either treated with medication or surgical ligation. If medication failed and surgical ligation was still necessary, it was registered as 'patent ductus arteriosus needing surgical ligation'. Necrotizing enterocolitis (NEC) was defined as a clinical presentation in combination with an abdominal X-ray, meeting Bell's criteria ≥2. Retinopathy of prematurity (ROP) was defined as ROP grade 1 and up in one or two eyes, diagnosed by a trained paediatric ophthalmologist. Intraventricular haemorrhage was defined as all subependymal or choroid plexus bleedings with breakthrough in the lateral ventricle. Both uni- and bilateral bleedings were included. Diagnosis was made by routine cerebral ultrasound performed by trained neonatologists.

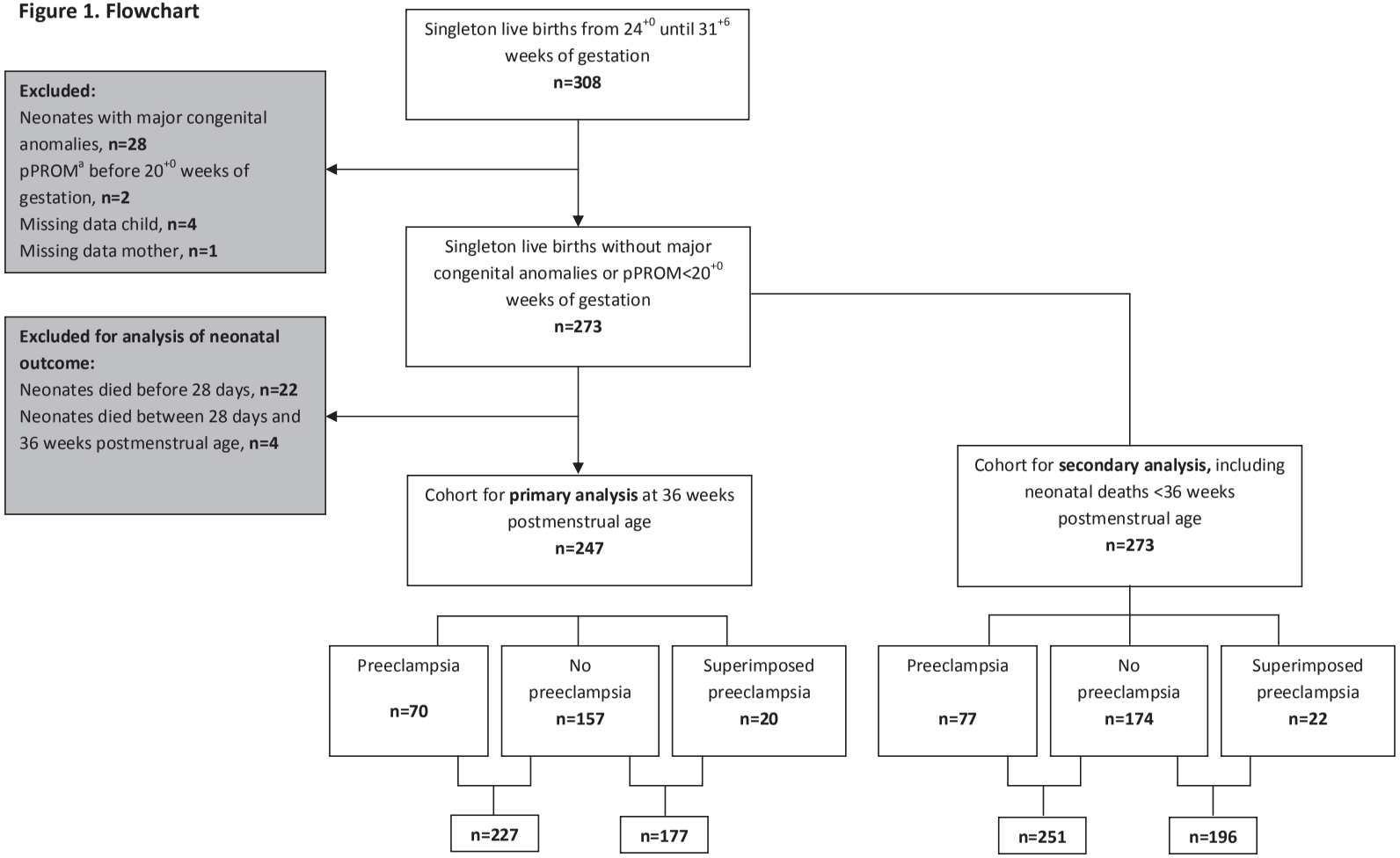
Statistical analysis

Descriptive statistics of continuous variables are presented as mean (SD) when distribution is normal, and as median (IQR) when distribution is skewed. Descriptive statistics of discrete variables are presented as valid percentage (absolute numbers); this means that percentages are calculated without taking missing values into account. Differences in baseline characteristics of continuous variables were tested using Student's *t* or if non parametric with the Mann-Whitney *U* test. Categorical variables were tested with the Chi-square test. We used univariable and multivariable binary logistic regression models to examine the associations of the primary determinant preeclampsia, with the primary outcome BPD of the neonate, and in addition with our secondary outcome measures 'deceased or BPD' and 'uneventful survival'. After crude analysis, models were adjusted for confounders: nulliparity, prolonged pPROM, gestational age at birth and child's gender.[6,15,18,27] Secondly, models were additionally adjusted for the following intermediates: administration of antenatal steroids, birth weight Z-scores, mode of delivery, RDS, invasive ventilation, administration of postnatal steroids, clinical or proven sepsis and treatment of a persistent ductus arteriosus. This adjustment served to show how an association can be disguised by over-adjusting. An intermediate is a cofactor which is in between the pathway from the determinant to the outcome measure. As adjustment for gestational age and birth weight could lead to multicollinearity, we choose to adjust for birth weight Z-scores. Results are presented as (adjusted) odds ratios (ORs) with 95% confidence interval (95% CI). We performed a sensitivity analysis excluding all mothers with superimposed preeclampsia. Statistical analyses were performed using IBM SPSS Statistics version 21 for Windows software (SPSS Inc.).

Results

The study profile is shown in Figure 1. The primary outcome measure was analysed in 247 mother-neonate pairs. The secondary outcome measures 'deceased or BPD' and 'uneventful survival' were analysed in 273 neonates. The cohort included 4 neonates who also participated in the SToP-BPD study[28] in which patients are randomized to either hydrocortisone or placebo for 22 days, to prevent the development of BPD at 36 weeks PMA. We included these neonates to prevent selection bias. All four were ventilator-dependent at 7-14 days PMA, one died before 36 weeks PMA and the other three developed severe BPD for which two were given postnatal steroids outside the study protocol.

Figure 1. Flowchart



[a]Preterm prelabour rupture of membranes (pPROM)

Causes for preterm labour were preeclampsia (19.8%), preterm contractions (29.1%), pPROM (15.8%), cervical insufficiency (1.6%), suspicion of foetal distress (30%) and other maternal morbidity (3.6%, i.e. severe maternal blood loss without foetal distress). Ninety mothers (36.4%) had been diagnosed with preeclampsia of whom 12 (14.1%) had HELLP syndrome. They had never prolonged pPROM, had less clinical chorioamnionitis, and delivered more often with a caesarean section. Infants of preeclamptic mothers were more often female and were on average born at a higher gestational age with a lower birth weight than children of mothers without preeclampsia (Table 1). Of 247 neonates, 59 (23.9%) developed BPD, which was classified as mild in 32 (13.0%), as moderate in 3 (1.2%) and severe in 24 (9.7%). Besides a lower risk for intra-ventricular haemorrhage and proven sepsis for neonates of mothers with PE, there were no statistically significant differences in comorbidity (Table 2).

The incidence of infants with BPD did not differ between women with preeclampsia (25.6%) or without preeclampsia (22.9%). Multivariable logistic regression analysis showed significant associations between preeclampsia and BPD, preeclampsia and moderate to severe BPD compared to none or mild and thirdly for preeclampsia and 'deceased or BPD' after adjusting for confounders; the ORs (95%CI) were respectively 4.79 (1.98, 11.54), 4.25 (1.43,12.65) and 4.21 (1.90, 9.32) (Table 3a and Table 3b). After additional adjustment for intermediates, these associations showed no statistical significance anymore. Therefore, neonates of mothers with and without preeclampsia had similar chances of developing BPD, to survive uneventfully or to decease in the first 36 weeks of life. The results of the sensitivity analysis, excluding all cases with superimposed preeclampsia, were similar to our main results (supplementary Table S2).

Preeclamptic mothers with an infant who developed BPD did not differ clinically from preeclamptic mothers with an infant who did not develop BPD with regard to blood pressure, severity of proteinuria, deviating laboratory results or intravenous treatment with magnesium sulphate or antihypertensive medication. There was no significant difference between neonates with or without BPD in the time elapsed between diagnosis of preeclampsia and date of birth, median (interquartile range) 5.0 (2.5-7.5) and 3.5 (2.0-8.8) days respectively ($p= 0.50$). Gestational age at birth did differ significantly, $p<0.001$ (supplementary Table S3).

Table 1. Baseline characteristics of mothers and their children, stratified by the presence of total preeclampsia.

Original data, n=247			
Baseline characteristics	**Total PE**[a] Valid % (n)[c]	**No PE** Valid % (n)[c]	***P*-value**[b]
Mothers	**36.4 (90)**	**63.6 (157)**	
Age at delivery (years)[d]	30.3 (5.6)	30.3 (5.4)	0.91
Body mass index (kg/m^2)[e]	24 (22-29)	23.0 (20-27)	0.10
Missing, n	*23*	*43*	
Nulliparity	73.3 (66)	60.5 (95)	**0.04**
First trimester ultrasound	95.2 (80)	97.3 (142)	0.43
Missing, n	*6*	*11*	
Prolonged pPROM[f]	0 (0)	28.0 (44)	n/a
Chorioamnionitis	1 (1,2)	39.0 (55)	**<0.001**
Missing, n	*9*	*16*	
Caesarean section	95.6 (86)	38.2 (60)	**<0.001**
Diabetes mellitus	3.3 (3)	1.3 (2)	0.29
Gestational diabetes	3.3 (3)	4.5 (7)	0.67
(Gestational) hypertensive disorder			
GH[g]	n/a	0.4 (1)	n/a
PE/ HELLP[h]	77.8 (70)	n/a	n/a
Chronic hypertension	22.2 (20)	1.3 (2)	**<0.001**
Superimposed PE	22.2 (20)	n/a	n/a
Neonates	**36.4 (90)**	**63.6 (157)**	
Gender, male	42.2 (38)	63.1 (99)	**0.002**
Gestational age at birth (weeks)[e]	29.9 (28.6-31.0)	28.9 (26.8-30.8)	**<0.001**
Birth weight (grams)[e]	1100 (945-1331)	1280 (983-1547)	**0.001**
Birth weight z-score[e]	-0.89 (-1.47; -0.60)	0.08 (-0.26; 0.60)	**<0.001**
Antenatal corticosteroids completed	78.9 (71)	52.2 (82)	**<0.001**
5 minutes Apgar <7	12.2 (11)	17.2 (27)	0.29
pH umbilical cord[e]	7.27 (7.22-7.32)	7.33 (7.27-7.37)	**<0.001**
Missing, n	*10*	*13*	

[a]Mothers with preeclampsia (PE) and superimposed preeclampsia. [b]Differences in baseline characteristics of continuous variables were tested using Student's *t,* or if non-parametric with the Mann-Whitney *U* test. Categorical variables were tested with the Chi-square test. [c]Values are valid percentages (absolute numbers), [d]means (SD) or [e]medians (IQR). [f]Preterm prelabour rupture of membranes >24 hours (prolonged pPROM), [g]Gestational hypertension (GH), [h]Haemolysis elevated liver enzymes low platelets syndrome (HELLP-syndrome).

Table 2. Incidence of neonatal morbidity and ventilation, stratified by presence of total preeclampsia (PE).

Original data, n=247				
Neonatal morbidity	**Total** Valid % (n)[c] **100 (247)**	**Total PE**[a] Valid % (n)[c] **36.4 (90)**	**No PE** Valid % (n)[c] **63.6 (157)**	***P*-value**[b]
BPD[d]	23.9 (59)	25.6 (23)	22.9 (36)	0.65
Mild	13.0 (32)	12.2 (11)	13.4 (21)	0.38
Moderate or severe	10.9 (27)	13.3 (12)	9.6 (15)	0.43
RDS[e]	44.9 (111)	52.2 (47)	40.8 (64)	**0.04**
Postnatal steroids	2.0 (5)	2.2 (2)	1.9 (3)	0.86
Missing, n	*1*	*1*	*0*	
Ventilation				
Invasive (days)	1 (0-5)	1 (0-5)	1 (0-6)	0.21
Non-invasive (days)	24 (6-39)	23 (6-37)	25 (6-42)	0.26
Nasal cannula (days)	8 (4-14)	7 (3-11)	10 (4-15)	**0.01**
Persistent ductus arteriosus	19.4 (48)	14.4 (13)	22.2 (36)	0.18
Sepsis				
Clinical diagnosis	26.3 (65)	31.1 (28)	23.6 (37)	0.64
Proven by culture	25.5 (63)	16.7 (15)	30.6 (48)	**0.04**
IVH[f] **≥ grade II**	10.1 (25)	3.3 (3)	14.0 (22)	**0.01**
ROP[g]				
ROP stage I, n(%)	15.0 (36)	15.9 (14)	14.5 (22)	0.78
ROP >stage II, n(%)	5.0 (12)	4.5 (4)	5.3 (8)	0.83
Missing, n	*7*	*2*	*5*	
NEC[h]**, Bells stage 2 or 3**	4.0 (10)	1.1 (1)	5.7 (9)	0.11

[a]Mothers with preeclampsia and superimposed preeclampsia. [b]Differences in baseline characteristics of continuous variables were tested using Student's *t* or if non parametric with the Mann-Whitney *U* test. Categorical variables were tested with the Chi-square test. [c]Values are valid percentages (absolute numbers) or medians (IQR). [d]Bronchopulmonary dysplasia, [e]Respiratory distress syndrome (RDS) defined as the need for surfactant therapy early postpartum, [f]Intraventricular haemorrhage (IVH), [g]Retinopathy of prematurity (ROP), [h]Necrotising enterocolitis (NEC).

Table 3a. Multivariable logistic regression analysis of bronchopulmonary dysplasia (BPD), in neonates of mothers with preeclampsia or superimposed preeclampsia.

Original data n=247			
	Crude OR (95% CI)	**Adjusted[a] OR (95% CI)**	**Adjusted[b] OR (95% CI)**
No BPD	*Reference*	*Reference*	*Reference*
BPD	1.15 (0.63, 2.11)	**4.79 (1.98, 11.54)**	2.12 (0.58, 7.69)
None or mild BPD	*Reference*	*Reference*	*Reference*
Moderate or severe BPD	1.46 (0.65, 3.27)	**4.25 (1.43, 12.65)**	2.89 (0.56, 14.85)

[a]Adjusted for potential confounders: nulliparity, prolonged pPROM, gestational age at birth and gender. [b]Adjusted for above-mentioned confounders and additionally for the following intermediates: antenatal corticosteroids, birth weight Z-score, mode of delivery, respiratory distress syndrome, invasive ventilation, admission of postnatal corticosteroids, clinical or proven sepsis, treatment of a persistent ductus arteriosus.

Table 3b. Multivariable logistic regression analysis of 'decease or BPD' and 'uneventful survival' in mothers with preeclampsia or superimposed preeclampsia.

Original data n=273			
	Crude OR (95% CI)	**Adjusted[a] OR (95% CI)**	**Adjusted[b] OR (95% CI)**
Not deceased and no BPD	*Reference*	*Reference*	*Reference*
Deceased[c] or BPD	1.09 (0.64, 1.85)	**4.21 (1.90, 9.32)**	2.27 (0.64, 8.02)
No uneventful survival[d]	*Reference*	*Reference*	*Reference*
Uneventful survival[d]	1.06 (0.62, 1.82)	0.64 (0.34, 1.22)	0.46 (0.11, 1.82)

[a]Adjusted for potential confounders: nulliparity, prolonged pPROM, gestational age at birth and gender. [b]Adjusted for above-mentioned confounders and additionally for the following intermediates: antenatal corticosteroids, birth weight Z-score, mode of delivery, respiratory distress syndrome, invasive ventilation, admission of postnatal corticosteroids, clinical or proven sepsis, treatment of a persistent ductus arteriosus. [c]Deceased within 24 hours: 1.5% (n= 4), between day 1 and 7a: 1.5% (n= 4), between day 7 and 28: 5.1% (n= 14), between 28days and 36 weeks postmenstrual age: 1.5% (n= 4). [d]Uneventful survival is defined as survival without BPD, retinopathy of prematurity, sepsis, necrotizing enterocolitis Bell's stage 1-3 or intraventricular haemorrhage ≥ grade 2.

Discussion

In this cohort of 247 mother-neonate pairs we found a strong association of preeclampsia in the mother with BPD in the neonate (OR, 95%CI: 4.79 (1.98, 11.54)). This association disappeared, however, when adjusting for intermediates on the pathway from preeclampsia to BPD, particularly low birth weight Z-scores.

Several strengths of this study are worth mentioning. First, it comprises of detailed data of all extreme preterm deliveries (i.e. <32 weeks of gestation) in 2011 and 2012 for a large region of the Netherlands. (The Erasmus MC-Sophia Children's Hospital has one of the largest level III NICU of Western Europe.) In countries with a referral-based health care system, registration of perinatal data and the diagnosis BPD in a national database may not be accurate.[22] Therefore, two dedicated researchers collected all maternal and neonatal data with very little loss to follow up, including site visits to the hospitals to which the neonates were discharged. Second, selection bias was prevented by selecting a cohort based on gestational age in two randomly chosen years. Cohorts based on 'very low birth weight infants' will automatically include many growth restricted neonates, particularly of mothers with preeclampsia and placental insufficiency. Given that the risk for BPD is declining significantly with an increase of gestational age, growth restricted neonates with a higher gestational age are relatively protected compared to infants with a birth weight on the 50th percentile, but with a much lower gestational age. As birth weight is an influential intermediate, adjusting for birth weight Z-scores cannot correct selection bias.[29] Overall, statistical association analysis in preterm births is difficult, as there is no healthy group to compare with. In addition it is arguable if gestational age is an intermediate as well, given iatrogenic preterm birth as a consequence of preeclampsia.[30] However, preeclampsia occurs independently at a certain gestational age (i.e. never before 20 weeks of gestation). A correct due date is of great importance when analysing data in preterm births. In our cohort 96.5% has had a first trimester ultrasound.

Some limitations need to be addressed as well. Although we thoroughly collected data, the retrospective nature of the data had some drawbacks. For example, reliable information on smoking habits and ethnicity was not available. As smoking decreases the risk for preeclampsia and increases the risk for IUGR and BPD, and BPD is probably partly a genetic/epigenetic disease, our results are potentially influenced by this missing information.

Although some studies assessing the association between preeclampsia and BPD find no statistical significant or negative associations[15,17,18], most recent studies show a positive association[4,6,14,16,19,20]. This discrepancy can be explained by the use of different definitions for the outcome measure[17], by considerable loss to follow up (probably mostly healthy neonates of healthy mothers) and by selecting cohorts based on very low birth weight[15,18] as

described above. Additionally, in most previous studies, analyses were adjusted for intermediates rather than for confounders alone, which could have influenced results.[31,32] Some studies show a strong significant association between very low birth weight and chronic lung disease (e.g. BPD).[33,34] It is not clear, however, if the low birth weight causes the higher risk or that causality lies in factors preceding an IUGR. As adjustment for, or selection on, birth weight influences results dramatically (disappearance of a strong association between preeclampsia and BPD), one could hypothesize that the association is rather based on placental insufficiency causing an altered angiogenic status and eventually an intra-uterine growth restriction. A recent study showed that pathologic changes of maternal vascular under perfusion of the placenta are significantly associated with BPD and subsequently with pulmonary hypertension.[35] In several cases of extremely preterm birth without signs of preeclampsia or foetal growth restriction, the pathologic changes in the placenta and the association with BPD were already present. This hampers epidemiologic association analyses.[35] Besides the hypothesis that the anti-angiogenic status disturbs lung development and is associated with BPD (as described in the introduction), also length of exposure to such an environment could hypothetically be of influence. Active management (iatrogenic preterm delivery) could therefore hypothetically also be beneficial to the neonate and not only to the mother.

Conclusion

This study shows that early-onset preeclampsia is associated with development of bronchopulmonary dysplasia in the very preterm neonate, and that adjusting for intermediates disguises this clinically relevant association. Future research should focus on elucidating not only the pathogenesis of BPD in the offspring of mothers with preeclampsia, but also on the pathogenesis of placental dysfunction and a disturbed angiogenetic status, as the latter may lead to disturbed foetal lung development in the offspring of woman with hypertensive diseases.

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Supplementary Table 1. Classification of bronchopulmonary dysplasia at 36 weeks postmenstrual age for neonates born <32 weeks who needed at least 28 days oxygen supply with FiO_2[a] >0.21.

Mild BPD	FiO_2 = 0.21; or 0.21< FiO_2≤ 0.30 without any incidents during phase out of O2 in an O2-reduction test.
Moderate BPD	0.21< FiO_2< 0.30 and an oxygen reduction test with incidents during phase out or an oxygen reduction test was indicated but not performed.
Severe BPD	FiO_2≥0.30, or requirement of admission of continuous positive airway pressure or mechanical ventilation.

[a]Fraction of inspired oxygen (FiO_2).

Supplementary Table 2. Sensitivity analysis. Multivariable logistic regression analysis of bronchopulmonary dysplasia (BPD), in mothers with preeclampsia, excluding all mothers with superimposed preeclampsia.

Original data, n=227

	PE[a] Valid % (n) **30.8 (70)**	**No PE** Valid % (n) **69.2 (157)**	**Crude OR (95% CI)**	**Adjusted**[b] **OR (95% CI)**	**Adjusted**[c] **OR (95% CI)**
No BPD	77.1 (54)	77.1 (121)	*Reference*	*Reference*	*Reference*
Total BPD	22.9 (16)	22.9 (36)	1.00 (0.51, 1.95)	**4.22 (1.63, 10.91)**	1.87 (0.49, 7.24)
None or mild BPD	87.1 (61)	90.4 (142)	*Reference*	*Reference*	*Reference*
Moderate or severe BPD	12.9 (9)	9.6 (15)	1.40 (0.58, 3.67)	**3.94 (1.24, 12.49)**	1.65 (0.30, 9.24)

[a]Mothers with preeclampsia excluding mothers with superimposed preeclampsia. [b]Adjusted for potential confounders: nulliparity, prolonged pPROM, gestational age at birth and gender. [c]Adjusted for above mentioned confounders and additionally for the following intermediates: antenatal corticosteroids, birth weight Z-score, mode of delivery, respiratory distress syndrome, invasive ventilation, admission of postnatal corticosteroids, clinical or proven sepsis, treatment of a persistent ductus arteriosus.

Supplementary Table 3. Characteristics of all mothers with preeclampsia having a neonate with or without bronchopulmonary dysplasia.

Original data, mothers with PE, n=90			
	BPD n=23	**No BPD n=67**	**P-value**
Gestational age, weeks[a]	28.1 (27.7, 29.6)	30.3 (29.0, 31.1)	**<0.001**
Days to delivery[a]	5.0 (2.5, 7.5)	3.5 (2.0, 8.8)	0.50
Blood pressure			
Highest systolic, mmHg[b]	175.2 (13.4)	172.7 (17.1)	0.53
Highest diastolic, mmHg[b]	105.7 (8.9)	107.3 (9.8)	0.50
Laboratory			
EKR, mg/mmol[a]	223 (94, 518)	199 (97, 516)	0.68
Missing, n	*2*	*9*	
Proteinuria, g/24h[a]	1.90 (0.4, 3.2)	1.6 (0.7, 6.1)	0.17
Missing, n	*4*	*9*	
Lowest platelets, $*10^9$/L[a]	110 (83, 166)	168 (88, 224)	0.12
Highest uric acid, mmol/l[a]	0.39 (0.36, 0.42)	0.43 (0.36, 0.48)	0.19
Highest ALAT, U/l[a]	72 (48, 162)	43 (21, 91)	0.84
Treatment (intravenously)			
Magnesium sulphate, % (n)	82.6 (19)	86.6 (58)	0.64
Antihypertensives,% (n)	69.6 (16)	68.7 (46)	0.94

Data are presented as valid percentage (n), [a]median (IQR) or as [b]mean (sd).

7

Maternal hypertensive disorders during pregnancy and childhood asthma. The Generation R Study

F.A. Wilmink

H.T. den Dekker

J.C. de Jongste

I.K.M. Reiss

V.W.V. Jaddoe

E.A.P. Steegers

L. Duijts

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Abstract

Objective

To examine the associations of maternal blood pressure and hypertensive disorders in pregnancy with the risk of lower lung function, wheezing and asthma in childhood.

Methods

In a population-based prospective cohort study (n=4,894 mother-child pairs) we measured maternal blood pressure in early, mid and late pregnancy. Information about gestational hypertension and preeclampsia was obtained from medical records. At age 10 years, spirometry was done in the children. Current wheezing and current asthma in children aged 10 years were assessed by parental questionnaires.

Results

We observed consistent associations of higher maternal blood pressure in early pregnancy and lower child FEV_1/FVC (Z-score (95% CI) -0,03 (-0,05, -0,01)), and a higher risk for current wheezing and current asthma in the child in late pregnancy (odds ratios (95% CI): 1.07 (1.02, 1.12), 1.06 (1.00, 1.11), respectively). Maternal hypertensive complications during pregnancy were not related to child lung function, current wheezing or asthma.

Conclusion

Higher blood pressure in pregnant women was associated with lower lung function and increased risks of current wheezing and current asthma in their offspring. The associations may be trimester specific.

Introduction

Maternal hypertensive disorders during pregnancy, including preeclampsia, are associated with adverse neonatal outcomes such as a 2 to 5-fold increased risk of preterm birth or low birth weight.[1-3] Lower gestational age and birth weight across the full range are independently associated with a higher risk for lower lung function and asthma in later life.[4-8] Next to this indirect effect via preterm birth and low birth weight, maternal hypertensive disorders during pregnancy could also have a direct effect on respiratory morbidity through disturbed placental function and an altered angiogenic status, affecting lung growth and lung maturation.[9-12] Hospital-based studies observed that preeclampsia is associated with a two- to four-fold increased risk of bronchopulmonary dysplasia. [9,13-16] Hypertension usually is accompanied with poorer maternal vascular health, which can disturb placental function leading to an anti-angiogenic status. We hypothesized that on a population-based level more common, small adverse changes in maternal blood pressure during pregnancy or gestational hypertension might increase the risk of chronic obstructive lung diseases such as asthma in childhood. A former prospective cohort study found no associations of preeclampsia with lower lung function and early wheezing.[17] Pre-existing hypertension was associated with an up to1.6 fold increased risk of childhood wheezing and asthma.[17] Results are inconsistent, mostly due to methodological issues. Furthermore, it is unclear if a critical window exists during pregnancy in which maternal blood pressure changes might affect respiratory morbidity in children, and what the potential influence is of lifestyle, socio-economic factors, growth and atopy.

Therefore, we examined the associations of maternal blood pressure during early, mid and late pregnancy, gestational hypertension, and preeclampsia with the risks of lower lung function, wheezing and childhood asthma in a population-based prospective cohort study among 4,894 children. We also explored if any association could be explained by lifestyle and socio-economic factors, or modified by child's gestational age, weight at birth or atopic mechanisms.

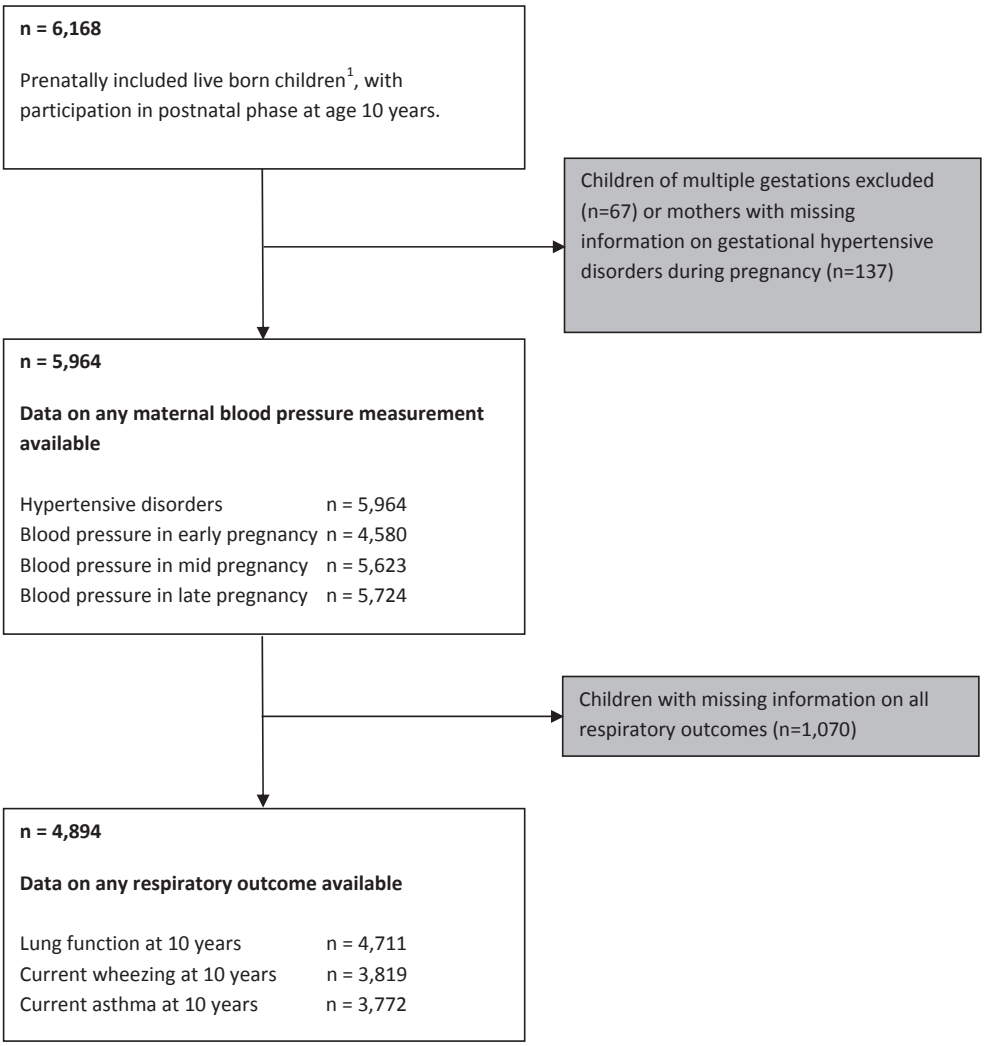
Methods

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards.[18] The study has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Centre in Rotterdam, the Netherlands (MEC 40020.078.12/2012/165). Written informed consent was obtained from either parents or legal guardians. For the current study we used the data of women enrolled during pregnancy with a live born child who participated in the postnatal phase at 10 years of age

and included only one child per mother (n=6,168). After applying exclusion criteria, our final population for analysis existed of n=4,894 children (Figure 1).

Figure 1. Flow chart of participants included for analysis



Maternal hypertensive disorders during pregnancy

Maternal systolic and diastolic blood pressures in early (<18 weeks), mid (18-25 weeks) and late pregnancy (>25 weeks) were measured with the validated Omron 907® automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands), as described previously.[19] Evidence of gestational hypertension or preeclampsia based on information in the clinical records was crosschecked with the original hospital charts. Details of these procedures have been described elsewhere.[20] Gestational hypertension and preeclampsia were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria and according to those of the American College of Obstetricians and Gynaecologists (ACOG)[21,22]. Haemolysis Elevated Liver enzymes and Low Platelet syndrome (HELLP syndrome) was defined as thrombocytes less than 100 × 10^9/L, both aspartate aminotransferase and alanine aminotransferase more than 70 U/L, and lactate dehydrogenase more than 600 U/L.[23]

Childhood lung function and asthma

Children visited our dedicated research centre at a mean age of 9.8 years (range 8.6, 12.0 years). Spirometry was performed according to the American Thoracic Society and European Respiratory Society recommendations.[24] Lung function variables tested were forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), FEV_1/FVC, mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) and forced expiratory flow at 75% of FVC (FEF_{75}). All spirometric variables were converted into sex-, height-, age-, and ethnicity-adjusted z-scores according to the Global Lung Initiative reference data.[25] Current wheezing, physician diagnosed asthma ever and use of inhaled medication (bronchodilators, corticosteroids) in the past 12 months was assessed by parental questionnaire at age 10 years. Current asthma was defined as physician diagnosed asthma ever, with either current wheezing or the use of inhaled medication in the past 12 months. Response rate for questionnaires ranged from 68 to 75%.

Covariates

Information on maternal age, ethnicity, pre-pregnancy body mass index (BMI), educational level, parity, psychological distress, smoking habits during pregnancy, folic acid use and a history of asthma and atopy were collected by multiple questionnaires during pregnancy. Child's sex, birth weight, gestational age and mode of delivery were obtained from midwife and hospital records at birth. Child's ethnicity was defined by country of birth of the parents and classified according to the GLI definitions.[25] Inhalant allergic sensitization for *Dermatophagoides pteronyssinus*, 5-grass mixture (*Dactylis glomerata, Festuca pratensis,*

Lolium perenne, Phleum pratense, Poa pratensis), bird (*Betula verrucosa*), cat (*Felis catus*) and dog (*Canis familiaris*) (ALK-Abelló B.V., Almere, The Netherlands) was measured by skin prick test using the 'scanned area method' at a median age of 9.7 years (range 8.6, 12.0 years).[26] Information on eczema was collected by a questionnaire at age 10 years.

Statistical analysis

We used multivariate linear and binary logistic regression models to examine the associations of maternal blood pressure and hypertensive disorders during pregnancy with lung function, current wheezing or current asthma. Selection of covariates was based on literature or if the effect estimate of the unadjusted analyses changed ≥10% when additionally was adjusted for a covariate. First, models were adjusted for child's sex only (crude analysis). Second, we adjusted for potential lifestyle and socio-economic confounders including maternal age, ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid and child's sex, which we considered the main model. Third, we adjusted our main model for intermediates including maternal psychological distress during pregnancy, mode of delivery, and child's gestational age at delivery and birth weight. Finally, we applied conditional regression analyses to our main model, to take account for the correlation between blood pressures measured at multiple time points in pregnancy.[27] Missing data for covariates within the population for analysis was <20%, except for maternal folic acid use (22.4%), inhalant allergies of the child (30.8%), and current eczema (21.0%). Missing data from covariates were imputed to reduce bias and improve efficiency using the Markov Chain Monte Carlo method to select the most likely value for a missing response.[28] Ten new datasets were constructed. No major differences in the magnitude or direction of the effect estimates were observed between analyses with imputed missing data and complete cases only. We only present the results based on imputed datasets. The modifying effects of a maternal history of asthma and atopy, children's gestational age at birth, birth weight, inhalant allergic sensitization and current eczema were tested by adding them as product terms with blood pressure and gestational hypertensive disorders in the models. All measures of association are presented as z-score differences for lung function and odds ratios (ORs) for current wheezing or asthma, with corresponding 95% confidence intervals (95% CI). Analyses were performed using SPSS version 21.0 for Windows (IBM, Chicago, Ill, USA).

Results

Maternal and child characteristics are presented in Table 1. Of n=4,894 women eligible for analyses, 206 (4.2%) had gestational hypertension and 1.9% (n=91) preeclampsia or HELLP syndrome. Current wheezing and asthma were reported in 18.1% (n=692) and 8.3% (n=313) at age 10 years. Loss-to-follow-up analysis showed that mothers not included in the analysis were younger, lower educated, smoked more and used less folic acid before and during pregnancy, had more psychological distress and were more often of non-Western origin. Their children were more often male, were born at a shorter gestational age with a lower birth weight (Table S1).

Maternal blood pressure and hypertensive disorders during pregnancy and child lung function

Crude analyses showed that higher maternal blood pressures in early, mid and late pregnancy were associated with lower FEV_1/FVC and FEF_{75} (Table S2). After adjusting for lifestyle and socio-economic factors, higher maternal blood pressure in early pregnancy (per 5 mmHg) was associated with lower FEV_1/FVC (Z-score (95% CI) -0.02 (-0.04, -0.01), -0.02 (-0.04, -0.01) and -0.03 (-0.05, -0.01), respectively), higher diastolic pressure in mid pregnancy with lower FEV_1 (-0.02 (-0.04, -0.00)), and higher systolic pressure in late pregnancy with lower FEV_1/FVC (-0.01 (-0.03, -0.00)) (Table 2). Effect estimates attenuated into non-significant when we additionally adjusted for intermediating factors (Table S3). Especially when adjusting for psychological distress during pregnancy and, to a lesser extent, when adjusting for gestational age at birth. Only the associations of maternal blood pressure in early pregnancy with FEV_1/FVC remained significant when conditional analyses adjusted for lifestyle and socio-economic factors were applied (Figure 2 and Table S4). Hypertensive disorders were not associated with any lung function measure.

Maternal blood pressure and hypertensive disorders during pregnancy and current wheezing or current asthma

Crude analyses showed that higher maternal blood pressure in early and late pregnancy was associated with an increased risk of current wheezing and current asthma (Table S5). After adjusting for lifestyle and socio-economic factors, higher systolic and mean arterial pressure in early pregnancy and a higher diastolic and mean arterial pressure in late pregnancy were associated with an increased risk of current wheezing (ORs (95% CI) 1.05 (1.01, 1.10), 1.07 (1.01, 1.13), 1.06 (1.01, 1.11) and 1.06 (1.01, 1.12), respectively). A higher systolic blood pressure in late pregnancy was associated with an increased risk of current asthma (1.06 (1.00, 1.12), Table 3). After additionally adjusting for intermediating factors, only the association of a higher systolic pressure in early pregnancy with a higher risk for current

wheezing at the age of 10 years remained significant (1.05 (1.00, 1.09), Table S6). When conditional analyses were applied, associations of maternal blood pressure with current wheezing attenuated into non-significant. The association of a higher systolic pressure with a higher risk for current asthma remained consistent (1.16 (1.01, 1.33), Figure 2 and Table S7). Hypertensive disorders were not associated with current wheezing or current asthma. For all associations, we did not observe modifying effects of maternal history of asthma and atopy, child's gestational age at birth, birth weight, inhalant allergic sensitization and current eczema (p-values for interaction > 0.05).

Table 1. Baseline characteristics of mothers and their children.

Maternal characteristics	**n=4,894**
Age (years)[1]	30.7 (4.8)
Ethnicity, western, % (n)	65.4 (3,201)
Body mass index (kg/m^2)[2]	23.7 (18.8, 35.7)
Educational level, higher, % (n)	49.2 (2,408)
Nulliparity, yes, % (n)	62.3 (3,049)
Psychological distress, yes	9.2 (448)
Smoking during pregnancy, % (n)	
No	74.6 (3,650)
Yes – stopped	9.5 (465)
Yes – continued	15.9 (779)
Folic acid use, % (n)	
No	22.5 (1,101)
Start before 10 weeks	32.5 (1,593)
Preconception start	45.0 (2,200)
Caesarean section, yes, % (n)	13.0 (637)
History of asthma or atopy, yes, % (n)	41.1 (2,013)
Blood pressure	
Early pregnancy (weeks)[2]	13.2 (10.5, 17.5)
SBP (mmHg)[1]	116 (12)
DBP (mmHg)[1]	69 (9)
MAP (mmHg)[1]	84 (9)
Mid pregnancy (weeks)[2]	20.5 (18.6, 23.3)
SBP (mmHg)[1]	117 (12)

Tabel 1. Continued

Maternal characteristics	**n=4,894**
DBP (mmHg)[1]	67 (9)
MAP (mmHg)[1]	84 (9)
Late pregnancy (weeks)[2]	30.4 (28.5, 32.9)
SBP (mmHg)[1]	119 (12)
DBP (mmHg)[1]	69 (9)
MAP (mmHg)[1]	85 (9)
Hypertensive disorder, % (n)	
Gestational hypertension	4.2 (206)
Preeclampsia / HELLP[7]	1.9 (91)
Child characteristics	
Sex, female, % (n)	50.4 (2,467)
Birth weight (grams)[1]	3428 (553)
Gestational age at birth (weeks)[2]	40.1 (35.7, 42.4)
Inhalant allergies, yes, % (n)	34.2 (1,673)
Current eczema, yes, % (n)	9.0 (439)
Spirometry	
FEV_1 (L/s)[1]	2.01 (0.30)
FVC (L)[1]	2.33 (0.37)
FEV_1/FVC (s)[1]	0.87 (0.06)
FEF_{25-75} (L/s)[1]	2.69 (0.65)
FEF_{75} (L/s)[1]	1.14 (0.35)
Ever asthma, % (n)	9.7 (368)
Current wheezing, % (n)	18.1 (692)
Current asthma, % (n)	8.3 (313)

Values are valid percentages (absolute numbers), [1]means (SD) or [2]medians (95% range) based on imputed data. Data on maternal blood pressure, hypertensive disorders, lung function, wheezing and asthma were not imputed.

Table 2. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.00, 0.03)	**-0.02 (-0.04, -0.01)***	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
DBP	-0.02 (-0.04, 0.00)	-0.00 (-0.02, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
MAP	-0.01 (-0.03, 0.00)	0.01 (-0.01, 0.02)	**-0.03 (-0.05, -0.01)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
Mid pregnancy					
SBP	0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.00)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	**-0.02 (-0.04, -0.00)***	-0.01 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
MAP	-0.02 (-0.03 ,0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
Late pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.01, 0.02)	**-0.01 (-0.03, -0.00)***	0.01 (-0.01, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.02 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	0.01 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
MAP	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.00)	0.01 (-0.02, 0.03)	-0.01 (-0.03, 0.01)
Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.05 (-0.11, 0.20)	0.44 (-0.10, 0.19)	0.02 (-0.12, 0.17)	0.01 (-0.16, 0.18)	0.02 (-0.13, 0.16)
PE/ HELLP	-0.16 (-0.38, 0.06)	-0.10 (-0.31, 0.11)	-0.05 (-0.27, 0.16)	-0.11 (-0.35, 0.14)	-0.10 (0.31, 0.11)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry are standardized by fetal gender, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's gender. *p-value < 0.05.

Figure 2. Associations of maternal blood pressure during pregnancy with lung function, current wheezing and current asthma at age 10 years, conditional regression analyses

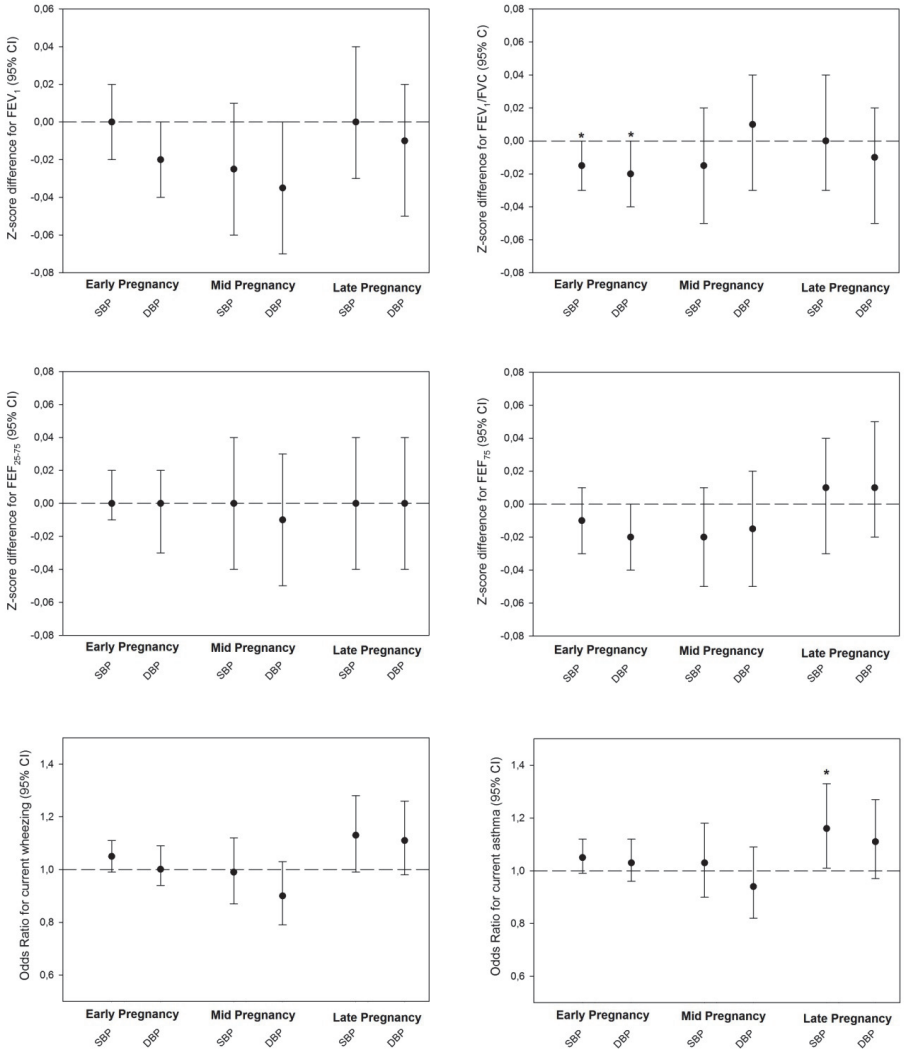


Table 3. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.05 (1.01, 1.10)***	1.04 (0.98, 1.10)
DBP	1.05 (0.99, 1.11)	1.03 (0.96, 1.11)
MAP	**1.07 (1.01, 1.13)***	1.04 (0.97, 1.13)
Mid pregnancy		
SBP	1.00 (0.96, 1.04)	1.00 (0.95, 1.05)
DBP	1.01 (0.97, 1.07)	0.95 (0.89, 1.02)
MAP	1.01 (0.96, 1.06)	0.96 (0.90, 1.04)
Late pregnancy		
SBP	1.04 (1.00, 1.08)	**1.06 (1.00, 1.12)***
DBP	**1.06 (1.01, 1.11)***	1.02 (0.96, 1.10)
MAP	**1.06 (1.01, 1.12)***	1.05 (0.98, 1.13)
Hypertensive disorder		
None	*Reference*	*Reference*
GH	0.95 (0.63, 1.42)	0.99 (0.57, 1.73)
PE/ HELLP	0.70 (0.36, 1.39)	0.80 (0.32, 2.01)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's gender. *p-value < 0.05.

Discussion

In this population-based prospective cohort study we observed that higher maternal blood pressure in early pregnancy was associated with a lower FEV_1/FVC in the child at 10 years, and higher pressure in late pregnancy was associated with a higher risk for current wheezing and current asthma in the child, taking lifestyle and socioeconomic factors into account. Results did not change after conditional analysis in which the measurements at multiple time points during pregnancy were taken into account. Hypertensive disorders during pregnancy were not associated with lung function, current wheezing or current asthma. Results were not modified by atopic mechanisms, gestational age or birth weight Z-score.

Comparison with previous studies

Currently, there are no studies available to compare the results of our association analyses between maternal blood pressure measurements during multiple time points in pregnancy and respiratory outcome measures in the child. Only one prospective cohort study assessed associations of maternal hypertension before pregnancy, gestational hypertension and preeclampsia with lung function, wheezing or asthma in children at 18 months and age 7-9 years.[17] They observed that pre-existing hypertension, and not gestational hypertension or preeclampsia, may be a risk factor for childhood wheezing and asthma with ORs (95% CI): 1.63 (1.16, 2.31) and 1.34 (1.00-1.79), respectively.[17] Our study did show that individual maternal blood pressure measures during different periods of pregnancy had distinctive associations with lower lung function and current wheezing or asthma. However, we could not confirm such associations with gestational hypertension or preeclampsia, most probably due to the low prevalence. Early and late pregnancy seemed critical windows, as we did not find any associations with maternal blood pressure measurements in mid-pregnancy.

Other population-based studies demonstrated inconsistent associations of gestational hypertension or preeclampsia with altered lung function or asthma in early or late childhood.[29-33] A pooled analysis of 14 birth cohorts (n = 85,509) demonstrated that preeclampsia is associated with an increased risk for wheezing between birth up to 12-24 months, however, they did not found associations for other hypertensive disorders. One historically matched cohort study might have lacked power due to the small sample size (n=617) and one study sub dived complications of pregnancy in "maternal related" (including hypertension and preeclampsia) versus "uterus related" (including placental insufficiency and intra-uterine growth restriction). Only "uterus related" complications were associated with an increased risk of bronchial obstruction in the first 2 years, and asthma at age 4 year. However both, similarly as intra-uterine growth restriction, can be seen as a consequence of placental insufficiency.[34] Additionally, adjusting outcome measures for intermediates, rather than for confounders alone, can influence results and therefore might cause inconsistent

associations.[32,35,36] A Danish registry-based cohort study (n=1,698,638) showed a higher risk for asthma in children born to mothers with preeclampsia (n= 62,728), (adjusted incidence rate ratio (95%CI), 1.09 (1.05, 1.12)).[31] This risk increased when the duration of preeclampsia was ≥ 14 days, (1.17 (1.11, 1.25)).[31] Finally, associations of preeclampsia with severe respiratory morbidity are mostly observed in cohorts of very preterm neonates. Our study consisted of a relatively healthy population with a relatively low prevalence of gestational hypertension or preeclampsia. However, the effect estimates for the associations of higher maternal blood pressure in early pregnancy with lung function, and higher maternal blood pressure in late pregnancy with a higher risk for wheezing and asthma were consistent and might have a potential large impact on a population level.

Potential underlying mechanisms

Preeclampsia is strongly associated with (iatrogenic) preterm birth and lower birth weight, and subsequently with wheezing, asthma and lower lung function[2]. Next to this, one could hypothesize that there is also an association of hypertensive disorders with childhood respiratory morbidity due to an underlying altered angiogenic status during pregnancies, and perhaps impaired fetal lung development. A prospective cohort study (n=69 preterm infants) showed that an anti-angiogenic status of the mother is reflected in the neonate, as neonates of mothers with preeclampsia had higher cord blood sFlt-1 and lower PLGF and VEGF levels.[37] A high concentration of endostatin, an anti-angiogenic growth factor, in human cord plasma predicts the development of bronchopulmonary dysplasia in very low birth weight infants.[12] In animal studies, inhibiting of VEGF resulted in reduced alveolarisation and persistent abnormalities of pulmonary vascular structures.[10,11] Additionally, administering of sFlt into the amnionic sac of pregnant rats, at a stage of lung development corresponding 24 to 26 weeks of human gestation, decreased VEGF signalling and increased apoptosis. Subsequently, reduced alveolarisation and pulmonary vascular growth was observed during infancy of the offspring.[38] We did find associations with higher maternal blood pressures in early and late pregnancy, but not with gestational hypertension disorders at term. This might be explained by a relatively small sample size, but also by a different angiogenic status in women with gestational hypertensive disorders before and at term. Whether this hypothesis applies to less extreme conditions in a relatively healthy cohort remains to be shown.

Strengths and limitations

The strength of the current study is the population-based prospective cohort design from early pregnancy onwards, with detailed information on maternal and child characteristics and validated maternal blood pressure measures throughout all stages of pregnancy. Spirometry is the preferred and robust method to assess lung function.[39] Some limitations

need to be addressed. Mothers who were lost to follow up showed marked differences with mothers included in our study population. This could have lead to selection bias if associations of maternal blood pressure and hypertensive disorders with child lung function, wheezing and asthma would have been different between the groups included and lost to follow-up. Our late pregnancy measurements were rather early (median 30.4 weeks) and this could have resulted in underestimated associations, as maternal blood pressures usually rise during the third trimester of pregnancy. However, we examined gestational hypertensive disorders at the end of pregnancy, and these were not associated with respiratory morbidity of the child. Part of our respiratory data were self-reported by questionnaires, and therefore we cannot exclude under- or overestimations of the observed associations.

In conclusion, our study shows that higher blood pressures in pregnancy were associated with lower FEV_1/FVC, and increased risks of current wheezing and current asthma in children at the age of 10 years. We did not show associations of specific gestational hypertensive disorders with childhood respiratory morbidity.

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Table S1. Comparison of the study population with individuals lost to follow-up.

Original data	Included	Lost to follow-up	P-value
Maternal characteristics	**n=4,984**	**n=1,070**	
Age (years)[1]	30.7 (4.8)	27.8 (5.5)	**<0.001**
Ethnicity, western	65.9 (3,173)	37.0 (362)	**<0.001**
Missing, % (n)[2]	*1.7 (81)*	*8.6 (92)*	
Body mass index (kg/m^2)[3]	23.7 (18.8-35.6)	24.6 (18.5-37.0)	**<0.001**
Missing, % (n)[2]	*0.6 (30)*	*1.21 (13)*	
Educational level, higher	50.1 (2,342)	19.8 (178)	**<0.001**
Missing, % (n)[2]	*4.5 (222)*	*15.8 (169)*	
Nulliparity	62.5 (3,046)	51.3 (542)	**<0.001**
Missing, % (n)[2]	*0.5 (22)*	*1.21 (13)*	
Psychological distress, yes	8.1 (331)	17.5 (121)	**<0.001**
Missing, % (n)[2]	*16.1 (790)*	*35.5 (380)*	
Smoking during pregnancy			**<0.001**
No	75.4 (3,334)	66.7 (607)	
Yes – stopped	8.4 (409)	6.7 (61)	
Yes – continued	13.9 (678)	26.6 (242)	
Missing, % (n)[2]	*9.7 (473)*	*15.0 (160)*	
Folic acid use			**<0.001**
No	20.9 (793)	47.2 (345)	
Start before 10 weeks	32.2 (1,224)	28.3 (207)	
Preconception start	46.9 (1,781)	24.5 (179)	
Missing, % (n)[2]	*22.4 (1,096)*	*31.7 (339)*	
Caesarean section, yes	12.8 (582)	12.0 (117)	0.52
Missing, % (n)[2]	*7.2 (351)*	*9.1 (97)*	
History of asthma or atopy, yes	40.0 (1,625)	36.6 (287)	0.08
Missing, % (n)[2]	*17.0 (830)*	*26.7 (286)*	
Hypertensive disorder			0.88
Gestational hypertension	4.2 (206)	3.8 (41)	
Preeclampsia / HELLP	1.9 (91)	2.1 (22)	
Child characteristics			
Sex, female	50.4 (2,467)	47.6 (509)	0.10
Gestational age at birth (weeks)[3]	40.1 (35.7-42.4)	40.1 (36.3-42.3)	0.38
Birth weight (grams)[1]	3428 (553)	3389 (548)	0.04
Inhalant allergies, yes	33.8 (1,147)	37.1 (33)	0.57
Missing, % (n)[2]	*30.8 (1,505)*	*91.7 (981)*	

Values are valid percentages (absolute numbers), [1]means (SD), [2]total percentages (absolute numbers) or [3]medians (95% range). Differences in baseline characteristics were tested using Student's *t*, Mann-Whitney *U* and Chi-square tests.

Table S2. Crude analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	FVC	FEV_1/FVC	FEF_{25-75}	FEF_{75}
	Z-score (95%CI)	Z-score (95%CI)	Z-score (95%CI)	Z-score (95%CI)	Z-score (95%CI)
Early pregnancy					
SBP	-0.00 (-0.17, 0.01)	0.01 (-0.00, 0.03)	**-0.03 (-0.04, -0.02)***	-0.01 (-0.02, 0.01)	**-0.02 (-0.03, -0.01)***
DBP	-0.01 (-0.28, 0.01)	0.01 (-0.01, 0.02)	**-0.03 (-0.05, -0.01)***	-0.01 (-0.03, 0.01)	**-0.02 (-0.04, -0.00)***
MAP	-0.01 (-0.03, 0.01)	0.01 (-0.01, 0.03)	**-0.04 (-0.05, -0.02)***	-0.01 (-0.03, 0.01)	**-0.03 (-0.04, -0.01)***
Mid pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.01 (-0.01, 0.02)	**-0.02 (-0.03, -0.01)***	-0.01 (-0.02, 0.01)	**-0.02 (-0.03, -0.01)***
DBP	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.01)	-0.02 (0.03, 0.00)	0.00 (-0.02, 0.02)	-0.02 (-0.03, -0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.01, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.02, 0.02)	**-0.02 (-0.04, -0.00)***
Late pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	**-0.02 (-0.03, -0.01)***	-0.01 (-0.02, 0.01)	**-0.02 (-0.03, -0.01)***
DBP	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.01)	-0.02 (-0.03, -0.00)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.01, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.02, 0.02)	**-0.02 (-0.03, 0.00)***
Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.05 (-0.10, 0.20)	0.07 (-0.07, 0.22)	-0.03 (-0.18, 0.11)	-0.03 (-0.20, 0.13)	-0.04 (-0.18, 0.10)
PE/ HELLP	-0.17 (-0.39, 0.06)	-0.09 (-0.03, 0.12)	-0.08 (-0.30, 0.13)	-0.12 (-0.36, 0.13)	-0.12 (-0.33, 0.09)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry values are standardized for fetal gender, age, ethnicity and height. Models were adjusted for child's gender. *p-value < 0.05.

Table S3. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years, additionally adjusted for intermediates

	Spirometry				
	FEV_1	FVC	FEV_1/FVC	FEF_{25-75}	FEF_{75}
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.02)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.01 (-0.04, 0.01)	-0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.00)	-0.01 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.00)	-0.00 (-0.03, 0.02)	-0.01 (-0.03, 0.01)
Mid pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
MAP	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Late pregnancy					
SBP	-0.00 (-0.02, 0.02)	-0.01 (-0.01, 0.02)	-0.01 (-0.03, 0.00)	0.01 (-0.01, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	0.01 (-0.02, 0.03)	0.00 (-0.02, 0.02)
MAP	-0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)	0.01 (-0.02, 0.03)	-0.00 (-0.02, 0.02)
Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.11 (-0.06, 0.27)	0.10 (-0.05, 0.26)	0.02 (-0.14, 0.18)	0.02 (-0.16, 0.21)	0.03 (-0.12, 0.19)
PE/ HELLP	-0.03 (-0.27, 0.22)	-0.03 (-0.26, 0.21)	0.03 (-0.21, 0.26)	0.02 (00.25, 0.30)	-0.05 (-0.28, 0.18)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry values are standardized for fetal gender, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use, child's gender and additionally for possible intermediates: psychological distress during pregnancy, mode of delivery, gestational age at delivery and birth weight Z-score. *p-value < 0.05.

Table S4. Conditional analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	0.00 (-0.02, 0.02)	0.01 (-0.00, 0.03)	**-0.02 (-0.03, -0.00)***	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.01)
DBP	-0.02 (-0.04, 0.00)	-0.01 (-0.02, 0.02)	**-0.02 (-0.04, -0.00)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	**-0.03 (-0.05, -0.01)***	0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.00)
Mid pregnancy					
SBP	-0.02 (-0.06, 0.01)	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.02)	-0.00 (-0.04, 0.04)	-0.02 (-0.05, 0.01)
DBP	-0.03 (-0.07, 0.00)	-0.03 (-0.07, 0.00)	0.01 (-0.03, 0.04)	-0.01 (-0.05, 0.03)	-0.02 (-0.05, 0.02)
MAP	-0.03 (-0.07, 0.00)	-0.03 (-0.06, 0.00)	0.01 (-0.04, 0.03)	-0.01 (-0.05, 0.03)	-0.02 (-0.05, 0.01)
Late pregnancy					
SBP	0.00 (-0.03, 0.04)	0.00 (-0.03, 0.04)	0.00 (-0.03, 0.04)	0.00 (-0.04, 0.04)	0.01 (-0.03, 0.04)
DBP	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.02)	0.01 (-0.03, 0.04)	0.00 (-0.04, 0.04)	0.01 (-0.02, 0.05)
MAP	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	0.01 (-0.03, 0.04)	0.00 (-0.04, 0.04)	0.01 (-0.02, 0.05)

Values reflect the change in Z-score (95% confidence interval) from conditional regression models. The Z-scores of spirometry values are standardized for fetal gender, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's gender. *p-value < 0.05.

Table S5. Crude analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.06 (1.02, 1.10)***	1.04 (0.99, 1.10)
DBP	**1.06 (1.01, 1.12)***	1.04 (0.97, 1.12)
MAP	**1.08 (1.02, 1.13)***	1.05 (0.98, 1.13)
Mid pregnancy		
SBP	1.01 (0.98, 1.05)	1.01 (0.96, 1.060
DBP	1.04 (0.99, 1.08)	0.97 (0.91, 1.04)
MAP	1.03 (0.99, 1.08)	0.99 (0.92, 1.05)
Late pregnancy		
SBP	**1.04 (1.01, 1.08)***	**1.06 (1.00, 1.11)***
DBP	**1.07 (1.02, 1.12)***	1.03 (0.97, 1.10)
MAP	**1.07 (1.02, 1.12)***	1.05 (0.99, 1.12)
Hypertensive disorder		
None	*reference*	*reference*
GH	1.03 (0.70, 1.53)	1.06 (0.61, 1.82)
PE/ HELLP	0.75 (0.38, 1.48)	0.85 (0.34, 2.12)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for child's gender. *p-value < 0.05.

Table S6. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years, additionally adjusted for intermediates.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.05 (1.00, 1.09)***	1.05 (0.99, 1.12)
DBP	1.05 (0.99, 1.11)	1.04 (0.96, 1.13)
MAP	1.06 (1.00, 1.12)	1.06 (0.97, 1.15)
Mid pregnancy		
SBP	1.00 (0.96, 1.04)	0.99 (0.93, 1.05)
DBP	1.02 (0.97, 1.08)	0.96 (0.89, 1.03)
MAP	1.01 (0.96, 1.07)	0.97 (0.89, 1.04)
Late pregnancy		
SBP	1.04 (0.99, 1.08)	1.06 (1.00, 1.12)
DBP	1.04 (0.99, 1.10)	1.0 (0.93, 1.07)
MAP	1.05 (1.00, 1.11)	1.03 (0.95, 1.11)
Hypertensive disorder		
None	*reference*	*reference*
GH	1.00 (0.65, 1.53)	1.02 (0.57, 1.84)
PE/ HELLP	0.71 (0.35, 1.44)	0.75 (0.29, 1.97)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use, child's gender and additionally for possible intermediates: psychological distress during pregnancy, mode of delivery, gestational age at delivery and birth weight Z-score. *p-value < 0.05.

Table S7. Conditional analysis of maternal blood pressure during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	Current asthma
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	1.05 (0.99, 1.11)	1.05 (0.99, 1.12)
DBP	1.01 (0.94, 1.09)	1.03 (0.96, 1.12)
MAP	1.04 (0.96, 1.12)	1.06 (0.97,1.14)
Mid pregnancy		
SBP	0.99 (0.87, 1.12)	1.03 (0.90, 1.18)
DBP	0.90 (0.79, 1.03)	0.94 (0.82, 1.09)
MAP	0.93 (0.81, 1.06)	0.97 (0.84, 1.12)
Late pregnancy		
SBP	1.13 (0.99, 1.28)	**1.16 (1.01, 1.33)***
DBP	1.11 (0.98, 1.26)	1.11 (0.97, 1.27)
MAP	1.13 (1.00, 1.29)	**1.15 (1.00, 1.32)***

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's gender. *p-value < 0.05.

PART 3

General Discussion, Summary and Addendum

8

General Discussion

Timing of delivery in the term period

Optimal timing of elective deliveries and more importantly elective caesarean sections (CSs), has been a subject of research and reviews over the past decade.[1-3] With increasing gestational age until an amenorrhoea of 39^{+0} weeks, the risk for neonatal morbidity, especially for respiratory morbidity, decreases significantly. Therefore, we recommend that all elective CSs should be planned from 39^{+0} weeks onwards.[3,4] In 2011, the Dutch guideline 'Indication for caesarean section' adapted its advice to preferably not perform an elective (or planned) CS before 39 completed weeks of gestation. In 2013 the American Committee Of Gynaecologists redefined the definition of the term period of pregnancy into early term (37^{+0}-38^{+6} weeks), full term (39^{+0}-40^{+6}weeks), late term (41^{+0}-41^{+6} weeks) and post term (beyond 42^{+0} weeks), emphasizing the risk difference of adverse neonatal outcome, which is significantly higher early term compared to full term.[5,6] The Dutch Society of Obstetricians and Gynaecologists should apply this definition to emphasize the importance of optimal timing of elective deliveries regarding neonatal outcome.

Risks of neonatal morbidity can be divided into short term and long term. Risks in short-term morbidity were already discussed in chapter 2. There is also an increasing number of publications on long-term follow up. A large population based cohort study (n=18,818) assessing the dose-response effects of early term births (37^{+0}-38^{+6} weeks) compared to full term births and the risk for asthma at the age of 5 years, identified an adjusted OR (95%CI) of 1.4 (1.1-1.8).[7] Additionally, a large retrospective cohort (n=407,503) identified a 'dose-response' relation between gestational age at birth and special educational needs with an OR (95%CI) for early term births (37^{+0}-38^{+6} weeks) compared to full term births of 1.2 (1.1-1.2).[8] A systematic review and meta-analysis of long-term development of early term compared to full term born infants found a risk ratio (95% CI) of 1.8 (1.3-2.3) for the risk for cerebral palsy.[9] A large birth cohort in the United States (n=3,483,496) showed that, besides neonatal morbidity, also the risk for neonatal mortality is higher in early term compared to full term born infants with relative risks (95% CI) of 1.9 (1.8-2.0) at 37 weeks and 1.2 (1.2-1.3) at 38 weeks of gestation.[10]

Summarizing, all these large cohort studies present worse outcomes for early term (37^{+0}-38^{+6} weeks) compared to full term (39^{+0}-40^{+6} weeks) born infants. However, these large cohort studies did not limit their study population to elective deliveries only. Therefore, underlying medical indications for early term deliveries may cause selection bias and may partly explain the adverse outcomes found early term compared to full term.

Fetal lung maturation with antenatal corticosteroids

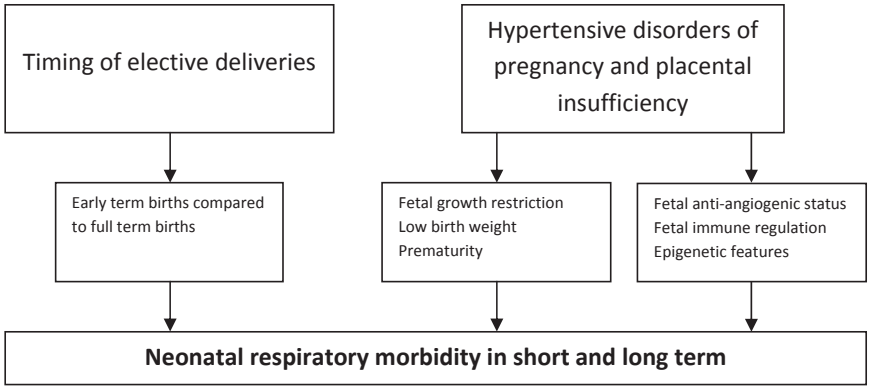
A strategy for minimisation of short-term respiratory morbidity at term is administration of antenatal corticosteroids to women with an elective CS between 37^{+0} and 39^{+0} weeks of gestation.[11] A randomized clinical trial, comparing all women undergoing a CS at term with and without prior administration of antenatal corticosteroids, showed an overall decrease of admittance to special baby care units, RR (95% CI) of 0.46 (0.23-0.93). However, when diagnoses of respiratory problems for admittance (transient tachypnea of the newborn (TTN), or respiratory distress syndrome (RDS)) were analysed separately, the decrease was not significant.[12,13] Follow-up of the treatment group into childhood did not show less asthma or less hospital admissions as compared to the control group. However, school assessment of the treatment group showed these children to be significantly more often in the lowest quartile of academic ability.[14] No objective testing, however, of academic ability was performed within this trial. When outcome measures of national standardized assessments were compared, no significant differences were found between the treatment and the control group. The trends, however, were in favour of the latter.[14,15] There is a biological plausible explanation that the use of antenatal synthetic corticosteroids (usually betamethasone sodium phosphate and dexamethasone phosphate) can adversely influence neurodevelopmental outcomes. Synthetic corticosteroids are poorly inactivated by 11beta-Hydroxysteroid Dehydrogenase-2 (11beta-HDS-2), which normally protects the foetus from high levels of cortisol. This may cause an (too) early switch from growth and proliferation to differentiation and maturation in the brain, which could lead to adverse neurodevelopmental outcome in the long term.[15,16]

Maternal hypertensive disorders and fetal lung development

Next to the influence of timing of delivery, neonatal (respiratory) morbidity in short and in long term could be the (in)direct result of maternal complications during pregnancy. Several publications showed an effect of preeclampsia mediated through preterm birth, fetal growth restriction and low birth weight.[17,18] Reduced airway growth and small airway size accompanied with low birth weight, even at term, is associated with impaired lung function in childhood.[17,19] The most important late-stage events in the fetal lungs are the formation of alveoli and an integrated capillary network combined with increasing production of surfactant by pneumocytes type II.[20] Hypertensive disorders, causing an anti-angiogenic status, can affect this fetal lung growth and development of lung vasculature. So far, the expertise in this field of research consists mainly of laboratory animal studies and epidemiological association analyses. Additionally, other factors caused by maternal complications during pregnancy could play a role in influencing neonatal respiratory morbidity in short or in long term. A recent publication describes how hypertensive

disorders during pregnancy can disrupt fetal immune regulation and represent a shared risk factor for asthma, eczema and allergy in childhood.[21] Also effects of genetic or epigenetic maternal features could play a role in the association of hypertensive disorders during pregnancy and the higher incidence of wheezing and asthma in these offspring.[21,22]

Figure 1. Different pathways in pregnancy influencing neonatal respiratory morbidity



Recommendations for clinical practice and future research

Using the results of this thesis, recommendations can be made for optimal timing of elective caesarean sections and for counselling women with hypertensive diseases during pregnancy with regard to neonatal lung maturity and respiratory morbidity.

Timing of elective caesarean sections:

- All elective caesarean sections of singleton pregnancies should be planned from 39^{+0} weeks onwards.
- All elective caesarean sections of uncomplicated twin pregnancies, with regard to lung maturity and hospital admission of the neonate, should be planned from 37^{+0} weeks of gestation onwards.

Counselling women with hypertensive disorders during pregnancy:

- Severe preeclampsia is associated with developing BPD in very preterm neonates.

- Higher maternal blood pressures are associated with lower offspring FEV_1/FVC, wheezing and asthma at the age of 10 years.

Future research

Following this thesis, several recommendations for future research can be made to improve clinical decision making and both predicting and improving short and long-term health of future children. First, research should focus on long-term effects of elective early term deliveries, not only in relation to respiratory morbidity but also to long-term health in general as well. Valid evidence of adverse effects for the offspring in the long term is necessary to create awareness for obstetricians in general, as well as for the general public, that negative consequences of elective early term delivery do not outweigh patient preferences or logistical reasons. Secondly, elucidating the pathogenesis of maternal hypertensive disorders, placental dysfunction and a disturbed fetal angiogenic status, and how this may lead to disturbed fetal lung development, can result in therapeutic strategies to improve lung development in utero.

Finally, in line with this thesis, clinical practice and decision making will greatly benefit from accurately **predicting fetal lung maturity (FLM)**.
Firstly, accurate prediction of FLM will be essential to determine the optimal timing of delivery. In cases where the indications to deliver late preterm (34^{+0}-36^{+6}) or early term (37^{+0}-38^{+6}) are not absolute, maternal, fetal and neonatal risks should be weighed and determination of FLM can be helpful. Secondly, valid prediction of FLM could prevent unnecessary exposure to corticosteroids, as currently administration of corticosteroids after 34^{+0} weeks of gestation is increasingly implemented. Administration of antenatal corticosteroids to women at risk for late preterm delivery reduced the rates of severe respiratory complications (number needed to treat, NNT: 25).[23] However, the rate of neonatal hypoglycaemia increased accordingly (24.0% vs. 15.0%).[23] Neonatal hypoglycaemia is associated with impaired neurologic outcome in childhood and results of long-term follow up are yet unknown.[23,24] Finally, in the Netherlands, all preterm births from 32^{+0} weeks of gestation onwards (without any other medical indication why the delivery should take place in a hospital with neonatal intensive care unit (NICU)) can take place in a hospital without a NICU. However, most, but not all, neonates have sufficiently matured lungs from 32^{+0} weeks of gestation onwards. In order to assess FLM, laboratory tests on amniotic fluid, needing invasive amniocentesis, are most commonly used. The purpose of these tests, such as Lecithin/sphingomyelin (L/S) ratio or lamellar body count (LBC), is to estimate the amount of surfactant production which is an indicator of fetal lung maturity.[20] A non-invasive method is available to predict FLM by quantitative texture analysis of fetal ultrasound images, by use of

specifically developed software.[25] The test characteristics for the period 34^{+0} until 38^{+6} weeks of gestation are as follows: sensitivity 62.1%, specificity 91.3%, positive predictive value 27.7%, and negative predictive value 97.8%. This is comparable to the current invasive tests.[26] Currently, a collaboration of obstetricians, the Medical Ultrasound Centre (MUSIC) and neonatologists at the Radboudumc is developing a non-invasive method aiming to improve these test characteristics, especially the sensitivity. MUSIC already has experience with computer-aided ultrasound diagnosis of liver steatosis and adjusted this method to characterize lesions on ultrasound images of breasts.[27,28] The hypothesis is that changes in the fetal lungs, as the formation of alveoli, forming of integrated capillary networks and the increasing production of surfactant, can be measured using quantitative texture analysis. To develop a method with improved sensitivity, in contrast to the already existing method, firstly a standardized preset is developed, turning all post processing features off. The first results, analyzing mean echo level and speckle size of ultrasound images of the proximal fetal lung on the four-chamber level, showed good correlation with gestational age. After developing this software, a clinical study is necessary to link the prediction method with clinical neonatal outcomes. Finally a multicentre study is needed to validate the results.

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9

Summary & Samenvatting

Summary

Fetal lungs develop in different stages throughout the pregnancy and after being born. Lung maturation starts from 24 weeks of gestation onwards with the production of surfactant, increasing every week. Neonatal respiratory morbidity in short term is usually defined as wet lung syndrome/ transient tachypnea of the newborn and as respiratory distress syndrome. The risks for neonatal respiratory morbidity and subsequently transfer rates to the Neonatal Intensive Care Unit (NICU) are significantly higher after a planned caesarean delivery compared to a planned vaginal delivery, even at term. The number of caesarean sections (CSs) is rising worldwide. Caesarean sections can be subdivided into an elective (or planned) CSs and an unplanned or emergency CSs. An elective CS is defined as a CS before spontaneous start of labour, without strict medical indication. As this risk for neonatal respiratory morbidity diminishes significantly with an increase of gestational age until 39^{+0} weeks, an optimal timing of elective CS is important to prevent unnecessary iatrogenic neonatal morbidity.

Part 1 Timing of elective Caesarean Sections

Given above knowledge, the aim of Part 1 of this thesis was to evaluate the number and timing of elective CS in singleton and twin pregnancies in the Netherlands, and to assess neonatal morbidity associated with this timing.

In Chapter 2 we evaluated the number and timing of elective CSs, and associated neonatal morbidity, of singleton pregnancies at term. We showed that, unfortunately, more than half of the neonates were born before 39^{+0} weeks of gestation, and that they were at significantly higher risk for neonatal (respiratory) morbidity and the composite primary outcome than neonates born thereafter, thus jeopardizing neonatal outcome. In Chapter 3, we evaluated whether the percentage of elective CSs before a gestational age of 39^{+0} weeks, relative to the total number of elective CSs, had decreased between 2000 and 2010 and what factors were associated with performing an elective CS too early. We found that the percentage of elective CSs before 39^{+0} weeks improved marginally from 2000 to 2009, while in 2010 a declining trend started, although 43% of elective CSs was still performed before 39^{+0} weeks. This results in an increased risk of neonatal morbidity and long-term health problems. Peripheral hospitals, performed elective CSs more often before 39^{+0} weeks than university hospitals. In hospitals where the number of deliveries per year is in the lower quartile (<25^{th} percentile), an elective CS before 39^{+0} weeks was performed more often than in hospitals were the total number of deliveries is in the upper quartile (>75^{th} percentile).

An argument not to postpone an elective CS until 39^{+0} weeks can be fear of earlier spontaneous labour resulting in unplanned CSs which has workforce and resource

implications, specifically in smaller obstetric units. In Chapter 4, with help of a decision tree model we calculated, in a policy of planning all elective CSs from 39^{+0} weeks onwards, the number of unplanned CSs which have to be performed to prevent one neonate with respiratory complications, as compared to performing all elective CSs early term (37^{+0}- 38^{+6} weeks). Planning all elective CSs at 39^{+0-6} weeks required 10.9 unplanned CSs to prevent one neonate with respiratory morbidity, compared to planning all elective CS at 38^{+0-6} weeks. Compared to planning all elective CSs at 37^{+0-6} week it is only required to perform 3.3 unplanned CSs to prevent one neonate with respiratory morbidity. Therefore, in our opinion, fear of early term labour and workforce disutility is not an argument for scheduling elective CSs before 39^{+0} weeks of gestation.

Besides singleton pregnancies, in Chapter 5 we assessed neonatal morbidity and mortality of elective CSs in uncomplicated twin pregnancies. More than 17% were born before 37^{+0} weeks of gestation and had a higher risk for mild and severe morbidity compared to neonates born from 38^{+0} weeks of gestation onwards. As the risk of intra-uterine fetal demise swiftly increased in our population from 40^{+0} weeks onwards, we concluded that in uncomplicated twin pregnancies, elective caesarean sections are best performed between 37^{+0} and 39^{+6} weeks of gestation.

Part 2 Hypertensive disorders during pregnancy and neonatal respiratory morbidity

The second part of this thesis focused on hypertensive diseases during pregnancy, and the risk of impaired lung development leading to respiratory morbidity in short and in long-term. Hypertensive diseases during pregnancy are associated with adverse neonatal outcomes such as fetal growth restriction and (iatrogenic) preterm birth. Lower gestational age and birth weight are independently associated with a higher risk for lower lung function and asthma in later life. Next to this indirect effect, it is hypothesized that hypertensive disorders could also have a direct effect on neonatal respiratory morbidity, through disturbed placental function and an altered angiogenic status, affecting fetal lung development and lung maturation. Animal studies already showed that dysregulation of angiogenesis, resulting in an anti-angiogenic status in the fetus, may be implicated in the development of bronchopulmonary dysplasia (BPD).

In Chapter 6 we focused on short-term neonatal outcome after preterm birth and assessed if preeclampsia is associated with development of BPD. After applying our exclusion criteria, we reported our primary outcome on 247 mother-neonate pairs. Fifty-nine neonates developed BPD (23.9%) which was moderate to severe in 27 of them (10.9%). Preeclampsia

was associated with BPD. However, after adjusting for additional intermediates no statistical significance remained, disguising a clinically relevant association.

In Chapter 7 we focused on respiratory morbidity in the long term. We examined the associations of maternal blood pressure in different periods of pregnancy and hypertensive disorders with the risk of lower lung function, wheezing and asthma in childhood. This study among 4,894 children was embedded in a population-based prospective cohort study. We observed consistent associations per 5 mmHg higher maternal blood pressure in early pregnancy with a lower FEV_1/FVC, and per 5 mmHg higher blood pressure in late pregnancy with a higher risk for wheezing and asthma at the age of 10 years. We found no associations of maternal hypertensive disorders during pregnancy with child lung function, current wheezing or current asthma. Our results suggest that higher blood pressure in pregnant women is associated with lower lung function and increased risks of wheezing and asthma in children. The associations may be trimester specific.

In the general discussion of this thesis, Chapter 8, we focussed on the main findings and their implications for clinical practice and decision making, as well as discussing suggestions for future research. Summarizing part one, the 'term' period should be redefined into early, full, late and post term to emphasize the risk differences of adverse neonatal outcome in the short and long term. Administration of antenatal corticosteroids to all pregnant women, to decrease respiratory morbidity in the short term, is no good alternative strategy and might be associated with long-term complications involving adverse neurodevelopmental outcome. Hypertensive disorders of pregnancy can influence neonatal respiratory morbidity in the short and in long term, mediated through fetal growth restriction and (iatrogenic) preterm birth, but also via an anti-angiogenic status in the fetus influencing lung growth and development. There are also recent publications describing how hypertensive disorders during pregnancy can disrupt fetal immune regulation and influence epigenetic mechanisms.

Future research should focus on developing a sensitive and specific method for prediction of fetal lung maturity. This method can help in future clinical decision making on timing of delivery. Furthermore future research should focus on pathofysiological pathways to get insight in causes and effects of impaired lung development and lung growth. Also more long-term follow-up of neonates and children with short-term respiratory morbidity is needed to determine the effects on long-term health.

Samenvatting

Foetale longen ontwikkelen zich in verschillende stadia, zowel tijdens de zwangerschap als na de geboorte. De rijping van de longen begint vanaf ongeveer 24 weken zwangerschap met de productie van surfactant, en neemt elke week toe. Neonatale respiratoire morbiditeit op korte termijn is gedefinieerd als wet lung syndroom, ook wel voorbijgaande tachypneu van de pasgeborene genoemd en respiratoir distress syndroom. Het risico op, voornamelijk respiratoire, neonatale morbiditeit en de daaropvolgende opname op een Neonatal Intensive Care Unit (NICU) is aanzienlijk hoger na een geplande sectio caesarea (SC) dan na een geplande vaginale bevalling, zelfs in de a terme periode. Het aantal SC neemt wereldwijd al jaren toe. Sectio caesarea kunnen worden onderverdeeld in primaire (electieve geplande) en secundaire (ongeplande of spoed) sectio's. Een electieve SC wordt gedefinieerd als een geplande SC voor de start van de bevalling zonder strikte medische indicatie. Omdat uit eerdere literatuur blijkt dat het risico op neonatale morbiditeit afneemt naarmate de amenorroeduur toeneemt, is een optimale timing van een electieve SC van belang om onnodige iatrogene neonatale morbiditeit te voorkomen.

Deel 1 Timing van electieve Sectio Caesarea

Het eerste deel van dit promotieonderzoek heeft zich gericht op het bestuderen van het aantal electieve sectio caesarea dat a terme wordt verricht, bij welke termijn dit plaatsvindt en wat de geassocieerde neonatale uitkomsten waren bij ongecompliceerde eenling- en tweelingzwangerschappen.

In Hoofdstuk 2 hebben we het aantal electieve SC van eenlingzwangerschappen a terme, de timing daarvan en de bijbehorende neonatale morbiditeit beschreven. We hebben aangetoond dat helaas meer dan de helft van de electieve SC vóór een zwangerschapsduur van 39^{+0} weken werd verricht en dat de neonaten daarmee een significant hoger risico hadden op neonatale (respiratoire) morbiditeit en onze samengestelde primaire uitkomstmaat dan neonaten die werden geboren na een zwangerschapsduur van 39^{+0} weken. In Hoofdstuk 3 evalueerden we of het percentage electieve SC vóór een zwangerschapsduur van 39^{+0} weken, ten opzichte van het totale aantal electieve SC tussen 2000 en 2010 was afgenomen en welke factoren verband hielden met het uitvoeren van een electieve SC vóór een zwangerschapsduur 39^{+0} weken. We beschrijven dat het percentage electieve SC vóór 39^{+0} weken licht afneemt van 2000 tot 2009, terwijl in 2010 een echt dalende trend begint. Helaas wordt nog steeds 43% van de electieve SC vóór 39^{+0} weken verricht. Dit resulteert in een verhoogd risico op neonatale morbiditeit op zowel de korte als lange termijn. In perifere ziekenhuizen werden electieve SC vaker uitgevoerd vóór 39^{+0} weken dan in academische ziekenhuizen. In ziekenhuizen waar het aantal bevallingen per jaar in het onderste kwartiel lag (<25^{e} percentiel), werd een electieve SC vóór 39^{+0} weken

vaker uitgevoerd dan in ziekenhuizen waar het totale aantal bevallingen in het bovenste kwartiel lag (>75^{e} percentiel).

Een argument om een electieve SC niet uit te stellen tot na 39^{+0} weken kan angst voor het eerder in partu komen van de zwangere zijn, wat resulteert in een niet-geplande SC. Dit heeft mogelijk gevolgen voor de operatieplanning, personeel dat buiten kantoortijden moet werken en de beschikbare middelen. Dit geldt wellicht vooral voor kleinere ziekenhuizen waar niet standaard een operatieteam in huis is. In Hoofdstuk 4 hebben we met behulp van een beslisboom berekend hoeveel niet-geplande SC moeten worden uitgevoerd om één neonaat met respiratoire complicaties te voorkomen wanneer je alle electieve SC plant na 39^{+0} weken, in vergelijking tot het plannen van alle electieve SC voor 39^{+0} weken. Planning van alle electieve SC vanaf 39^{+0} weken vereiste 10,9 ongeplande SC om één neonaat met respiratoire morbiditeit te voorkomen, in vergelijking met het plannen van alle electieve SC bij een zwangerschapsduur van 38^{+0-6} weken. Vergeleken met het plannen van alle electieve SC bij een zwangerschapsduur van 37^{+0-6} weken, moeten 3,3 niet-geplande SC worden verricht om één neonaat met respiratoire morbiditeit te voorkomen. Naar onze mening zijn daarom de angst voor vroegtijdig in partu komen en logistieke redenen geen goed argument voor het plannen van een electieve SC vóór een zwangerschapsduur van 39^{+0} weken.

Naast eenlingzwangerschappen, hebben we in Hoofdstuk 5 de neonatale morbiditeit en mortaliteit van electieve SC beoordeeld in ongecompliceerde tweelingzwangerschappen. Meer dan 17% werd geboren vóór een zwangerschapsduur van 37^{+0} weken en pasgeborenen hadden een hoger risico op milde en ernstige neonatale morbiditeit vergeleken met pasgeborenen geboren vanaf 38^{+0} weken zwangerschap. Omdat het risico op intra-uteriene foetale dood vanaf 40^{+0} weken snel toenam in onze populatie, concludeerden we dat electieve SC van ongecompliceerde tweelingzwangerschappen het best kunnen worden uitgevoerd tussen 37^{+0} en 39^{+6} weken.

Deel 2 Hypertensieve aandoeningen tijdens zwangerschap en neonatale respiratoire morbiditeit

Het tweede deel van dit proefschrift richtte zich op hypertensieve ziekten tijdens de zwangerschap, en het risico op een verminderde longontwikkeling leidend tot respiratoire morbiditeit op korte en lange termijn. Hypertensieve ziekten tijdens de zwangerschap worden in verband gebracht met ongunstige neonatale uitkomsten zoals een beperking van de foetale groei en (iatrogene) vroeggeboorte. Een kortere zwangerschapsduur en een lager geboortegewicht zijn onafhankelijk geassocieerd met een hoger risico op een verminderde longfunctie en astma op latere leeftijd. Naast dit indirecte effect, wordt verondersteld dat hypertensieve ziektes tijdens de zwangerschap ook een direct effect kunnen hebben op neonatale respiratoire morbiditeit, door een gestoorde placenta functie en een anti-

angiogene status die de foetale longontwikkeling en longrijping beïnvloedt. Dierstudies hebben al aangetoond dat ontregeling van de angiogenese, resulterend in een anti-angiogene status bij de foetus, mogelijk betrokken is bij de ontwikkeling van bronchopulmonale dysplasie (BPD).

In Hoofdstuk 6 hebben we ons gericht op neonatale uitkomsten op de korte termijn na vroeggeboorte en beoordeeld of pre-eclampsie geassocieerd is met de ontwikkeling van BPD. Na toepassing van onze exclusiecriteria rapporteren we onze primaire uitkomst bij 247 moeder-neonaat-paren. Vijfenvijftig pasgeborenen ontwikkelden BPD (23,9%), die in 27 van hen matig tot ernstig was (10,9%). Pre-eclampsie was geassocieerd met BPD; na correctie voor aanvullende intermediaire factoren bleef er echter geen statistische significantie over. Het is belangrijk om een onderscheid te maken tussen confounders en intermediaire factoren die zich in het pathway bevinden tussen ziekte entiteit en uitkomst, zodat klinisch relevante associaties aantoonbaar blijven.

In Hoofdstuk 7 hebben we ons gericht op respiratoire morbiditeit op de lange termijn. We onderzochten de associaties van maternale bloeddruk in verschillende perioden van zwangerschap en hypertensieve stoornissen met het risico van een lagere longfunctie, piepende ademhaling en astma bij kinderen op de leeftijd van 10 jaar. Deze studie onder 4.894 kinderen werd ingebed in een prospectieve cohortstudie. We constateerden consistente associaties per 5 mmHg hogere maternale bloeddruk in de vroege zwangerschap met een lagere FEV1 / FVC en per 5 mmHg hogere bloeddruk tijdens de late zwangerschap met een hoger risico op piepende ademhaling en astma op de leeftijd van 10 jaar. We vonden geen associaties van maternale hypertensieve ziektes tijdens de zwangerschap met een lagere longfunctie, een piepende ademhaling of astma op de leeftijd van 10 jaar. Onze resultaten suggereren dat een hogere bloeddruk bij zwangere vrouwen geassocieerd is met een lagere longfunctie en een verhoogd risico op piepende ademhaling en astma bij kinderen. De gevonden effecten zijn mogelijk afhankelijk van het trimester van de zwangerschap waarin de bloeddruk afwijkend is.

In de algemene discussie van dit proefschrift, Hoofdstuk 8, legden we de nadruk op de belangrijkste bevindingen en hun implicaties voor de klinische praktijk en bespraken we suggesties voor toekomstig onderzoek. Als we deel 1 samenvatten, zou de a terme periode ook in Nederland opnieuw moeten worden gedefinieerd in vroeg a terme, volledig a terme, laat a terme en serotien. Dit om het risico op een ongunstige neonatale uitkomst op korte en lange termijn te benadrukken wanneer een kind vroeg a terme wordt geboren ten opzichte van volledig a terme. Toediening van antenatale corticosteroïden aan alle zwangere vrouwen, om respiratoire morbiditeit op korte termijn te verminderen, is geen goede alternatieve strategie en kan in verband worden gebracht met complicaties op de lange termijn, onder andere mogelijk een verminderde neurologische ontwikkeling.

Hypertensieve aandoeningen van de zwangerschap kunnen de neonatale respiratoire morbiditeit beïnvloeden op zowel de korte als lange termijn. Dit kan indirect, via foetale groeirestrictie en (iatrogene) vroeggeboorte, maar ook direct via een anti-angiogene status bij de foetus die de longgroei en longontwikkeling beïnvloedt. Er zijn ook recente publicaties die beschrijven hoe hypertensieve stoornissen tijdens de zwangerschap de immuunregulatie van de foetus kunnen verstoren en epigenetische mechanismen kunnen beïnvloeden.

Toekomstig onderzoek moet zich richten op het ontwikkelen van een zowel sensitieve als specifieke methode voor het voorspellen van de foetale long rijpheid. Deze methode kan helpen bij toekomstige klinische beslissingen met betrekking tot het timen van de bevalling. Verder moet toekomstig onderzoek zich richten op de pathofysiologie ten aanzien van oorzaken van verminderde longontwikkeling. Ook is er behoefte aan meer langdurige follow-up van pasgeborenen en kinderen met respiratoire morbiditeit op de korte termijn.

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Addendum

Authors and affiliations

H.T. den Dekker	The Generation R Study Group, Erasmus MC, Rotterdam, the Netherlands
L. Duijts	Department of Paediatrics, Division of Neonatology, Erasmus MC, Rotterdam, the Netherlands
N. Edge	Department of Obstetrics and Gynaecology, Mildura, Victoria, Australia
C.W. Hukkelhoven	Perined, Utrecht, the Netherlands
Prof. V.W.V. Jaddoe	The Generation R Study Group, Erasmus MC, Rotterdam, the Netherlands
R.C.J. de Jonge	Department of Paediatrics, Division of Neonatology, VU Medical Centre, Amsterdam, the Netherlands
Prof. JC de Jongste	Department of Paediatrics, Division of Respiratory Medicine and Allergology, Erasmus MC, Rotterdam, the Netherlands
S. Lunshof	Department of Obstetrics and Gynaecology, Amphia Hospital, Breda, the Netherlands
Prof. B.W.J. Mol	Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre, Clayton, Victoria 3168, Australia
D.N.M. Papatsonis	Department of Obstetrics and Gynaecology, Amphia Hospital, Breda, the Netherlands
C.T. Pham	School of Public Health, University of Adelaide, Adelaide, South Australia
Prof. J.A.M. van der Post	Department of Obstetrics and Gynaecology, AMC, Amsterdam, the Netherlands
J. Reijnierse	Department of Paediatrics, Erasmus MC, Rotterdam, the Netherlands
Prof. I.K.M. Reiss	Department of Paediatrics, Division of Neonatology, Erasmus MC, Rotterdam, the Netherlands
Prof. E.A.P. Steegers	Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, the Netherlands

List of abbreviations

ACOG	American Committee of Obstetricians and Gynecologists
BMI	Body Mass Index
BPD	Bronchopulmonary Dysplasia
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CS	Caesarean Section
CSs	Caesarean Sections
DBP	Diastolic Blood Pressure
FEV_1	Forced Expiratory Volume in 1 second
FEF	Forced Expiratory Flow
FLM	Fetal Lung Maturity
FVC	Forced Vital Capacity
GH	Gestational Hypertension
HELLP	Haemolysis Elevated Liver enzymes Low Platelets
IPPV	Intermittent Positive Airway Pressure
IUGR	Intra-Uterine Growth Restriction
LBC	Lamellar Body Count
L/S ratio	Lecithin/ Sphingomyelin Ratio
MAP	Mean Arterial Pressure
NA	Not Applicable
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
OR	Odss Ratio

PDA	Persistent Ductus of Botalli
PE	Preeclampsia
PEH	Pre-existent Hypertension
PMA	Post Menstrual Age
PPROM	Prelabour Premature Rupture of Membranes
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
SC	Sectio Caesarea
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TTN	Transient Tachypnea of the Newborn/ Wet lung
VEGF	Vascular Endothelial Growth Factor

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WH Backes, RJ Nijenhuis, WH Mess, **FA Wilmink**, GW Schurink, MJ Jacobs. Magnetic resonance angiography of collateral blood supply to spinal cord in thoracic and thoracoabdominal aortic aneurysm patients. J Vasc Surg. 2008 Aug;48(2):261-71.

PhD portfolio

Name PhD student:	Freke A. Wilmink-Penders
Erasmus MC department:	Obstetrics and Gynaecology: division of Obstetrics
PhD period:	2010-2018
Promotors:	Prof.dr. E.A.P. Steegers, Prof.dr. B.W.J. Mol

Summary of PhD training and teaching activities		ECTS
General courses		
2014	Biostatistical Methods I: Basic principles (CC02), NIHES, ErasmusMC, Rotterdam (4 weeks)	5.7
2012	Evidence Based Medicine, DOO, Erasmus MC	1
2012	Endnote, Erasmus MC	0.25
Presentations		
Oral presentations:		
2016	Werkgroep vroeggeboorte, Utrecht. Pre-eclampsie en het risico op bronchopulmonaire dysplasie bij vroeggeboorte < 32 weken.	0.5
2016	European Congress on Perinatal Medicine, Maastricht. Preeclampsia and risk of developing bronchopulmonary dysplasia in very preterm neonates.	1
2014	Wladimiroff Award Meeting, Afdeling Verloskunde&Gynaecologie, Erasmus Medisch Centrum, Rotterdam. Trends in timing of elective caesarean sections at term in the Netherlands.	0.5
2010	Aios in de dop: leren zwemmen of verzuipen, Afscheidssymposium M.J. ten Kate-Booij, Amphia Ziekenhuis, Breda.	0.25
2010	30th Annual Meeting, SMFM, Chicago, IL, US. Neonatal outcome following primary elective caesarean section beyond 37 weeks of gestation: a 7-year retrospective analysis of a national registry.	2
Poster presentation:		
2011	31st Annual Meeting, SMFM, February 7-12, 2011, San Francisco, CA,	2

US. Poster presentation: Neonatal outcome following planned caesarean section of dichorial twins beyond 35 weeks of gestation; an 8-year retrospective analysis of a national registry.

(Inter)national Conferences and Symposia

2010	30th annual pregnancy meeting, Society of Fetal and Maternal Medicine, Chicago, IL, United States	1
2010	Gynaecongres, Breda, the Netherlands	0.5
2010	Gynaecongres, Arnhem, the Netherlands	0.25
2011	Gynaecongres, Den Haag, the Netherlands	0.5
2012	Wim Schellekens Symposium: De kunst van beeldvorming in de obstetrie en gynaecologie	0.25
2012	Gynaecongres, Arnhem, the Netherlands	0.5
2013	Gynaecongres, Arnhem, the Netherlands	0.5
2014	Gynaecongres, Leeuwarden, the Netherlands	0.5
2014	Fetal Medicine Foundation World Conference, Nice, France	1
2015	Gynaecongres, Arnhem, the Netherlands	0.5
2016	Vroeggeboorte: van preventive tot lange termijn consequenties, SCEM, Utrecht, the Netherlands	0.25
2016	Gynaecongres, Eindhoven, the Netherlands	0.5
2016	European Conference of Perinatal Medicine, Maastricht, the Netherlands	0.5
2017	37th annual pregnancy meeting, Society of Fetal and Maternal Medicine, Las Vegas, NV, United States	1
2017	International Society of Ultrasound in Obstetrics and Gynecology, World Congress, Vienna, Austria	0.75
2017	Gynaecongres, Amersfoort, the Netherlands	0.5
2018	CCP, Bologna, Italy	0.5
2018	Gynaecongres, Utrecht, the Netherlands	0.25

Teaching activities

Supervising

2018	Mw. M. Huiskes, TU Twente, Technical Medicine, Master year 1, internship 1: Non-Invasive Quantitative Ultrasound to predict fetal lung maturity' part 3, Radboudumc	1

2018	Mw. T. Brouwers, TU Twente, Technical Medicine, Master year 1, internship 1: Quantitative computer-aided ultrasound texture analysis to predict fetal lung maturity part 2, Radboudumc	1
2017	Mw. S. Koenders, TU Twente, Technical Medicine, Master year 2, internship 4: Quantitative computer-aided ultrasound texture analysis to predict fetal lung maturity, Radboudumc	1

Other

2016-2018	Supervisor of 10 interns, supervising and teaching professional behaviour during their internships, Radboudumc	4
2016-2018	Teaching in medical curriculum, Radboudumc	2
2016-2018	Teaching in Obstetric specialization for nursing	1

Miscellaneous

2017	Granted with 'Open Mind Scholarship' €50.000, 'Teknology Conference', Stichting Technologische Wetenschappen, the Netherlands: What do lungs of unborn baby's sound like?	0.25
2016-heden	Development of a Non-Invasive Quantitative Ultrasound (NIQU) method to assess fetal lung maturity. Radboudumc, Nijmegen. Ir. G Weiers, Prof.Ir. C. de Korte en Prof.dr. F.P.H.A. Vandenbussche.	2
2016-2018	Fellowship Perinatology, Radboudumc, Nijmegen. Supervisors: Prof.dr. F.K. Lotgering and Prof.dr. F.P.H.A. Vandenbussche.	
2009-2015	Obstetrics and Gynaecology, Cluster Rotterdam. Supervisors: Prof.dr. C.W. Burger, dr. M.J. Ten Kate-Booij, dr. R.M.F. van der Weiden. Differentiation Perinatology, Erasmus Medisch Centrum, Rotterdam	
2009-2014	Commissie Cluster Onderwijs, Rotterdam	2
Total ECTS		**37.20**

About the author

Freke Wilmink is the eldest daughter of Henk Wilmink and Francis van de Wouw. She was born on June 1st 1982 in Loon op Zand, the Netherlands. She grew up in Loon op Zand together with her younger sister Anne. After secondary school at the Paulus Lyceum, Tilburg (1994-2000) she moved to Maastricht to start medical school at the University of Maastricht. In 2003 she went to The Starship Children's Hospital in Auckland, New Zealand for six weeks of Paediatric Radiology. During internships she became interested in the field of obstetrics and gynaecology and went to the Obstetrics department at the Academic hospital in Paramaribo, Suriname for six weeks. In 2006 she graduated cum laude and started working as a resident gynaecology at the Amphia Hospital, Breda (Dr. M.J. Ten Kate-Booij). Here she started her research under supervision of Dr. D.N.M. Papatsonis and Prof.dr. B.W.J. Mol. After her oral presentation at the Society of Maternal and Fetal Medicine in 2010 and the publication of her first original research article, her PhD project started under supervision of Prof.dr. E.A.P. Steegers and Prof.dr. B.W.J. Mol.

Meanwhile, starting in 2009, Freke followed her training in Obstetrics and Gynaecology at the Sint Franciscus Gasthuis in Rotterdam (Dr. R.J.M. van der Weiden) and the Erasmus Medical Centre (Prof.dr. C.W. Burger and dr. M.J. Ten Kate-Booij). Her last year of training consisted of a differentiation in perinatology. She finished her specialization on December 2nd 2015. January 1st, 2016 she started her fellowship Perinatology at the Radboudumc, Nijmegen (Prof.dr. F.K. Lotgering and Prof.dr. F.P.H.A. Vandenbussche). In addition to her PhD trajectory, she set up a new research project, in collaboration with the Medical Ultrasound Centre in the Radboudumc, to antenatally predict fetal lung maturity with quantitative texture analysis of ultrasound images. In November 2017, she and her colleague were granted with a scholarship (Open Mind). After finishing her fellowship in June 2018, she became part of the obstetric staf at the Radboudumc.

On April 5th 2014 Freke married Ronald Penders. Together they have two daughters, Maud and Yfke, who were born on February 2nd 2015. They live in Nijmegen, the Netherlands.

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