Risk assessment during pregnancy and labor:
optimal fetal growth and monitoring of contractions

Blanka Vasak

Risk assessment during pregnancy and labor: optimal fetal growth and monitoring of contractions
Thesis, University of Utrecht, the Netherlands

Author	B.Vasak
Cover Illustration	Maggy Kukler
Cover lay-out	Mijke van 't Slot
Printed by	Ridderprint, Ridderkerk, the Netherlands

ISBN 978-94-6299-486-7

The author gratefully acknowledges financial support for this thesis by the Division Woman and Baby of the University Medical Center Utrecht, Vrienden UMC Utrecht, ChipSoft B.V., BMA B.V. (Mosos), Memidis Pharma B.V., Nemo Healthcare B.V., ABN AMRO, Origio B.V., Olympus Nederland B.V., Ferring B.V., and Gedeon Richter B.V.

Risk assessment during pregnancy and labor: optimal fetal growth and monitoring of contractions

Risico selectie tijdens de zwangerschap en de baring:
optimale foetale groei en monitoring van weeën
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 23 december 2016 des middags te 12.45 uur

door

Blanka Vasak

geboren op 23 oktober 1985 te Nairobi, Kenia

Promotoren:	Prof. dr. G.H.A. Visser
	Prof. dr. A. Franx
Copromotoren:	Dr. S.V. Koenen
	Dr. B.C. Jacod

For my parents

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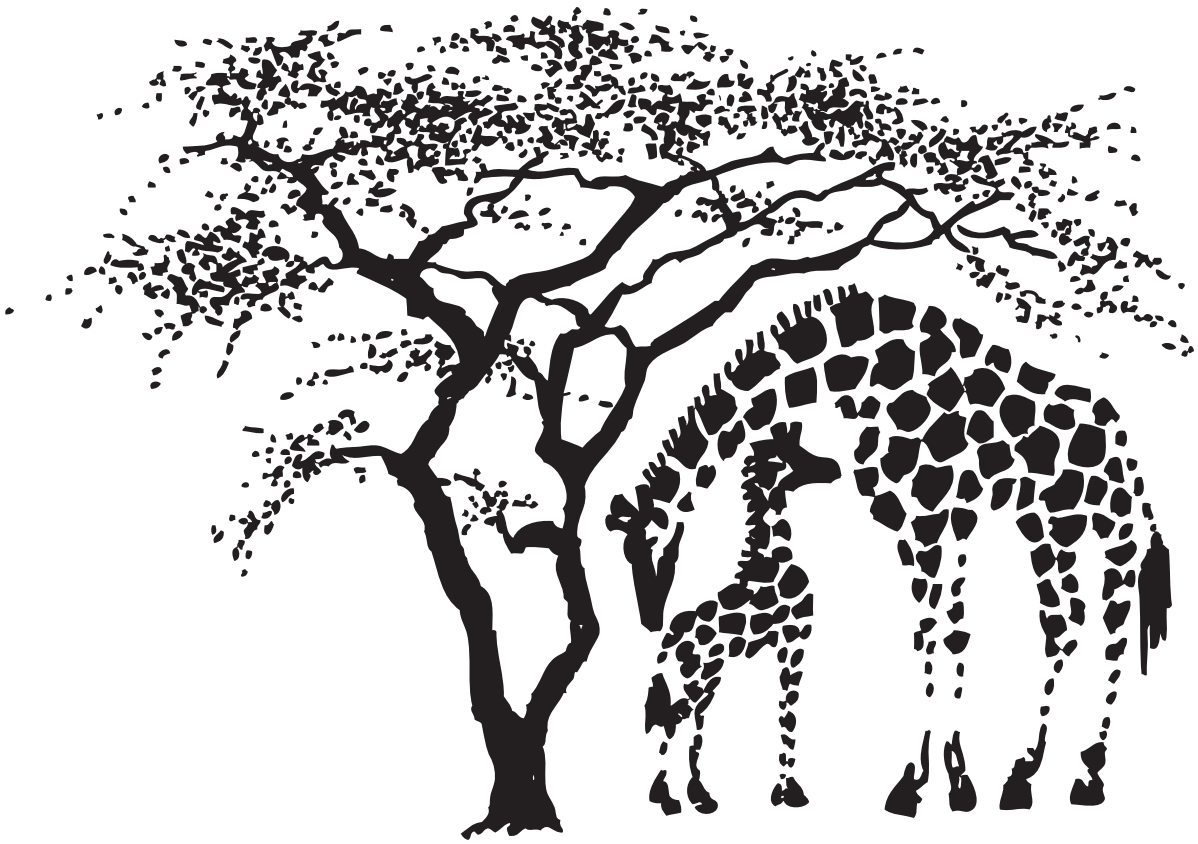

Chapter 1

General Introduction

Pregnancy and birth are key periods of life. In the majority of cases both take place without complications. However, if complications occur, these can be disastrous for mother and child, with lifelong health consequences for both. During pregnancy and birth, monitoring of the fetal and maternal condition is important. High risk pregnancies require more extensive monitoring than low risk pregnancies. The first challenge lies in determining which pregnancies are at risk and which are not. The next challenge is to find the optimal management strategy, where therapeutical options are limited.

Monitoring fetal growth throughout pregnancy is an essential component of care because both impaired and excessive fetal growth may result in an increased risk of perinatal morbidity and mortality.[1-5] Recognizing abnormal fetal growth is therefore important and ultrasound is an indispensable tool for this. However, identification of abnormal fetal growth remains challenging, especially at and near term, as most assessment tools including ultrasound, are less accurate than as compared to the preterm period.

During labor it is also important to recognize which individual patient is at risk. A low risk pregnancy may result in a high-risk birth and vice versa. Worldwide cesarean delivery (CD) rates have increased rapidly over the years.[6] The majority of intrapartum CD are performed for failure to progress in term nulliparous women with a fetus in cephalic position. Current monitoring techniques of uterine contractility have not shown to improve outcomes.[7]

The search for optimal diagnostic and prognostic tools for early recognition of the high-risk patient during pregnancy and labor can provide a window for targeted interventions to improve maternal and neonatal outcome.

PART 1. RISK ASSESSMENT DURING PREGNANCY; FOCUSING ON FETAL GROWTH

Fetal growth is a complex process influenced by maternal, fetal and placental factors. Abnormal growth has consequences on perinatal and long term outcomes. Being small for gestational age, defined as a birth weight below the 10th population percentile, is associated with an increased risk of adverse perinatal outcome[1,2,5] and of impaired cardiovascular and metabolic health at adult age.[8-11] This implies that health during adulthood has already partially been determined in utero. Being too large for gestational age, is also an important risk factor for perinatal morbidity and mortality due to an increased risk of labor complications.[3,4] Extremes in growth have negative effects on outcome, however the majority of perinatal deaths still occur in fetuses with a so called "normal" weight. So where does optimal growth lie? There is no consensus for this yet.

Identification of optimal fetal growth may help to identify risk groups and manage pregnancy accordingly. The importance of being able to identify fetuses at risk resides in the possibility to target interventions with potential adverse effects if used too liberally.[12] However, even if optimal growth would be known, there remains the challenge of recognizing these and higher risk children in utero.

Distinction between pathologically small fetuses, those with true intra-uterine growth restriction (IUGR) most likely accompanied by a suboptimal placental function, and constitutional healthy small fetuses also remains difficult. Throughout the years ultrasound has become an important tool in identification of growth restriction by using biometry and Doppler indices. Doppler of the umbilical artery (UA) is most commonly used to identify placental pathology. However, in the term period flow patterns of the UA are mostly normal in small-for gestational age fetuses and have not shown to improve outcome.[13] This is due to the fact that a high placental resistance occurs only when more than 1/3rd of placental function is deficient.[14,15] Promising results have been found for other Doppler indices to predict adverse outcome, such as the cerebro-placental ratio (CPR)[16-18] and flow patterns in the uterine artery (UtA).[19-22] However, there is still no consensus on optimal management of term IUGR pregnancies.

Intra uterine growth restriction does not only have consequences for the child, it also has implications for the mother. Pregnancy can be viewed as the "ultimate stress test" for the cardiovascular system, revealing underlying cardiovascular pathology that may cause cardiovascular morbidity or mortality later on in life. Other placental disorders such as preeclampsia have revealed an increased prevalence of cardiovascular (CV) disease risk factors after delivery.[23-28] We hypothesize that women with a history of an IUGR pregnancy also may be at increased risk for cardiovascular disease later on in life.

Whether it concerns fetal, neonatal or maternal morbidity, early identification of pathology provides opportunities to identify risk groups and improve obstetrical management with the opportunity for targeted interventions.

Aims of part 1 of this thesis

- To determine optimal fetal growth for singleton pregnancies
- To determine optimal fetal growth for twin pregnancies
- To compare perinatal mortality between singleton and twin pregnancies according to gestational age and birth weight
- To evaluate different diagnostic tools for identification of term small for gestational age fetuses at risk for impaired outcome
- To study the cardiovascular profile of women with a history of a pregnancy complicated by intra uterine growth restriction

PART 2. RISK ASSESSMENT DURING LABOR; MONITORING UTERINE CONTRACTIONS USING ELECTROMYOGRAPHY

Cesarean delivery (CD) rates have increased rapidly over the last years. Based on data from 150 countries currently 18.6% of all births occur by CD, ranging from an average of 6% to 27% in the least

and most developed countries. In Europe the CD rate is around 25%.[6] Almost half of the CDs are performed because of failure to progress during labor.[29,30] Current monitoring techniques of uterine contractions, either by external tocography or by intrauterine pressure catheters, have not shown to improve outcomes.[7] Therefore new monitoring techniques are being studied. A relatively old technique, the measurement of electrical uterine activity through the maternal abdominal wall surface (uterine electromyography; EMG) developed 70 years ago, has obtained new interest recently.[31-35] This non invasive technique correlates well with the invasive 'gold' standard of intra-uterine pressure monitoring[36-38] and has shown promising results in threatened preterm labor, identifying patients delivering at short term more accurately than by current monitoring methods.[39-41] If these results could be translated into the possibility to differentiate between normal and protracted labor in the term period, this could provide a new tool for monitoring uterine activity during labor.

Aims of part 2 of this thesis

- To study whether uterine electromyography can identify inefficient contractions leading to first stage labor arrest followed by cesarean delivery, in term nulliparous women in spontaneous onset of labor
- To determine the effect of oxytocin on contraction characteristics measured by uterine electromyography
- To investigate whether uterine electromyography can identify inefficient contractions leading to first stage labor arrest followed by cesarean delivery, in term nulliparous women after induction of labor

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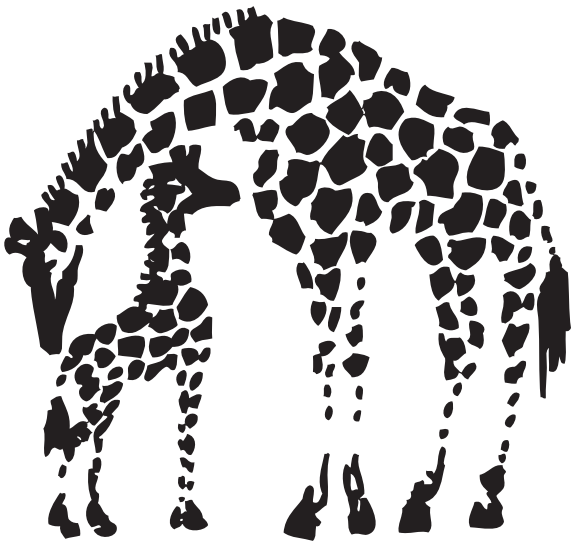
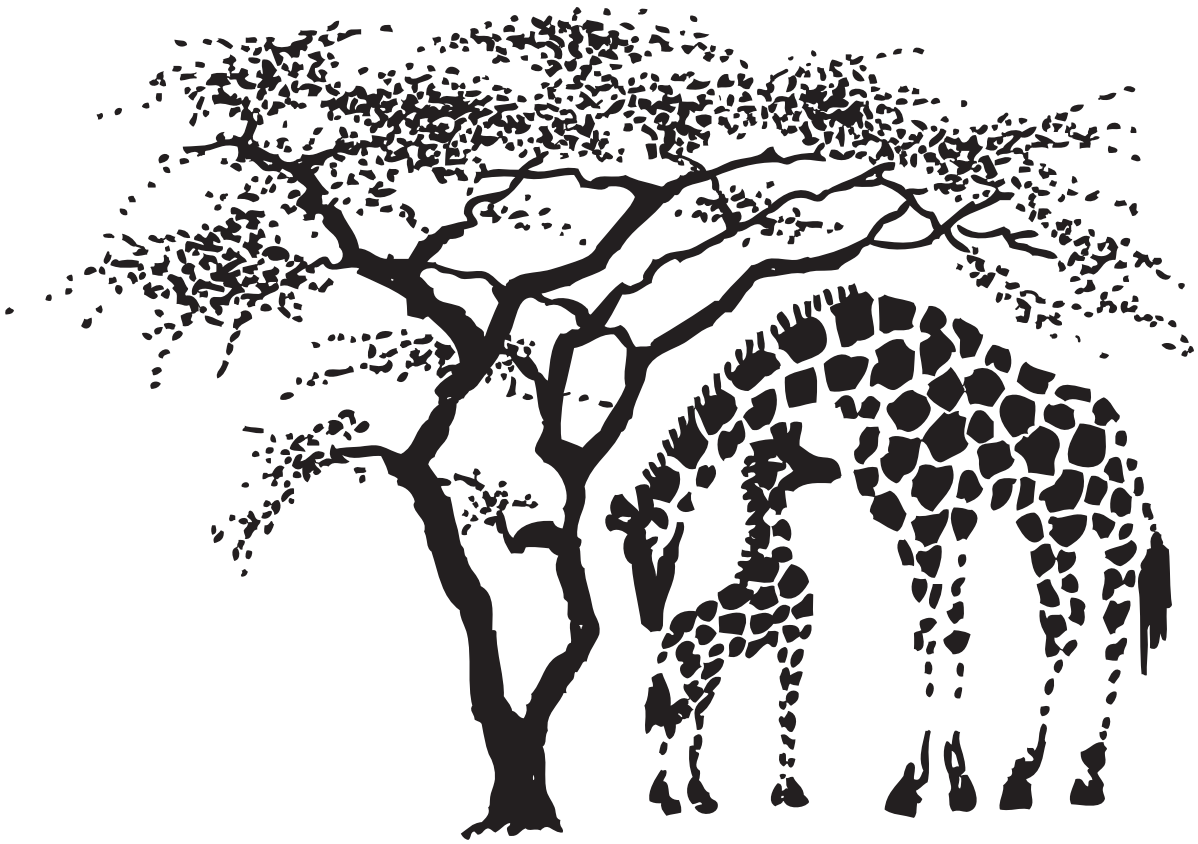


Part I

Risk assessment during pregnancy; focusing on fetal growth



Chapter 2

Human fetal growth is constrained below optimal for perinatal survival

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Ultrasound in Obstetrics and Gynecology. 2015 Feb;45(2):162-7

ABSTRACT

Objective The use of fetal growth charts assumes that the optimal size at birth is at the 50th birth-weight centile, but interaction between maternal constraints on fetal growth and the risks associated with small and large fetal size at birth may indicate that this assumption is not valid for perinatal mortality rates. The objective of this study was to investigate the distribution and timing (antenatal, intrapartum or neonatal) of perinatal mortality and morbidity in relation to birth weight and gestational age at delivery.

Methods Data from over 1 million births occurring at 28–43 weeks' gestation from singleton pregnancies without congenital abnormalities in the period from 2002 to 2008 were collected from The Netherlands Perinatal Registry. The distribution of perinatal mortality according to birth-weight centile and gestational age at delivery was studied.

Results In the 1 170 534 pregnancies studied, there were 5075 (0.43%) perinatal deaths. The highest perinatal mortality occurred in those with a birth weight below the 2.3rd centile (25.4/1000 births) and the lowest mortality was in those with birth weights between the 80th and 84th centiles (2.4/1000 births), according to routinely used growth charts. Antepartum deaths were lowest in those with birth weights between the 90th and 95th centiles. Data were almost identical when the analysis was restricted to infants born at ≥ 37 weeks' gestation.

Conclusion From an immediate survival perspective, optimal fetal growth requires a birth weight between the 80th and 84th centiles for the population. Median birth weight in the population is, by definition, substantially lower than these centiles, implying that the majority of fetuses exhibit some form of maternal constraint on growth. This finding is consistent with adaptations that have evolved in humans in conjunction with a large head and bipedalism, to reduce the risk of obstructed delivery. These data also fit remarkably well with those on long-term adult cardiovascular and metabolic health risks, which are lowest in cases with a birth weight around the 90th centile.

INTRODUCTION

The evolution of a large head, combined with the changes in pelvic dimensions and orientation associated with bipedalism, constitute a major challenge for vaginal delivery in humans because the fit between the fetal head and the pelvic canal is much tighter than in our closest relative, the chimpanzee.[1] Without intervention, obstructed labor is likely to be fatal for the fetus and to increase the risk of urogenital damage and death of the mother. For this reason, we are the only mammal known to utilize a birth assistant. Nonetheless, in the absence of modern medicine, the incidence of perinatal death remains high in some low-income settings.[2] It is believed that human fetal growth is constrained below its genetic potential in all pregnancies, to a greater or lesser degree, to match size at birth to maternal physical characteristics.[3] The classical studies of Ounsted and Ounsted,[4-6] reporting on surrogate pregnancy,[7] and a wide range of animal studies[8-10] support this concept of a strong link between maternal, but not paternal, size and fetal birth weight.[11] The relationship between size at birth and the health outcome of the offspring is, however, complex. Both impaired and excessive fetal growth lead to an increased risk of perinatal morbidity and mortality. Thus, in small-for-gestational-age (SGA) fetuses, defined as those with a birth weight below the 10th centile, there is an increased risk of intrauterine fetal death across all gestational ages compared with non-SGA fetuses, with the highest risk found in those with a birth weight below the 3rd centile.[12-14] However, while greater fetal growth in late gestation reduces the risk of perinatal death, large-for-gestational-age or macrosomic fetuses (birth weight >90th centile) are at risk of labor complications and thus of perinatal morbidity and mortality.[15,16]

The use of standardized fetal growth charts assumes that the optimal size at birth for the best outcome is at the 50th centile, but the complex interaction between maternal constraints and the different risks associated with a small or large size at birth suggests that this assumption may not be valid. However, this issue has not been examined in a sufficiently large contemporary population in a high-income setting. The objective of this study was to investigate the distribution and timing of perinatal mortality and morbidity in relation to birth weight and gestational age at delivery.

METHODS

This was a retrospective population-based cohort study. Data on 1 170 127 births between 2002 and 2008 were collected retrospectively from The Netherlands Perinatal Registry. Data on all births occurring between 28 and 43 weeks' gestation from singleton pregnancies in the period 2002–2008 were collected. Twenty-eight weeks was chosen as the lower cut-off point to permit comparison with data from other countries in which there may be differences in registration practices at earlier gestational ages.[17] Children with congenital abnormalities were excluded.

Birth weight was displayed in centile groups according to standardized population reference curves, which were based on nationwide data from the year 2002.[18] 'Binning' of data according to birth-weight centiles included −2 (2.3rd centile), −1 (16th centile), 0, +1 (84th centile) and +2 (97.7th centile) SDs. Gestational age was calculated from the first day of the last menstrual period or from an early ultrasound dating scan. Perinatal death was defined as fetal or neonatal death up to 7 days after delivery: antepartum death was defined as death occurring before labor, intrapartum death as death during labor and neonatal death as death occurring within 0–7 days following live birth. Congenital abnormalities were defined as those recognized at birth, or at first admission, by the neonatologist.

Statistical analysis

The distribution of perinatal mortality according to birth weight was studied. Mortality rates were subdivided into antepartum, intrapartum and neonatal death to assess these relationships separately for the different time periods of occurrence of death. The relationship between perinatal mortality, birth weight and gestational age at delivery was studied. Mortality was expressed as rate (number of deaths per 1000 infants). For perinatal mortality according to gestational age, the mortality rate at 43 weeks' gestation was not displayed owing to the extremely small number of cases. Given that more than half of perinatal mortality occurred at or after 37 weeks, analysis was carried out separately for both the total data set and for pregnancies delivering at or after 37 weeks. Data of births with missing birth-weight centiles were excluded from the analysis.

RESULTS

We studied 1 170 534 singleton pregnancies delivered between 2002 and 2008 after 28 weeks' gestation and without congenital abnormalities. There were 5075 (0.43%) perinatal deaths. For 407 (0.03%) children, of whom 17 died, birth-weight centiles were not recorded, and these were therefore excluded from the mortality rates. Of all perinatal deaths, 54% occurred at or after 37 weeks' gestation; 29% occurred in infants with a birth weight below the 10th centile, but 64% occurred in infants with a weight between the 10th and 90th centiles, with a similar distribution at all gestational ages (Figure 1). The distribution of perinatal mortality by birth weight is shown in Table 1 and Figure 2a. The distribution according to birth-weight centile (Table 1) corresponds well with that of The Netherlands Perinatal birth-weight chart, which was based on the births in 2002 only.[18]

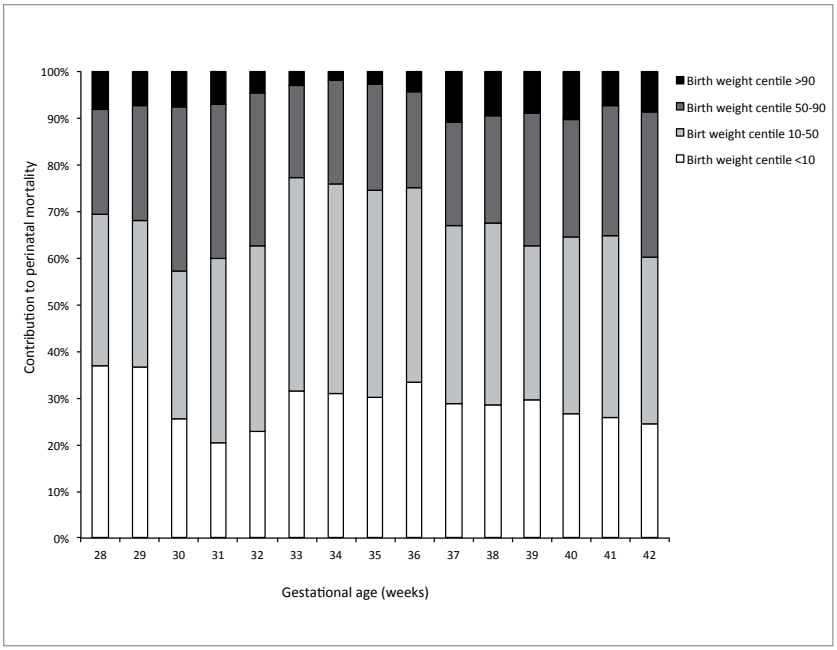


Figure 1. *Relative contribution of birth weight centiles to perinatal mortality according to gestational age at delivery of babies born between 28 and 42 weeks' gestation in The Netherlands during 2002–2008.*

Table 1. *Perinatal mortality according to birth-weight centile (p) of babies born after 28 weeks' gestation in The Netherlands from 2002–2008*

Birth weight centile	Total births	Perinatal mortality*			
	(n (cumulative %))	Antepartum	Intra-partum	Neonatal	Total
< p2.3	26.805 (2.29)	540 (20.15)	54 (2.01)	88 (3.28)	682 (25.44)
p2.3-< p5	28.296 (4.71)	247 (8.73)	27 (0.95)	52 (1.84)	326 (11.52)
p5-< p10	52.401 (9.19)	358 (6.83)	28 (0.53)	67 (1.28)	453 (8.64)
p10-< p16	63.805 (14.64)	300 (4.70)	37 (0.58)	73 (1.14)	410 (6.43)
p16-< p20	45.378 (18.52)	170 (3.75)	22 (0.48)	34 (0.75)	226 (4.98)
p20-< p50	353.219 (48.70)	926 (2.62)	114 (0.32)	247 (0.70)	1287 (3.64)
p50-< p80	359.603 (79.44)	686 (1.91)	107 (0.30)	221 (0.61)	1014 (2.82)
p80-< p84	48.139 (83.55)	82 (1.70)	13 (0.27)	21 (0.44)	116 (2.41)
p84-< p90	69.010 (89.45)	99 (1.43)	24 (0.35)	45 (0.65)	168 (2.43)
p90-< p95	57.731 (94.38)	81 (1.40)	20 (0.35)	44 (0.76)	145 (2.51)
p95-< p97.7	32.384 (97.15)	56 (1.73)	9 (0.28)	22 (0.68)	87 (2.69)
≥ 97.7	33.356 (100.00)	100 (3.00)	19 (0.57)	25 (0.75)	144 (4.32)
Total	1.170.127	3.645 (3.12)	474 (0.41)	939 (0.80)	5.058 (4.32)

** Mortality rate within centile group per 1.000 births*

The incidence of perinatal death was highest in those with a birth weight below the 2.3rd centile, falling gradually with an increasing birth weight up to the 80th and 90th centiles, at which the lowest death rates occurred. At centiles higher than this, mortality increased again. Perinatal mortality of infants with a birth weight between the 80th and 90th centiles was significantly lower than that of infants with a birth weight between the 50th and 80th centiles or ≥ 90th centile (chi-square test, P = 0.02 and 0.004, respectively). The distribution of mortality according to birth weight and perinatal timing of death is shown in Figure 2b. Antepartum deaths accounted for 72% of all perinatal deaths and were lowest in infants with a birth weight between the 90th and 95th centiles. Intrapartum and neonatal deaths were lowest between the 80th and 84th centiles. The same patterns were found when data were restricted to infants born at or after 37 weeks' gestation (Figure 3), or to those born between 39 and 40 weeks (data not shown).

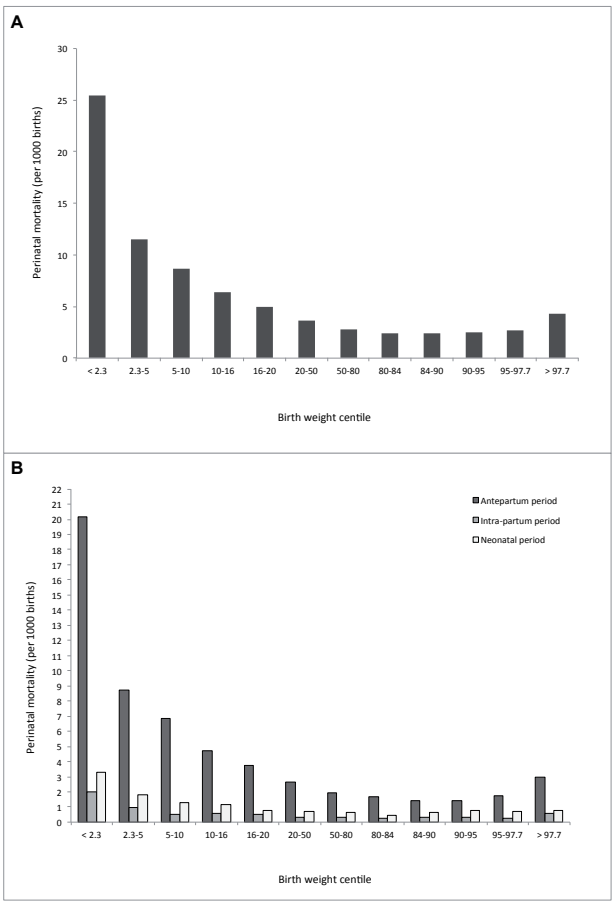


Figure 2. *Perinatal mortality according to birth weight centile (a) and timing of perinatal mortality (b) for babies born between 28 and 42weeks' gestation in The Netherlands during 2002–2008.*

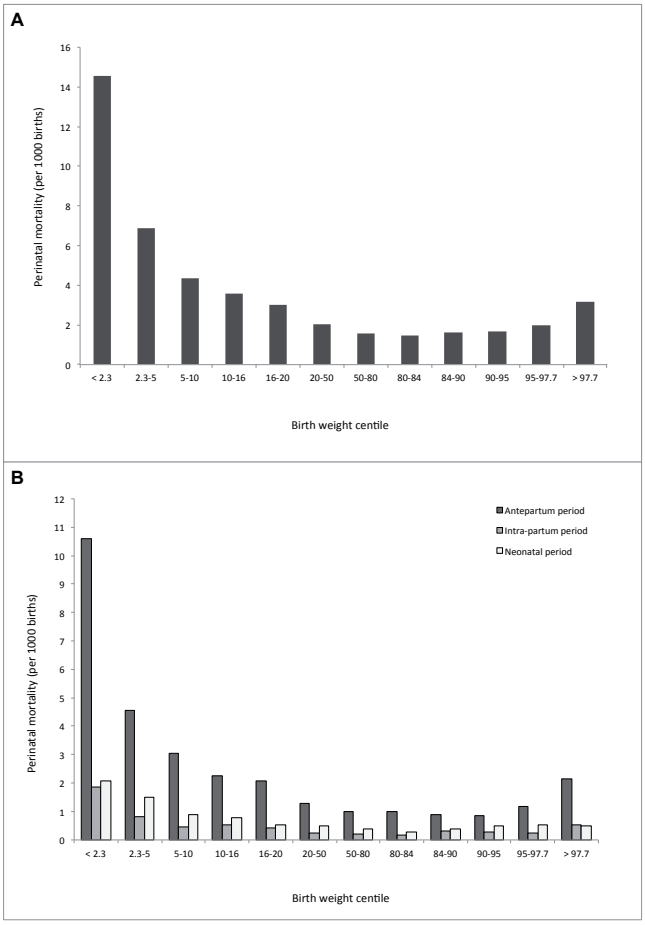


Figure 3. *Perinatal mortality according to birth weight centile (a) and timing of perinatal mortality (b) for babies delivered at or after 37 weeks' gestation in The Netherlands during 2002–2008.*

Perinatal mortality decreased as gestation progressed for all groups (Figure 4). Admission to the neonatal intensive care unit (NICU) and/or a low 5-min Apgar score, representing the morbidity rate, were lowest for those with a birth weight between the 50th and 84th centiles (Figure 5; data restricted to infants born ≥ 37 weeks to avoid the effects of prematurity).

Figure 4. *Perinatal mortality rate according to birth weight centile and gestational age at delivery of babies born at 28–42 weeks' gestation in The Netherlands during 2002–2008.*

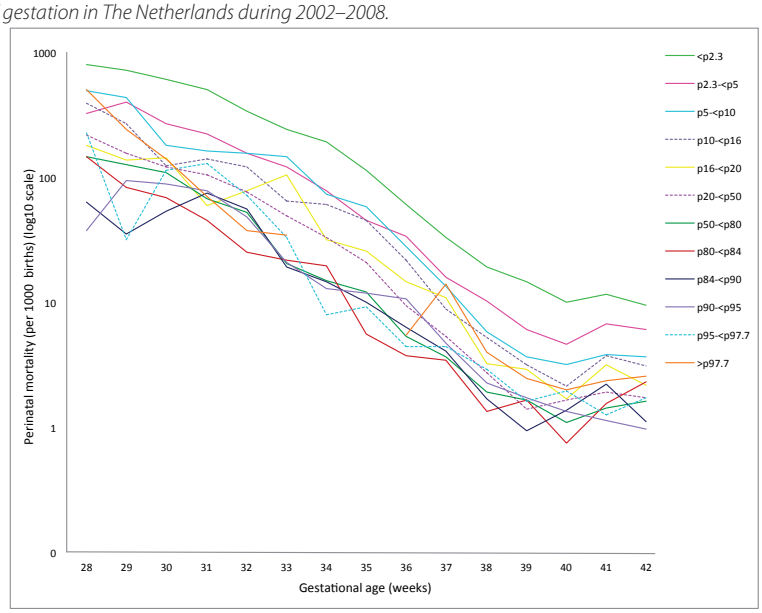
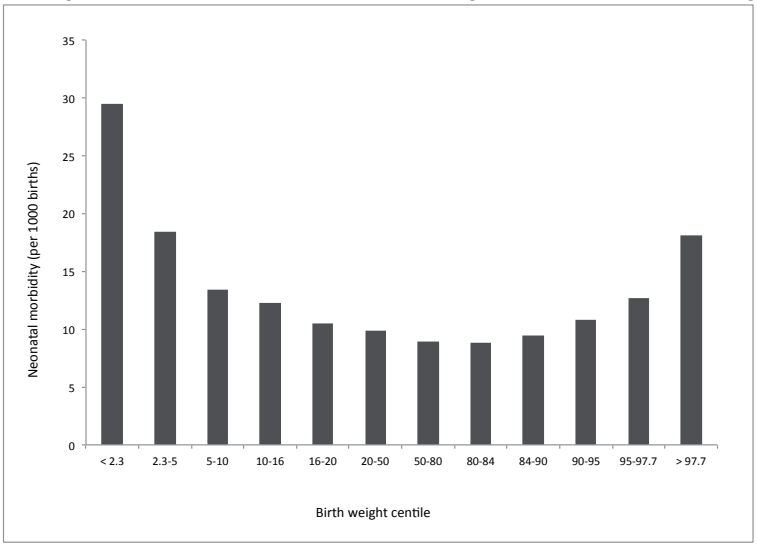


Figure 5. *Neonatal morbidity, defined by admission to neonatal intensive care unit and/or 5-min Apgar score < 7, according to birth-weight centile of babies delivered at or after 37 weeks' gestation in The Netherlands during 2002–2008.*



DISCUSSION

This study shows that, in a very large contemporary population of infants without congenital abnormalities born after 28 weeks' gestation in a high-income country, the median birth weight is substantially lower than is that associated with the lowest perinatal mortality, regardless of gestational age at delivery and perinatal timing of death. In addition, a low Apgar score and/or admission to the NICU were less common in infants with a birth weight between the 50th and 84th centiles. Most perinatal deaths occurred in fetuses with a birth weight in the so-called 'normal' range. For antepartum survival, an even higher birth-weight centile (90th–95th) was optimal, but this was associated with a higher neonatal morbidity and death rate, possibly related to complications during labor. Our findings confirm the hypothesis of the involvement of maternal constraint on fetal growth, a process evolved to facilitate vaginal delivery, in normal contemporary human pregnancies.

Our observations build on those of previous studies. A study conducted in Newcastle in the UK, using Z-scores for the distribution of birth weight, showed that the lowest stillbirth rate and infant mortality occurred in infants with a Z-score of +1, for both periods 1961–1980 and 1981–2000, during which the overall stillbirth rate in the UK fell from 23.4 to 4.7 per 1000 live births.[19] In a larger nationwide study in Norway, the lowest mortality rate was found among those with a birth-weight Z-score between +1 and +2.[20] In neither study was detailed information given on mortality, in relation to precise centiles or on the mortality pattern of infants born at or after 37 weeks' gestation. Thus, there are currently three studies indicating that the lowest rate of perinatal mortality occurs in infants with a birth weight around 1 SD above the mean, which makes the evidence quite convincing. Similarly, in another study the lowest prevalence of cerebral palsy by Z-score of weight for gestational age was found in infants with a Z-score of +1.[21] Our data also correspond well with those of a recent study of almost 12 000 term fetuses,[22] in which the Doppler pulsatility index (PI) was measured in the umbilical artery (UA) and fetal middle cerebral artery (MCA), and the cerebroplacental ratio (CPR) was calculated as the ratio MCA-PI:UA-PI. With increasing birth-weight centiles, the UA-PI fell progressively, the MCA-PI increased significantly and the multiples of the median of CPR decreased significantly. Failure to reach their growth potential, defined by the authors as an increased CPR, was only absent in fetuses with a birth weight > 90th centile and was increasingly present at lower centiles.[22] Also, our data showed the lowest antenatal death rate in infants with a birth weight >90th centile. In other words, optimal antenatal fetal growth seems to be consistently present only in large-for-gestational age fetuses.

Our finding, that the lowest perinatal mortality and morbidity are not present in infants with a birth weight around the 50th centile, but at a much higher centile, raises important issues about human development. As this effect did not depend on gestational age, it suggests that it is not linked to the timing of the onset of labor. The protective effect of a higher, although not the highest, birth weight against perinatal mortality is consistent with good nutrition in late gestation and the deposition of fat stores.[23] Similarly, the increased mortality rate in the smallest infants may result from inadequate pla-

cental function and/or nutrition in late gestation. However, our finding that between these extremes the majority of infants had a lower birth weight than that associated with a low mortality risk suggests that maternal constraint processes operate to reduce late-gestation growth to a degree optimal for the mother rather than her baby.[3] This may represent a mechanism that has evolved to optimize maternal survival in order to reproduce again as an aspect of Darwinian fitness.

The higher birth weight (centile) favorable for perinatal survival is also associated with a reduced risk of non-communicable disease in adult life. Studies on the Developmental Origins of Health and Disease (DOHaD) concept have shown that birth weight is inversely related, in a graded manner, to a risk of later cardiovascular and cerebrovascular death and to the development of impaired glucose tolerance and Type-2 diabetes.[24-28] Thus, in historical studies in the UK, the lowest risk for developing adult cardiovascular disease was found in infants weighing around 4 kg at birth, approximately the 90th centile at 40 weeks' gestation.[25,28] A high birth weight, indicative of absence of intrauterine growth restraint, and resulting in a low perinatal mortality, is therefore also favorable for long-term health.

The strength of the present study is the large population size, with information from The Netherlands Perinatal Registry, which contains data on approximately 95% of all births in The Netherlands.[29] Limitations include the lack of information on the cause of death, and possible inaccuracies in discriminating between antepartum and intrapartum death.[30] Moreover, the use of customized growth charts,[31] correcting for ethnicity and maternal height and weight, might have refined our data, but such information is unfortunately not present in The Netherlands Perinatal Registry.

It is sometimes said that birth is the second most-dangerous time in our lives. Our study shows that, from a survival perspective, optimal late-gestation fetal growth requires a live birth weight around the 80–90th centile. Such a high birth weight is favorable not only for short-term survival but also for long-term health. However, normative maternal constraint processes, believed to have evolved for a maternal fitness advantage, result in the majority of fetuses having a lower birth weight than this. This is associated with higher perinatal mortality, even in a high-income country today. When developing risk scores for perinatal mortality, including maternal characteristics such as age, parity, socioeconomic class, body mass index, height, smoking and estimated fetal weight, not only fetal weights < 10th centile should be included, but so should a graded, more sophisticated, risk-centile distribution.

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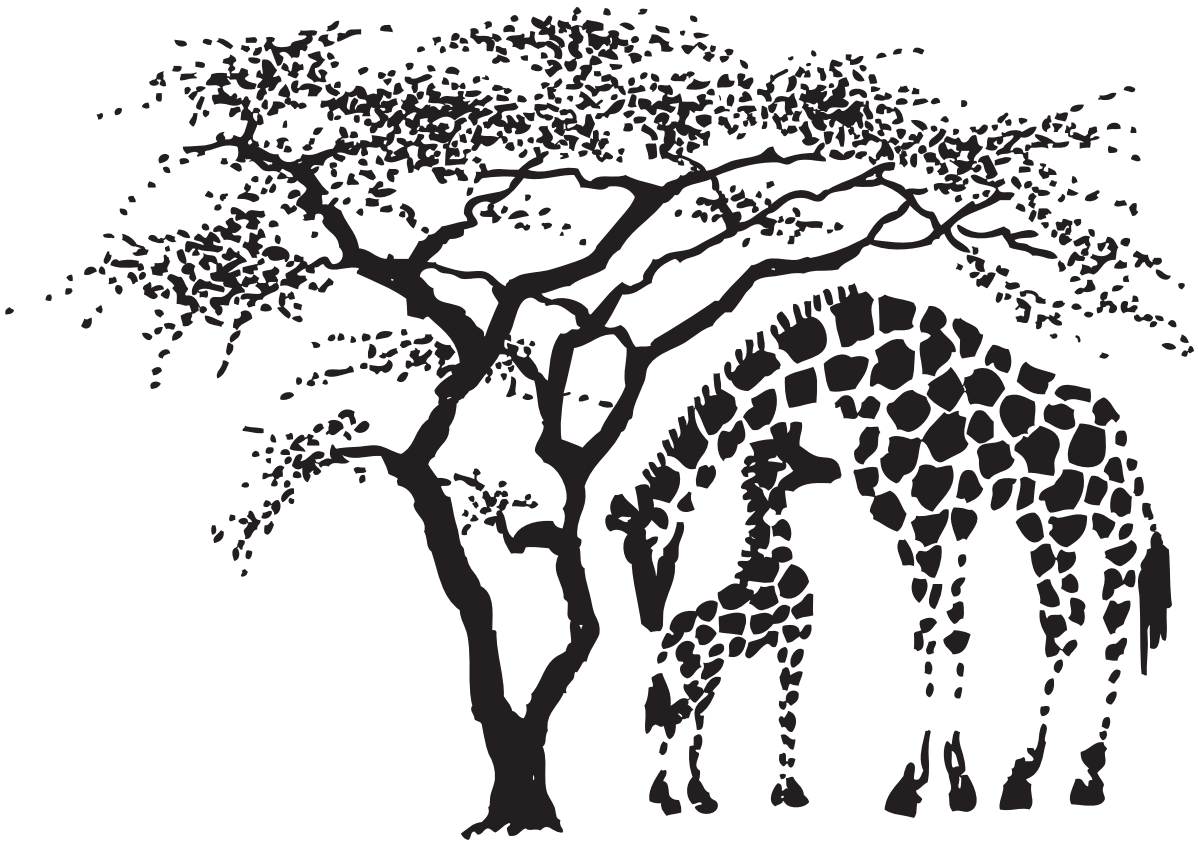

Chapter 3

Optimal fetal growth for survival in twins

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In preparation for submission

ABSTRACT

Background From an immediate survival perspective, optimal fetal growth in singletons requires a birth weight between the 80th and 90th centile for the population. However, studies on optimal fetal growth for survival in twin pregnancies, in relation to birth weight for gestational age, have not been conducted.

Objective To investigate the distribution of perinatal mortality in relation to birth weight for gestational age in children from twin pregnancies as compared to singletons.

Methods We studied perinatal mortality according to birth weight for gestational age in 1.170.534 singletons and 41.090 twins without congenital malformations and whom were delivered between 2002 and 2008 after 28 weeks of gestation. Data were collected from the nationwide Netherlands Perinatal Registry. Zygosity was determined by using the Weinberg formula.

Results Overall perinatal mortality was higher in twins compared to singletons, (7.28 vs 4.32 per 1000). Lowest perinatal mortality in twins occurred in infants with a birth weight between the 10-50th centile. However, after stratification for zygosity, lowest mortality rates for dizygotic twins were found to be at the 90th centile, which is comparable with singletons. For monozygotic twins, mortality was high at both low and high birth weight centiles.

Conclusion From an immediate survival perspective, optimal birth weight for all twins requires a birth weight between the 10-50th centile. However, after stratification, this only held for the monozygotic twins. Optimal birth weight for dizygotic twins was comparable to that of singletons and around the 90th centile, indicating that in these twins fetal growth is generally constrained below optimal for perinatal survival, just like in singletons.

INTRODUCTION

For singletons we know that, from an immediate survival perspective, optimal fetal growth in a high income country in babies without congenital abnormalities requires a birth weight between the 80th and 90th centile for the population.[1-5] This implies that the majority of such infants are born with a suboptimal weight for perinatal survival.[1] For long term health a higher birth weight also seems to be favorable, as risks for non-communicable diseases in adult life are lower with increasing birth weight.[6-9] In twins fetal growth is a more complex process than in singletons and zygosity and chorionicity have important influences. Twin-related pathologies, such as twin-to-twin transfusion syndrome (TTTS), with the resulting haemodynamic imbalance due to vascular anastomoses in the shared placenta, may also influence growth.[10-14] Twins have a fetal weight identical to singletons until around 30 weeks of gestation, whereafter it lags behind, possibly related to inadequate maternal cardiovascular adaptation or non-optimal placental location and/or perfusion.[15-17] Studies on perinatal mortality for twin pregnancies, accounting for birth weight for gestational age, for example by using birth weight centile groups or Z-scores, are lacking. Defining optimal fetal growth, and identifying high-risk groups with suboptimal or poor fetal growth is however important for the development of optimal risk reduction strategies and health-care programs. This study aims to investigate the distribution of perinatal mortality in relation to birth weight for gestational age in children from twin pregnancies as compared to singletons, with further investigation of the effect of zygosity of the distribution.

METHODS

This was a retrospective population-based cohort study. We collected data on births between 2002 and 2008 from The Netherlands Perinatal Registry (Perined). Data on all births occurring between 28 and 43 weeks gestation from singleton and twin pregnancies in the period 2002-2008 were collected. Twenty-eight weeks was chosen as the lower cut-off point to permit comparison with data from other countries in which there may be differences in registration practices at earlier gestational ages.[18] Children with congenital abnormalities were excluded. Gestational age was calculated from the first day of the last menstrual period or from an early ultrasound dating scan. Perinatal death was defined as fetal or neonatal death up to 7 days after delivery. Congenital abnormalities were defined as those recognized at birth, or at first admission, by the neonatologist.

Statistical analysis

The distribution of perinatal mortality according to birth weight for gestational age was studied in both twin and singleton pregnancies. Mortality was expressed as rate (number of deaths per 1000 infants). Comparisons were made between groups by using the Chi Square test. Data on births with missing birth-weight centiles were excluded from the analysis. As information on zygosity could not

directly be obtained from the database, we estimated both mono- and dizygotic perinatal mortality. We used an adaptation of the Weinberg formula (Weinberg 1902) which reads [using absolute numbers]: A. total twin mortality – B. dizygotic (DZ) twin mortality (mortality in dichorionic (DC) twins of different gender x 2) = C. mortality in monozygotic (MZ) twins.[19] With this formula it is assumed that a) the number of dizygotic twins with unequal gender is the same as that of dizygotic twins of equal gender, b) within dizygotic twins the mortality of one member of the twin is independent from the gender of the other member of the twin and c) within dizygotic twins a perfect balance exists between the number of male-male and female-female twins.

RESULTS

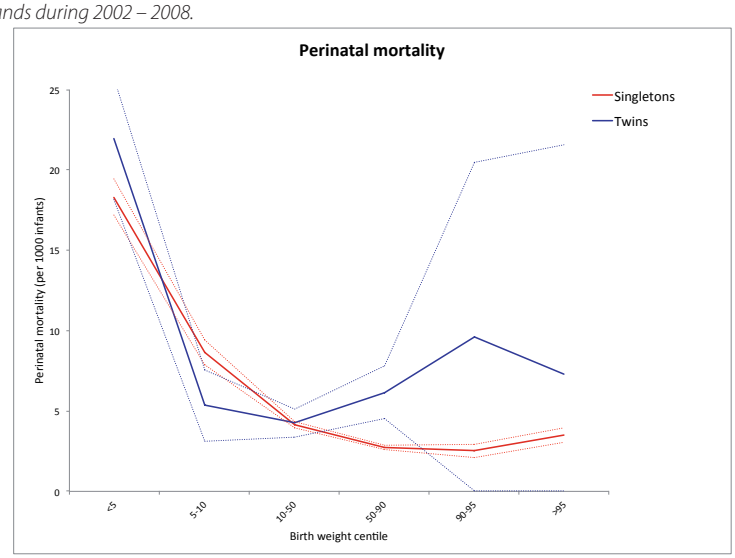
We studied 41.090 children of twin pregnancies and 1.170.534 children of singleton pregnancies, born between 2002 and 2008 after 28+0 weeks' gestation and without congenital abnormalities. The data on singletons have been published before.[1] There were 300 (0.73%) perinatal deaths in twins, and 5075 (0.43%) in singletons ($p<0.001$). For 4 (0.01%) children of twin pregnancies, of whom 1 died, and for 407 (0.03) singletons, of whom 17 died, birth weight centiles were not recorded, and these were therefore excluded from the analysis. 46% of twins were born preterm, in contrast to only 5% of singletons. Twins had on average a lower birth weight (centile) than singletons and 78% and 49% respectively had a birth weight below the 50th centile ($p<0.001$). In twins born preterm, 68% had a birth weight below the 50th centile and, in those delivered at term, 86% had a weight below the median for gestation. The distribution of perinatal mortality for twins and singletons by birth weight is shown in Table 1 & Figure 1. In both groups the highest mortality occurred in fetuses with a weight below the 5th centile. In singletons the lowest mortality occurred in fetuses with a birth weight between 80-90th centiles, whereas in twins the lowest mortality was found in those with a birth weight between the 10-50th centiles (Table 1; Figure 1). Data for infants born at term were almost identical to those of the whole population studied (Figure 2). For the preterm period, mortality rates were higher for singletons than for twins, 36.7 per 1000 vs 11.7 per 1000 respectively ($p<0.001$). In this period the lowest mortality rates for both singletons and twins were found between the 50-90th centiles (Figure 3).

Table 1. *Perinatal mortality according to birth-weight centile of singletons and twins born after 28 weeks' gestation in The Netherlands during 2002 – 2008*

	Singletons			All twins			Dichorionic twin unequal gender			Estimated Dizygotic twins **			Estimated Monozygotic twins**		
Birth weight centile	Total deaths (n)	Total infants (n)	PMR within centile group *	Total deaths (n)	Total infants (n)	PMR within centile group *	Total deaths (n)	Total infants (n)	PMR within centile group *	Total deaths (n)	Total infants (n)	PMR within centile group *	Total deaths (n)	Total infants (n)	PMR within centile group *
< 2.3	682	26805	25.44	107	3130	34.19	29	1108	26.17	58	2216	26.17	49	914	53.61
2.3-5	326	28296	11.52	18	2562	7.03	7	897	7.80	14	1794	7.80	4	768	5.21
5-10	453	52401	8.64	22	4110	5.35	6	1502	3.99	12	3004	3.99	10	1106	9.04
10-16	410	63805	6.43	14	4243	3.30	7	1508	4.64	14	3016	4.64	0	1227	0.00
16-20	226	45378	4.98	11	2760	3.99	1	1006	0.99	2	2012	0.99	9	748	12.03
20-50	1287	353219	3.64	69	15062	4.58	26	5358	4.85	52	10716	4.85	17	4346	3.91
50-80	1014	359603	2.82	39	7737	5.04	7	2787	2.51	14	5574	2.51	25	2163	11.56
80-84	116	48139	2.41	5	492	10.16	2	172	11.63	4	344	11.63	1	148	6.76
84-90	168	69010	2.43	10	541	18.48	2	191	10.47	4	382	10.47	6	159	37.74
90-95	145	57731	2.51	3	312	9.62	0	106	0.00	0	212	0.00	3	100	30.00
95-97.7	87	32384	2.69	0	78	0.00	0	31	0.00	0	62	0.00	0	16	0.00
> 97.7	144	33356	4.32	1	59	16.95	0	26	0.00	0	52	0.00	1	7	142.86
Total	5058	1170127	4.32	299	41086	7.28	87	14692	5.92	174	29384	5.92	125	11702	10.68

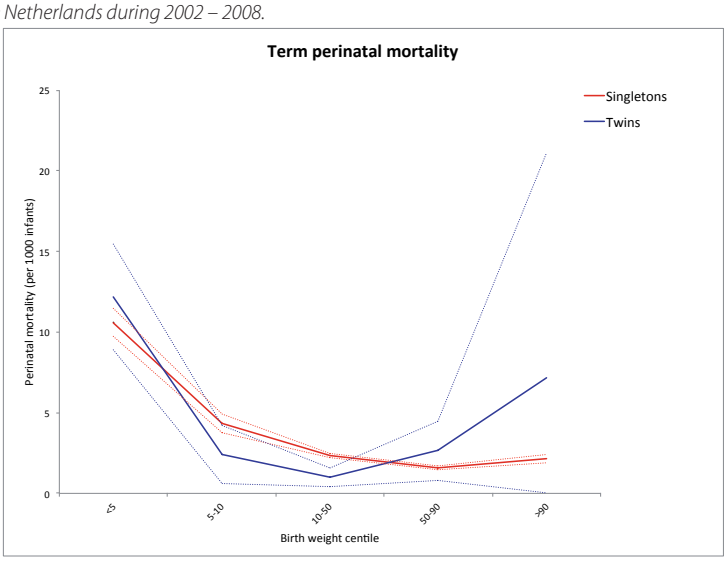
*n= number, PMR= perinatal mortality rate *Per 1000 infants , ** Calculated with Weinberg formula*

Figure 1. *Perinatal mortality according to birth-weight centile of singletons and all twins born after 28 weeks' gestation in The Netherlands during 2002 – 2008.*



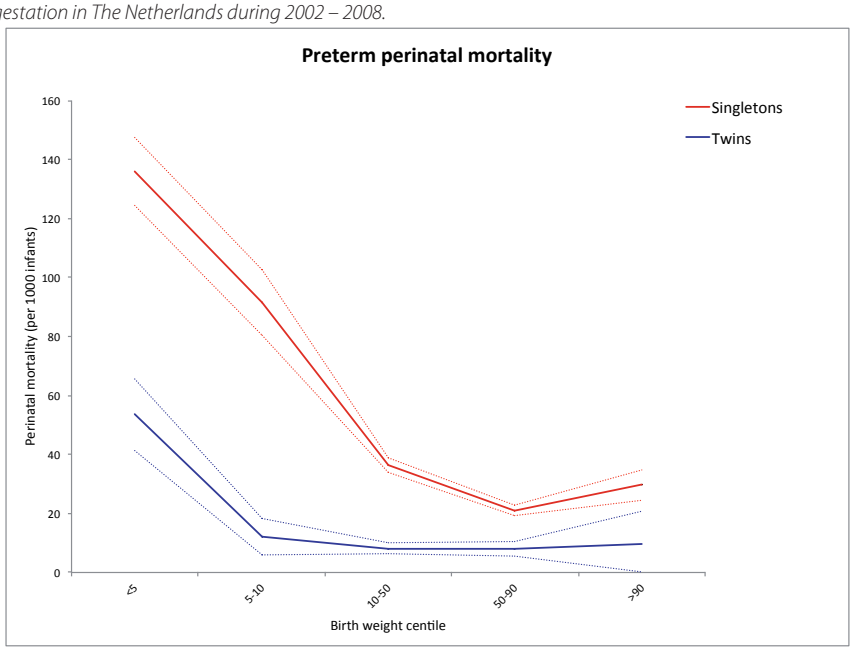
Perinatal mortality rates per 1000 infants with 95% confidence intervals.

Figure 2. *Term perinatal mortality according to birth-weight centile of singletons and all twins born after 37 weeks' gestation in The Netherlands during 2002 – 2008.*



The mortality rates for infants with a birth weight >90th centile were displayed in a combined group owing to the extremely small number of cases. Perinatal mortality rates per 1000 infants with 95% confidence intervals.

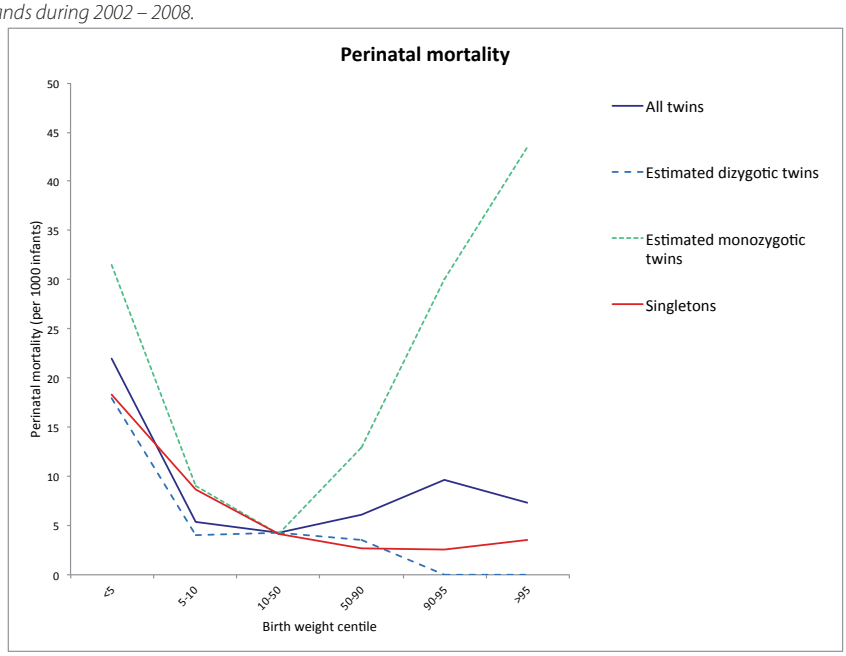
Figure 3. *Preterm perinatal mortality according to birth-weight centile of singletons and all twins born between 28-37 weeks' gestation in The Netherlands during 2002 – 2008.*



The mortality rates for infants with a birth weight >90th centile were displayed in a combined group owing to the extremely small number of cases. Perinatal mortality rates per 1000 infants with 95% confidence intervals.

The overall perinatal mortality rate in dizygotic twins was only slightly higher than in singletons, 5.92 as compared to 4.32/1000 respectively, but it was considerably higher in monozygotic twins (10.68/1000; Table 1). In DZ twins mortality fell with increasing weight centiles, whereas in MZ twins mortality was high at both low and high weight centiles, and equal to that in singletons and DZ twins only in the birth weight range between the 10-50th centiles (Table 1, Figure 4).

Figure 4. *Perinatal mortality according to birth-weight centile and zygosity of twins born after 28 weeks' gestation in The Netherlands during 2002 – 2008.*



Perinatal mortality rates per 1000 infants. (95% confidence intervals not displayed for clarity of the figure)

DISCUSSION

This study shows that, in a very large contemporary population of infants without congenital abnormalities, born after 28 weeks' gestation in a high-income country, overall perinatal mortality is higher in twins than in singletons. Earlier we have shown that this is largely due to a higher incidence of preterm delivery, and antenatal mortality in twins was found to be lower than in singletons before 37 weeks of gestation. (Chapter 4, this thesis) Twins born after 28 weeks of gestation had a lower weight for gestation than singletons and this held especially for the term period. This is in agreement with the literature.[15-17]

From an immediate survival perspective, the optimal birth weight for twins requires a birth weight between the 10-50th centiles. In contrast, for singletons the lowest perinatal mortality was found for a birth weight between the 80th and 90th centiles. However, after stratification for zygosity, the lowest mortality rates for dizygotic twins were found at the 90th centile, which is comparable with singletons. This implies that the difference for optimal fetal weight between singletons and twins as a group is caused by monozygotic twins.

All published studies on optimal birth weight for immediate survival in singletons are consistent, indicating that lowest perinatal mortality occurs in infants with a weight around the 90th centile.[1-5] Long term health perspectives are also highest in these infants.[6-9,20] The dizygotic twin data indicate

that this phenomenon also holds true for these twins, and consequently that it seems intrinsic to the human fetus. Earlier we have concluded that in singletons fetal weight is restrained below optimal for perinatal survival. We have postulated that maternal constraint processes operate to reduce late-gestation growth to a degree optimal for the mother rather than her baby, given the risk of obstructed delivery due to a large fetal head in conjunction with adaptations necessary due to bipedalism.[21,22] In twins birth weight centiles are lower than in singletons and this is likely to be due to a lesser degree of maternal cardiovascular adaptation to a twin pregnancy and/or to inadequate placental localization and perfusion.[15-17] Growth in dizygotic twins is consequently more constrained than in singletons.

The data on monozygotic twins show a different relation between birth weight centiles and perinatal mortality. The bimodal distribution of mortality may be due to the occurrence of TTTS with restricted growth in one fetus and overgrowth in the other one.[11,23] Unfortunately we could not examine this aspect in the perinatal database. In addition, it is possible that the processes controlling fetal growth, from the fetal demand rather than the maternal supply side, differ in monozygotic vs. dizygotic twins, perhaps due to genetic differences.

In the literature there are, to our knowledge, no data on perinatal mortality according to birth weight centiles in twin pregnancies. Most papers focus on birth weight discordance, showing an increased mortality in case of a weight discordance > 25%.[24,25] Only a few studies report on perinatal mortality based on birth weight, however none of these studies report on centiles. In a study from the USA, fetal and neonatal mortality rates in twins have been found to be lowest with a birth weight between 2500-3999g. For singletons the lowest mortality rates were found in children with a birth weight above 4000g.[26] In a study from Tanzania lowest mortality occurred at a weight of 3000 and 3738 g, respectively.[27] The differences in optimal weight for survival are likely to be related to the on average three weeks earlier delivery of twins as compared to singletons.[28,29]

A strength of this study is the large population size, with information from The Netherlands Perinatal Registry, which contains data on approximately 95% of all births in the Netherlands. However, some limitations need to be considered. First, the number of twins and the relatively low perinatal mortality rate hamper the strength of our findings. Moreover, information on the cause of death is lacking. Another important limitation is the lack of data on placental chorionicity and multiplet related conditions such as TTTS. The number of monozygotic twins was estimated using the Weinberg formula, a method frequently used in literature on twin pregnancies.[30] The reliability of this rule's assumptions has never been conclusively verified, nor rejected.[30] Finally, the use of customized growth charts,[31] correcting for ethnicity and maternal height and weight, might have refined our data, but unfortunately these data were not available.

CONCLUSION

Overall perinatal mortality was higher in twins than in singletons. From an immediate survival perspective optimal birth weight for all twins requires a birth weight between the 10-50th centiles. However, after stratification this only held for the monozygotic twins. Optimal birth weight for dizygotic twins was comparable to that of singletons and is around the 90th centile, indicating that in such twins, fetal growth is constrained below optimal for perinatal survival, as previously reported for singletons. Growth in dizygotic twins is more constrained than in singletons. In monozygotic twins the consequences of conditions such as TTTS are likely to have overridden the otherwise universal association between survival and high birth weight centile.

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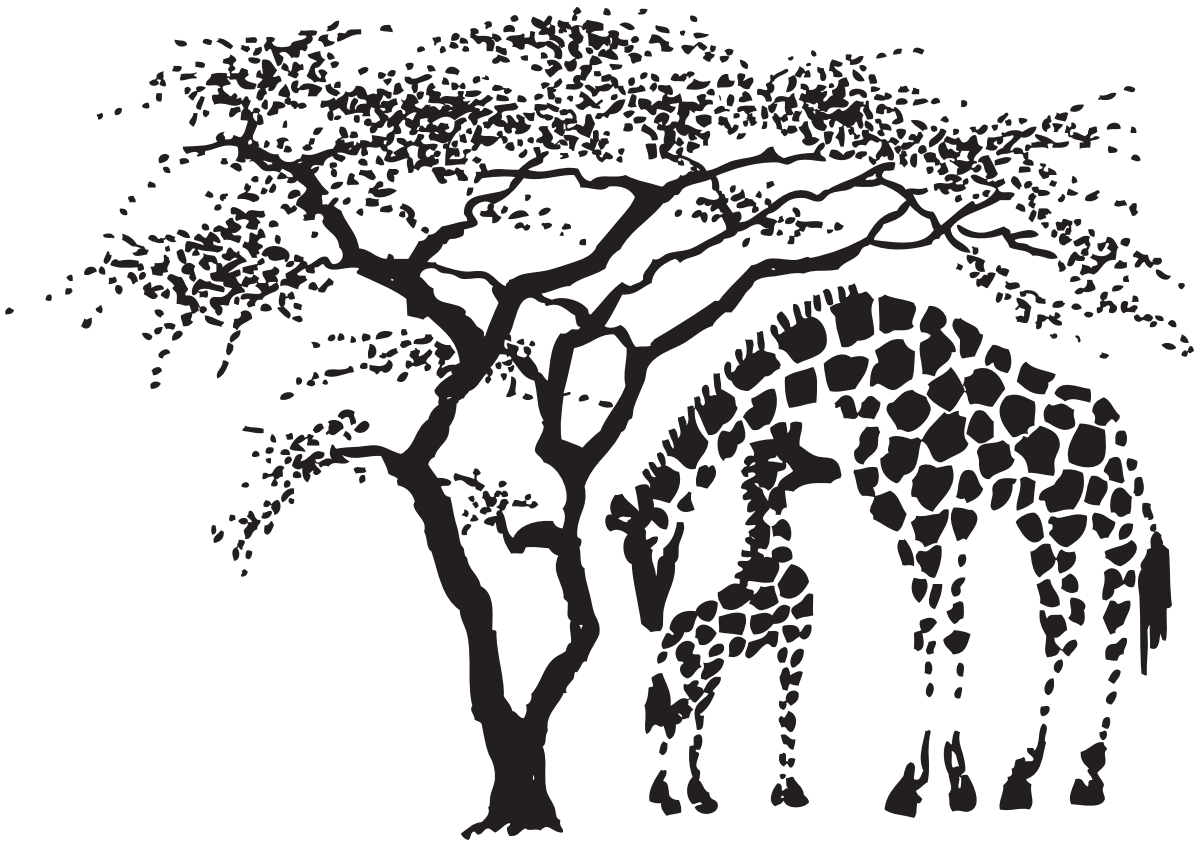

Chapter 4

Lower perinatal mortality in preterm born twins than in singletons; a nationwide study from The Netherlands

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Am J Obstet Gynecol. 2016 Oct.8, Epub ahead of print

ABSTRACT

Background Twin pregnancies are at increased risk for perinatal morbidity and mortality, due to many factors including a high incidence of preterm delivery. Compared to singleton pregnancies overall perinatal mortality risk is higher in twin pregnancies; however, for the preterm period perinatal mortality has been reported to be lower in twins.

Objective To compare perinatal mortality rates in relation to gestational age at birth between singleton and twin pregnancies, taking into account socioeconomic status, fetal sex and parity.

Study design We studied perinatal mortality rates according to gestational age at birth in 1.502.120 singleton pregnancies and 51.658 twin pregnancies without congenital malformations who were delivered between 2002 and 2010 after 28 weeks of gestation. Data were collected from the nationwide Netherlands Perinatal Registry.

Results Overall the perinatal mortality rate in twin pregnancies (6.6/1000 infants) was higher than in singleton pregnancies (4.1/1000 infants). However, in the preterm period, the perinatal mortality rate in twin pregnancies was substantially lower than in singleton pregnancies, 10.4 per 1000 infants as compared to 34.5 per 1000 infants, respectively, for infants born < 37 weeks; this held especially for antepartum deaths. After 39 weeks of pregnancy, the perinatal mortality rate was higher in twin pregnancies. Differences in parity, fetal sex and socioeconomic status did not explain the observed differences in outcome.

Conclusion Overall the perinatal mortality rate was higher in twin pregnancies than in singleton pregnancies, which is most likely caused by the high preterm birth rate in twins and not by a higher mortality rate for gestation, apart from term pregnancies. During the preterm period, the antepartum mortality rate was much lower in twins than in singleton pregnancies. We suggest that this might be partially due to a closer monitoring of twin pregnancies, which indirectly suggests a need for closer surveillance of singleton pregnancies.

INTRODUCTION

Twin pregnancies are at increased risk for preterm birth, intrauterine growth restriction, and a number of multiplet-related conditions. Monochorionic twins have additional risks for mortality and morbidity, primarily due to the twin-to-twin transfusion syndrome (TTTS) and congenital abnormalities.[1-5]

While registry data in Western countries (Euro-Peristat) confirm a crude 2- to 3-fold increased perinatal mortality risk of a twin pregnancy,[6] only few reports have compared mortality and morbidity rates between twin and singleton pregnancies by taking into account differences in gestational age at delivery. They all found a lower perinatal mortality rate in twins born before 37 weeks of gestation.[7-9] These studies were all small, with the exception of one (Kahn) and did not include separation between zygosity and chorionicity in twins, nor did they take into account known prognostic important factors such as parity and socioeconomic status (SES) of the mother and sex of the child.

The objective of this study was to compare perinatal mortality rates in relation to gestational age at birth between singleton and twin pregnancies, taking into account parity, SES, fetal sex and mode of delivery. For this study, we used a large national anonymized data set from the Netherlands Perinatal Registry (Perined).[10]

MATERIALS AND METHODS

General

This was a retrospective population-based cohort study. We obtained, after prior permission from the Perinatal Registry (Perined),[11] aggregated data and analyses on all births in the Netherlands between 2002 and 2010. This registry contains information on approximately 95% of all births from 16.0 weeks gestational age onwards, where coverage of twins is even higher. Details of this dataset can be found elsewhere.[10]

Variables

The Perined dataset includes routine maternal data on age, parity, socioeconomic background (zip-code based), and ethnic background. Information is available on intervention (induction of labor, mode of delivery [instrumental, elective and emergency cesarean delivery]), NICU admission of the child and specific features of the delivery.

Data on the child comprise of: singleton or multiplet, sex of the child, presence of congenital anomalies, gestational age at birth, birth weight, and Apgar score at 5 minutes. From birth weight, sex and gestational age, the birth weight is computed as centile score.[12]

Data are recorded on the size of the multiplet and for each child its rank number at birth. No information is available on zygosity/chorionicity. Congenital abnormalities were recorded if they were present and recognized, either at birth or at first NICU admission by the neonatologist. This includes

any abnormality already noticed during antenatal ultrasound scanning or, occasionally, with genetic tests. All children with congenital abnormalities were excluded. Gestational age was calculated from the first day of the last menstrual period or from an ultrasound dating scan by measurement of the crown-rump length (CRL) in the first trimester. In this period, 91% of the pregnancies had a reliable dating, which was obtained by a first- trimester dating scan.[10] For twins conceived spontaneously, dating was based on the mean CRL of both fetuses. Pregnancies achieved by assisted reproductive technology (ART) were dated based on the ART-derived gestational age.

In this report a gestational age of 37 weeks means: 37 weeks + 0 days - 37 weeks + 6 days containing whole-week groups. For this analysis births between 28+0 and 43+6 gestation were included, to allow comparison with data from other countries in which registration practices may differ at earlier gestational ages.[6] Children with missing gestational age at birth were excluded from the analysis. A total of 1839 children from a twin pregnancy were excluded because a twin pair could not be linked or information on congenital malformations or gestational age of one of the twins was missing. In this group there were 42 perinatal deaths. If one of the twins died before 28 weeks gestation both children were excluded from analysis. If one of the twins died after 28 weeks gestation and the pregnancy continued for the benefit of the other twin, the gestational age at birth was registered for both twins; the exact gestational age of death for the demised twin was not available in this database.

Perinatal mortality rate was defined as fetal or neonatal death up to 7 days after birth; antepartum mortality was defined as death occurring before labor, intrapartum mortality as death during labor, and neonatal mortality as death occurring within 0–7 days following live birth. This information is always available in all cases.

Statistical analysis

Perinatal mortality was expressed as rate (number of deaths per 1000 infants, including stillbirths). Mortality rate was subdivided to time of occurrence: antepartum, intrapartum and neonatal. Perinatal mortality rate was compared between singleton and twin pregnancies, according to gestational age. The mortality rates at 42 and 43 weeks gestation were not displayed owing to the extremely small number of cases. Comparisons were made between groups with the use of multivariate logistic regression with gestational age in the model or chi square test.

The mode of delivery in singletons and twins was studied. Vaginal delivery was divided in spontaneous vaginal delivery and instrumental delivery defined as delivery by forceps or a vacuum device. Cesarean delivery was divided into planned cesarean section, defined as a scheduled or elective cesarean delivery, and an emergency cesarean defined as any cesarean delivery that was not planned or scheduled.

To investigate the influence of parity, maternal SES, and child sex, we calculated perinatal mortality rates for each parameter for twins and singletons: for parity (0 vs. ≥1), SES ($p<20$ poor vs. $p>20$) and child sex (male/female). For classification of SES, the "socio-economic status score" was used as a proxy. This score takes into account the average income per household in a given four-digit postcode

area and the percentage of households with low income, without paid job and with low education level.[13,14] The level of SES was categorized as low if the score was under the 20th centile.

No information on zygosity was available in the data set. The only information we could obtain on zygosity indirectly were the twin pairs with unequal gender; male-female twins, these twins are per definition dizygotic and dichorial.

RESULTS

We studied 1.502.120 singleton infants and 51.658 twin infants born between 2002 and 2010 after 28 weeks of gestation. In singleton pregnancies there were 6.087 perinatal deaths (4.1/1000). For twins a total of 340 deaths occurred resulting in a perinatal mortality rate of 6.6 per 1000 infants. The perinatal mortality rate according to gestational age is displayed in table 1.

Table 1: *Perinatal mortality according to gestational age in singleton and twin pregnancies*

	Singletons			All twins			Dizygotic twins unequal gender		
Gestational age (weeks)	Total deaths (n)	Total infants (n)	PMR within week	Total deaths (n)	Total infants (n)	PMR within week	Total deaths (n)	Total infants (n)	PMR within week
28	326	1443	225.92	15	406	36.95	1	96	10.42
29	308	1718	179.28	23	592	38.85	5	174	28.74
30	278	2285	121.66	22	730	30.14	3	208	14.42
31	275	2899	94.86	16	1048	15.27	4	362	11.05
32	285	4130	69.01	21	1666	12.61	11	510	21.57
33	289	6337	45.61	22	2496	8.81	4	773	5.17
34	309	10732	28.79	41	3900	10.51	9	1270	7.09
35	350	17319	20.21	42	5088	8.25	14	1783	7.85
36	371	33999	10.91	47	8088	5.81	15	2684	5.59
37	530	85521	6.20	42	13588	3.09	19	5102	3.72
38	648	215586	3.01	25	9374	2.67	8	3621	2.21
39	720	357042	2.02	15	3502	4.28	4	1377	2.90
40	696	420017	1.66	8	1039	7.70	1	415	2.41
41	567	274563	2.07	1	129	7.75	0	59	0.00
42	134	67638	1.98	0	10	0.00	0	4	0.00
43	1	891	1.12	0	2	0.00	0	0	0.00
Total	6087	1502120	4.05	340	51658	6.58	98	18438	5.32

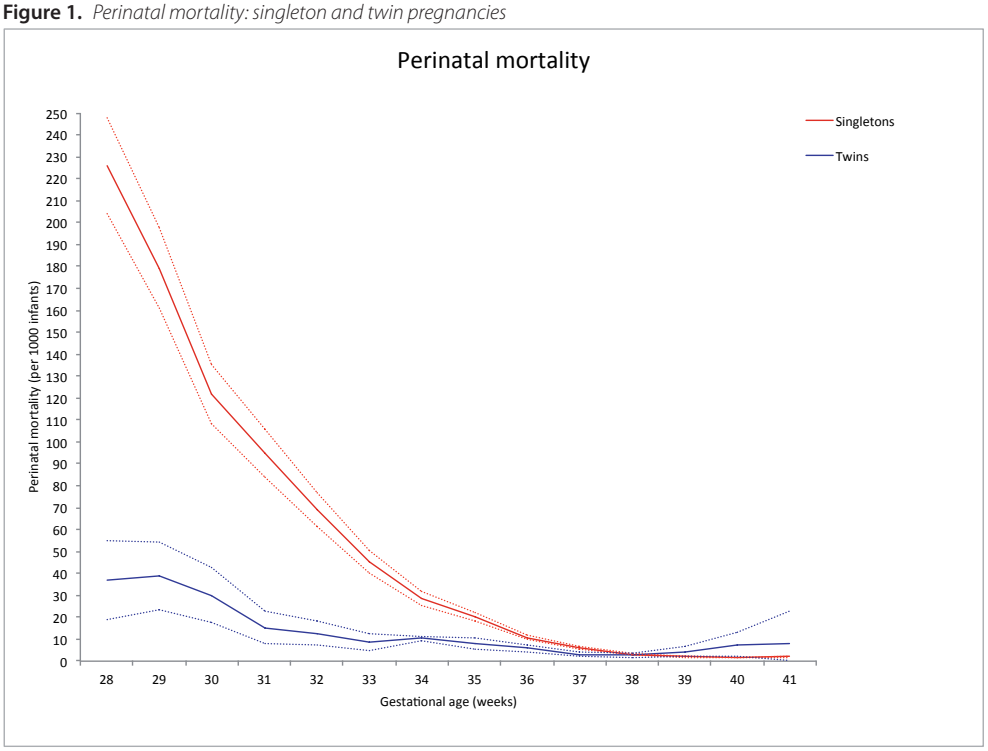
n= number, PMR= perinatal mortality rate, per 1000 infants

Multivariate logistic regression analysis: Singletons versus all twins p <0.001. Singletons versus dizygotic twins unequal gender p <0.001. All twins versus dizygotic twins unequal gender p 0.18.

Of all twins, 46% were born before 37 weeks of gestation, in contrast to only 5% in the singletons. For deliveries before 37 weeks perinatal mortality rate in twins was 10.4 per 1000 infants compared to 34.5 per 1000 infants in singletons. For infants born before 34 weeks mortality rates were 17.2 per 1000 infants in twins and 93.6 per 1000 infants in singletons.

In singleton pregnancies, perinatal mortality rate decreased with increasing gestational age, with the lowest mortality rate at 40 weeks gestational age. In twin pregnancies, mortality rates also decreased with increasing gestational age, with the lowest mortality rate at 38 weeks of gestation and an increase thereafter (Fig 1). In the preterm period, perinatal mortality in twins was substantially lower

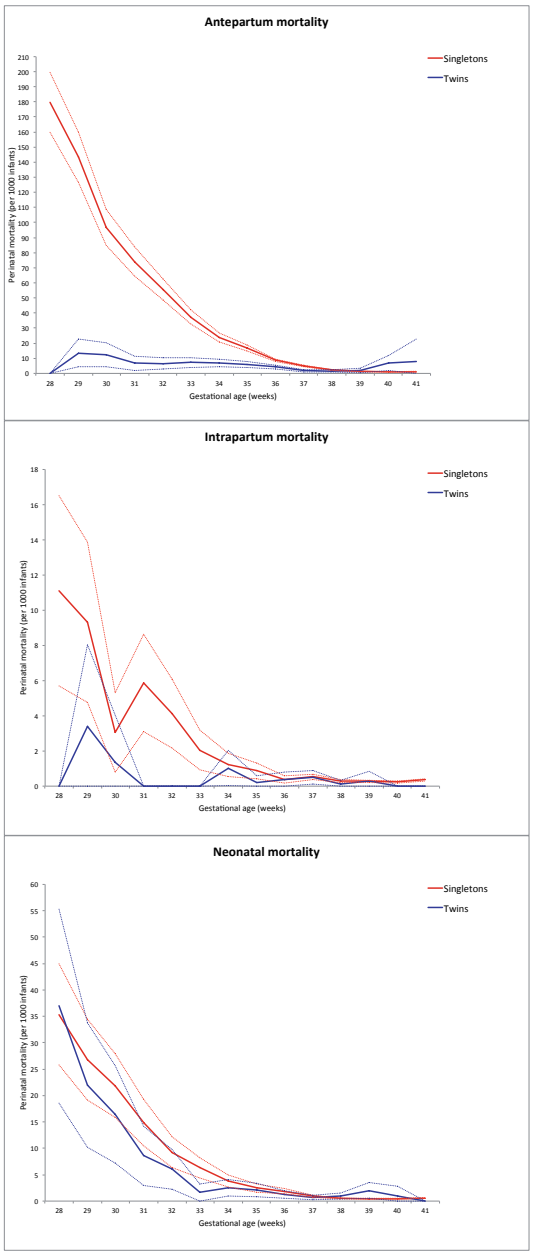
Figure 1. *Perinatal mortality: singleton and twin pregnancies*



The perinatal mortality rate in singleton and twin pregnancies according to gestational age at birth. Perinatal mortality rates per 1000 infants with 95% confidence intervals.

than in singleton pregnancies. After 39+0 weeks, the mortality rate was higher in twin pregnancies. In figure 2 perinatal mortality is displayed according to time period of occurrence of death. In both singletons and twins the majority of perinatal deaths occurred in the antepartum period, followed by the neonatal period and the intrapartum period, respectively. In singletons, the distribution of the

Figure 2. *Antepartum, intrapartum and neonatal mortality rates*



The perinatal mortality rate in singleton and twin pregnancies according to time of occurrence of death and gestational age at birth. Perinatal mortality rates per 1000 infants with 95% confidence intervals.

time period of death was, 72% antepartum, 9% intra partum and 19% neonatal; for twins this distribution was 59% antepartum, 6% intra partum and 35% neonatal. Antepartum mortality was significantly lower in twins as compared to singletons during the whole preterm period (p<0.001). After 40 weeks of gestation, antepartum mortality was significantly higher for twins (p 0.02). The intrapartum mortality rate was significantly lower between 31-33 weeks of gestation but did not differ in the term period. The neonatal mortality rate was more or less similar during the whole preterm period, mortality rates were higher for twins in the term period. Twins were more often delivered by cesarean section than singletons (Table 2).

Table 2: *Mode of delivery in singleton and twin pregnancies*

	Singletons		All twins		
Delivery mode	n	%	n	%	p value
Spontaneous	1.129.542	75.20	26.628	51.55	<0.001
Instrumental delivery	153.354	10.21	5.006	9.69	0.23
Planned cesarean delivery	95.792	6.38	10.720	20.75	<0.001
Emergency cesarean delivery	120.141	8.00	9.171	17.75	<0.001
Unknown	3.291	0.22	133	0.26	0.92

n=number, %=percentage

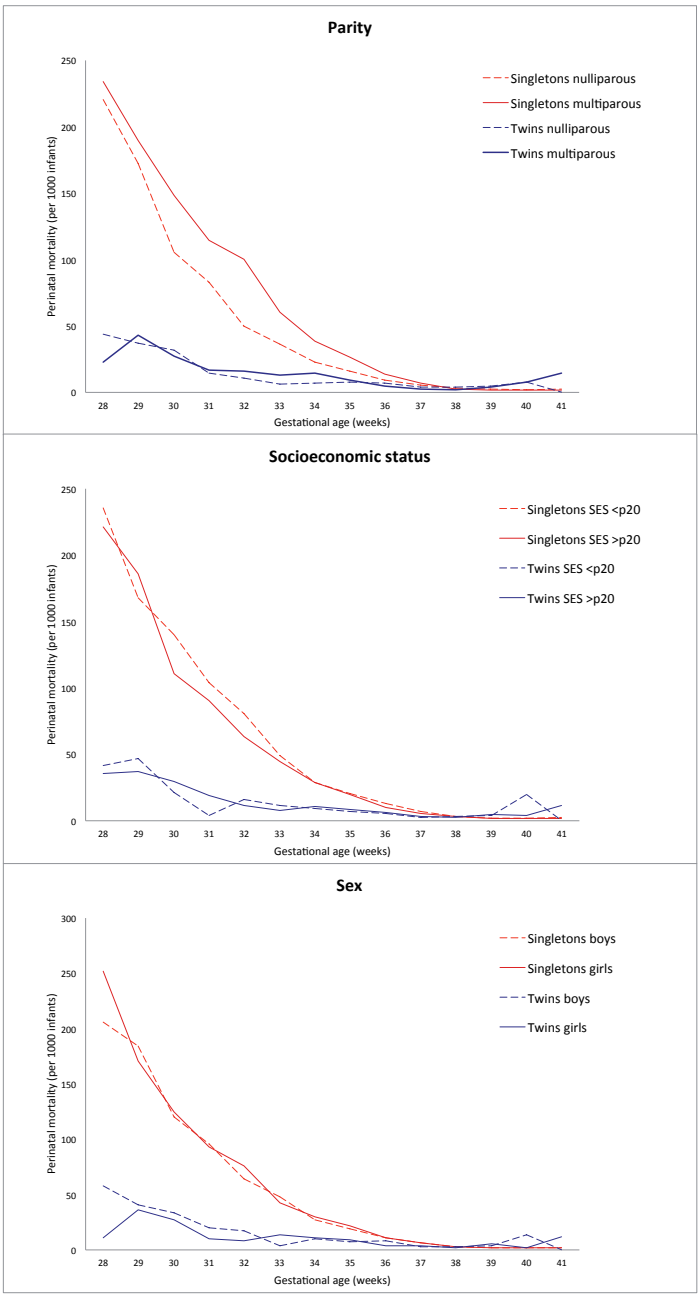
In both singleton and twin pregnancies, nulliparity was related to higher overall mortality rates. Poor maternal socioeconomic status (SES <20th centile) and male fetal sex were related to higher overall perinatal mortality rates in singleton pregnancies; in twin pregnancies, the rates were also higher in these groups but this was not significant (Table 3). Figure 3 shows twin and singleton mortality rates per parameter for gestational age. Within the singleton and twin pregnancy groups, mortality rates did not differ for parity, fetal sex and socioeconomic status.

Table 3: *Perinatal mortality in singleton and twin pregnancies according to parity, sex, and socioeconomic status*

	Parity			Socioeconomic status			Child sex		
	Nulliparous	*Multiparous*		*SES < p20*	*SES > p20*		*Boys*	*Girls*	
	PMR	PMR	p value	PMR	PMR	p value	PMR	PMR	p value
Singletons	4.53	3.65	<0.001	4.80	3.76	<0.001	4.16	3.92	<0.001
Twins	7.56	5.72	0.01	6.55	6.52	0.97	7.15	6.02	0.11

PMR: perinatal mortality rate per 1000 infants, SES: socioeconomic status

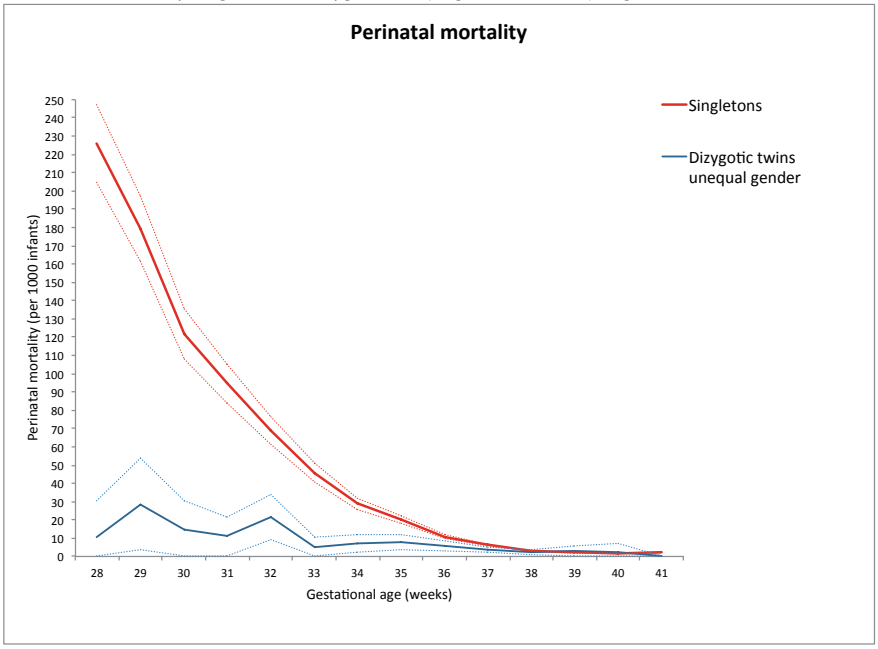
Figure 3. *Parity, socioeconomic status and sex*



The perinatal mortality rate in singleton and twin pregnancies according to parity, sex, and socioeconomic status (SES) at birth. Perinatal mortality rates per 1000 infants. P20= 20th centile.

Overall the perinatal mortality rate was slightly lower in dizygotic twins of unequal gender as compared to all twins; this held for most gestational ages (Table 1 & Fig 4). For infants born preterm, mortality rates were lower in dizygotic unequal gender twins than in singletons.

Figure 4. *Perinatal mortality: singleton and dizygotic twin pregnancies of unequal gender*



The perinatal mortality rate in singleton and dizygotic twin pregnancies with unequal gender (female-male twins) according to gestational age at birth. Perinatal mortality rate per 1000 infants with 95% confidence intervals. The mortality rates after 41 weeks gestation were not displayed owing to the extremely small number of cases.

COMMENT

This study shows that, in a large contemporary population of infants without congenital abnormalities born after 28 weeks' gestation, the overall perinatal mortality rate was higher in twins compared to singletons, which is in accordance with literature.[5] However, the perinatal mortality rate in preterm twins was considerably lower than in singleton pregnancies. For antepartum mortality rates, this held for the whole preterm period and for intrapartum mortality rates between 31 and 33 weeks of gestation, but not for neonatal mortality rates. Data did not change when parity, sex, socio-economic status were taken into account.

An explanation for the lower preterm perinatal death rates in twin pregnancies, as compared to singleton pregnancies, might be a difference in the etiology of preterm delivery. In the latter popula-

tion, many of the preterm deliveries are associated with pathologic conditions such as preeclampsia and fetal growth restriction, whereas in twins preterm contractions due to uterine overdistention is the most likely causative mechanism in the majority of cases.[15,16] However, it is unlikely that this may explain the lower antepartum mortality rate, especially since we included both mono- and dizygotic twins in our study. An explanation for the lower antenatal mortality rate may be that, in twin gestations with one fetal death, pregnancy might have been continued for the benefit of the other twin, resulting in a later (term) delivery and inaccuracy in determination of the timing of the fetal death. This is unlikely to occur in a singleton pregnancy. This may have lowered the preterm antenatal mortality rate and increased the term mortality rate in twin pregnancies. However, in this study, 73% of deaths in twins were recorded as having occurred during the preterm period (Table 1), i.e. this will not account for the differences found. Another important reason might be that twin pregnancies are considered to be at high risk and are therefore more closely monitored than singleton pregnancies in the same period. According to the national guidelines, this includes longitudinal ultrasound measurements of fetal biometry, screening for signs of TTTS in monochorionic twins, and care given by an obstetrician.[17] Such a monitoring does not occur in case of singleton pregnancies, which may be cared for by midwives, general practitioners or obstetricians. Uncomplicated dichorial twins are advised to be induced into labor before 40 weeks gestational age. For uncomplicated monochorial diamniotic and monoamniotic twin pregnancies, the induction of labor is advised at 36-37 and 32-34 weeks of gestation, respectively. For uncomplicated singletons pregnancies, induction of labor is advised at 42+0 weeks of pregnancy, induction may be considered between 41-42 weeks if the parents prefer this.[17]

Our observations regarding mortality in relation to gestational age at birth are supported by some previous studies. Kahn et al. evaluated the prospective risk of fetal mortality in singleton, twin, and triplet pregnancies and found lower antepartum mortality rates in twins compared to singletons, until week 37 of gestation.[7] In another study from Korea, 609.643 singleton and 9805 twin pregnancies were studied; the neonatal mortality rate was lower in twins than in singletons with a gestational age >29 weeks.[8] A third study on fetal and neonatal mortality rates for singleton and multiple births in the United States over the years 1985-1988 and 1995-1998 showed that, for deliveries before 37 weeks' gestation, fetal mortality rates were lower in twins than in singletons.[9] Finally a large study from Canada,[18] has shown that the risk of stillbirth in non-malformed twins was less than 1 per 1000 for infants born preterm, which is considerably lower than antenatal stillbirth rates that have been reported by us and others in singletons.[19,20]

The lower antenatal mortality rate in twin pregnancies, as compared to singleton pregnancies, may well imply that monitoring of singletons should be intensified to lower the stillbirth rate during the preterm period. However, it remains uncertain which assessment tools should be used (e.g., Doppler uterine artery, umbilical artery, middle cerebral artery; longitudinal growth assessment, markers of placentation, maternal risk factors). Moreover, identification of singletons at risk of stillbirth may prove difficult, given the fact that the majority will have a fetal weight within the normal range. [20]

In dizygotic twins of unequal gender, there was no clear increase in mortality until 40 weeks of gestation, which suggests that, in dizygotic twin pregnancies, modern surveillance expectant management may last until that age, although nowadays most authors suggest induction around 38 weeks of gestation.[18,21-23] Data from the Cochrane library indicate that delivery at 37 weeks' gestation, compared to ongoing expectant management for women with an uncomplicated twin pregnancy does not appear to be associated with an increased risk of morbidity or mortality; however specific data on chorionicity could not be provided.[21]

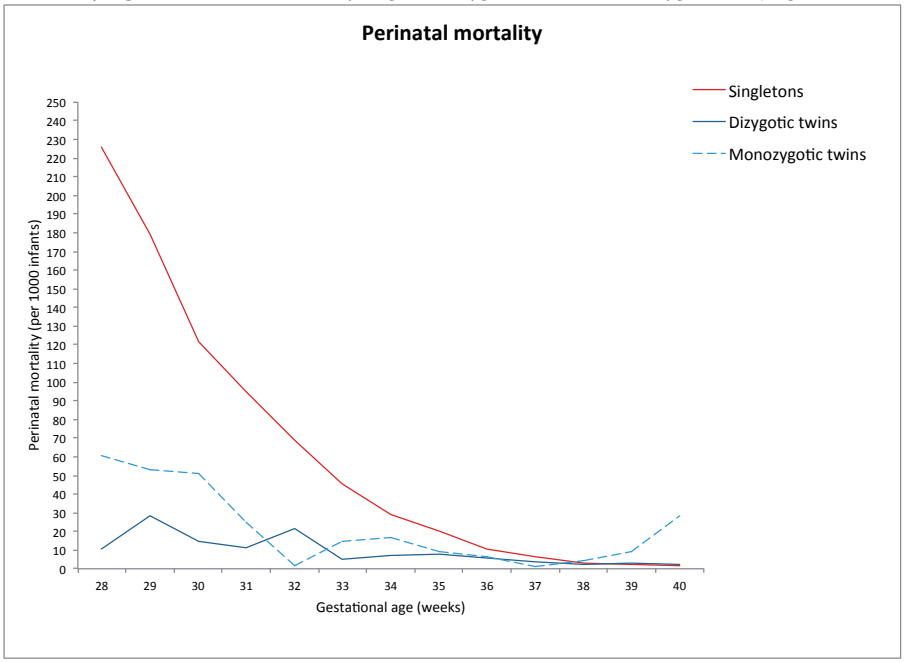
A strength of this study is its large population-based sample size. However, some limitations of this study need to be mentioned. Twin pregnancies with missing data of one or both children were excluded, as were singletons with missing data. In case all 42 deaths that were excluded in the twin group had occurred in the preterm period, mortality rates in twin pregnancies would have been about 17% higher, which would still be considerably lower than that in singleton pregnancies during the preterm period. The overall perinatal mortality rate in twins born before 37weeks of gestation was 10.4/1000 and in singletons 34.5/1000 (Table 1); addition of 42 deaths to the twin cohort born <37 weeks, would increase perinatal mortality to 12.1/1000. Other limitations include the lack of information on the causes of death and possible inaccuracies in the registration of the time of occurrence of death, especially for distinction between antepartum and intrapartum death.[24] Another limitation is the lack of data on zygosity and placental chorionicity. The perinatal mortality rate is higher in monozygotic/monochorial twins.[2] To estimate perinatal mortality rates in monozygotic twin pregnancies the Weinberg formula may be used.[25] With this formula, it is assumed that a) the number of dizygotic twins with unequal gender is the same as that of dizygotic twins of equal gender, b) within dizygotic twins, the death of one member of the twin is independent from the gender of the other member of the twin and c) within dizygotic twins, a perfect balance exists between the number of male-male and female-female twins. With this formula, mortality in monozygotic twins may be calculated as follows using absolute numbers: A. total twin mortality – B. dizygotic twin mortality (mortality in dizygotic twins of different gender x 2) = C. mortality in monozygotic twins. By using this formula, we found that overall the perinatal mortality rate was higher in monozygotic twins than in dizygotic twins; this held for most gestational ages (supplementary figure 1). However, preterm mortality rates were lower in monozygotic twins than in singletons. This method has been used frequently in previous literature on twin pregnancies. The reliability of this rule's assumptions has never been conclusively verified, nor rejected.[26] We have chosen not to include these data in the results section.

CONCLUSION

Overall perinatal mortality was higher in twin pregnancies than in singleton pregnancies. This is most likely caused by the high preterm birth rate in twins and not by a higher mortality rate for gestation, apart from term pregnancies. During the preterm period, the perinatal mortality rate, and especially

stillbirth, was much lower in twin deliveries than in singleton deliveries. We hypothesize that this might, among others, be due to the closer monitoring of twin pregnancies, which indirectly suggests a need for closer monitoring of singleton pregnancies. Future research should concentrate on data on zygosity and causes of death to develop optimal risk reduction strategies.

Supplementary Figure S1. *Perinatal mortality, singleton, dizygotic twins and monozygotic twin pregnancies*



The perinatal mortality rate in singleton and twin pregnancies according to zygosity and gestational age at birth. Data on twin zygosity were estimated using the Weinberg formula. The mortality rates after 41 weeks gestation were not displayed owing to the extremely small number of cases.

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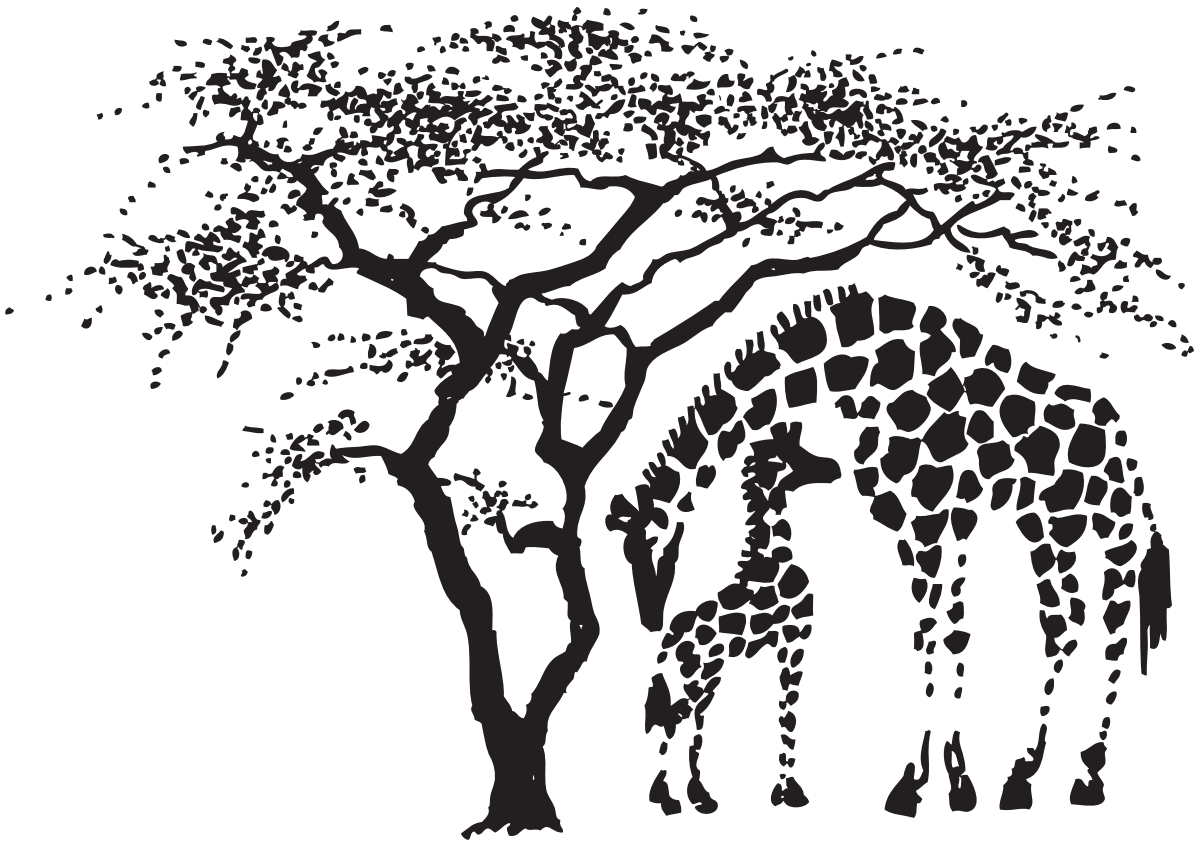

Chapter 5

Identification of near term small-for-gestational age fetuses at risk for impaired outcome (SAFARI study)

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ABSTRACT

Background Term small-for-gestational-age (SGA) fetuses are difficult to identify since most assessment tools fail during the term period. Moreover, it remains a challenge in clinical practice to distinguish between pathologically small fetuses and constitutionally healthy small fetuses.

Objective To systematically evaluate the potential of diagnostic antenatal ultrasound variables to identify small-for-gestational-age fetuses at risk of short term adverse outcome at inclusion and during antenatal follow-up.

Study design Data were combined of two prospective longitudinal observational studies conducted between August 2012 and October 2015 at the University Medical Centers of Utrecht and Groningen, the Netherlands. Women with singleton pregnancies between 34 and 37 weeks' gestation with fetuses suspected to be small for gestational age were included. SGA was defined as an estimated fetal weight or fetal abdominal circumference below the 10th population centile.

Results A total of 43 women were included. There was no correlation for any single Doppler measurement at intake with neonatal outcome. However, Doppler changes with time from normal to abnormal values were related with impaired outcome, with the cerebro-placental ratio (CPR) and the pulsatility index (PI) of the ductus venosus (DV) as the best parameters to identify the SGA fetus at risk.

Conclusion In (near) term SGA fetuses a change of CPR or DV PI from normal to abnormal is associated with adverse neonatal outcome. Integrated risk models based on large study populations are necessary to determine optimal clinical management.

INTRODUCTION

Term small-for-gestational-age (SGA) fetuses present the obstetrician with at least two difficulties. Firstly they are difficult to identify. After identification, the second challenge concerns the distinction between pathologically small fetuses, those with true intra-uterine growth restriction (IUGR) due to a suboptimal placental function, and constitutionally healthy small fetuses. Identification of IUGR fetuses is important because of the increased risk of perinatal morbidity and mortality.[1-4] A low birth weight also has consequences for the future development, especially for cardiovascular, metabolic and neurological development.[5-8] When recognized, another challenge is formed by limited therapeutical options. To date the only possible intervention is adequately timing and mode of delivery. Adequate recognition of small fetuses at risk would allow targeted intervention and prevent too liberal and unnecessary interventions with the potential of adverse effects in low risk small fetuses.[9]

Many ultrasound variables have been evaluated to distinguish between constitutionally small and pathologically small fetuses. However such a distinction is difficult, since most assessment tools fail during the term period. Doppler evaluation of flow patterns in the umbilical artery (UA) are used routinely in preterm growth restricted fetuses but are normal in most cases in term small-for-gestational-age fetuses.[10] This is due to the fact that a high placental resistance occurs only when more than 1/3rd of placenta function is deficient.[11,12] Abnormal values of the cerebroplacental ratio (CPR), defined as the ratio between the UA and the middle cerebral artery (MCA), has been shown to be related to a higher incidence of obstetrical intervention due to fetal distress, a lower cord blood pH level and increased admission rate to the neonatal intensive care unit (NICU).[13-15] Doppler flow patterns of the UtA seem to be more often abnormal than flow patterns in the umbilical arteries and have also been related to adverse perinatal outcome.[16-19]

The aim of this study was to systematically evaluate the potential of diagnostic antenatal ultrasound variables to identify small-for-gestational-age fetuses at risk of short term adverse outcome. Data on ultrasound parameters at inclusion in the study and on changes in ultrasound parameters with time were studied separately.

MATERIALS AND METHODS

Study population

A prospective longitudinal observational pilot study was conducted between August 2012 and August 2015 at the University Medical Center Utrecht, in The Netherlands. Data were combined with a similar prospective observational cohort study performed between June 2012 and September 2014 at the University Medical Center Groningen, in the Netherlands. Both studies were approved by the local Medical Board and Medical Research Ethics Committee. All participants provided written informed consent. Women with singleton pregnancies between 34 and 37 weeks' gestation with

fetuses suspected to be small for gestational age (SGA) were eligible to participate. SGA was defined as an estimated fetal weight (EFW) or fetal abdominal circumference (AC) below the 10th population centile measured by ultrasound twice, with at least 7 days between both measurements. The EFW centile was based on sonographic measurements of the head circumference (HC), femur length (FL) and abdominal circumference (AC) (Hadlock-3).[20,21] Exclusion criteria were multiple gestations, pregnancies complicated by chromosomal and/or structural anomalies, antenatal intra-uterine infection or signs of an intra-uterine infection during labor (maternal rectal temperature >38.5 degrees and fetal tachycardia with a fetal heart rate > 170 beats per minute).

For all participants, the pregnancies were reliably dated using an early ultrasound scan. Medical information and demographic characteristics were collected from the medical charts. All participants obtained an advanced ultrasound investigation at inclusion, including biometric measurements, Doppler measurement of the umbilical artery (AU), middle cerebral artery (MCA), the ductus venosus (DV), and the uterine artery (UtA). For all Doppler measurements the pulsatility index (PI) was calculated by the following equation: PI = (peak systolic velocity - end diastolic velocity) / time averaged velocity = (PSV - EDV) / TAV. The cerebroplacental ratio (CPR) was calculated as UA PI divided by MCA PI.[22] All participants were followed at least once a week until delivery according to standard clinical care. We conducted a weekly ultrasound examination, with measurement of the Amniotic Fluid Index (AFI), Doppler measurements of the UA, MCA and routine CTG surveillance. Fetal biometry, including HC, AC, FL and EFW was performed every 14 days. Because neonatal mortality or severe morbidity was expected to be rare, we created a composite measure of adverse outcomes as the primary outcome. Composite measure of adverse outcome was defined as mortality, intra-uterine death or death before hospital discharge, and/or antepartum obstetrical intervention for suspected fetal distress based on cardiotocography (CTG) abnormalities and/or asphyxia (pH level <7.05 immediately after birth), and/or 5-min Apgar score <7, and/or admission to the neonatal intensive care unit (NICU).

Clinicians were blinded for the MCA, DV and UtA Doppler measurements that were performed solely for research. However, the other measurements were also conducted for routine standard care and used for analysis. For these standard care measurements clinicians were not blinded.

Data preparation and statistical analysis

All biometric and Doppler measurements were transformed into Z-scores (standard deviation scores; SDS) before analysis. Z-scores were calculated with the use of gestational age-specific means and standard deviations derived from tables and/or mathematical formulae provided in published articles with normative reference charts. The following well-established reference charts were used: for FAC, FL, and HC (Verburg B et al., 2008);[23] for umbilical artery PI, middle cerebral artery PI, and CPR (Baschat & Gembruch, 2003),[24] ductus venosus PI (Hecher et al., 1994),[25] and uterine artery PI (Gómez et al., 2008).[26]

Doppler values were considered abnormal if a PI measurement was ≥ P95 for a particular reference chart (umbilical artery, uterine artery, DV). For CPR and MCA, a PI value ≤P5 was considered abnormal.

According to criteria, each included fetus had a FAC and/or EFW value at inclusion below the 10th percentile (P10). Note that the P10 equals -1.28 SDS. Fetal birth weight was expressed as Z-score according to Dutch norm charts, adjusted for parity, sex, and gestational age.[27] Pearson correlation coefficients were calculated for the FAC/EFW Z-scores measured at inclusion and birth weight Z-scores.

Statistical analyses were performed with the use of the Statistical Package for the Social Sciences (IBM SPSS, version 23.0, Chicago, IL, USA). Demographics and baseline characteristics were presented using summary statistics. For 9 cases information on the umbilical arterial pH value at birth was missing. Therefore, we applied a previously validated multiple imputation (10x) method using observed patient characteristics.[28,29] Missing data were imputed using a logistic regression model that included the following variables: parity, birth weight, gestational age at birth, fetal gender, smoking, and the arterial pH level after birth.

Statistical analysis was conducted in two (complimentary) steps. First, generalized linear modeling (GLM) was used to create prediction models for the composite adverse outcome measure. Model 1 included the FAC/EFW Z-score at inclusion as continuous predictor (risk) factor and a number of potential co-variables. In Model 2, various Doppler indices (either as a continuous or dichotomized variable) obtained at inclusion were added and each evaluated for their contribution to the model. A logistic regression model was used for prediction of the composite measure of adverse outcome in relation to fetal birth weight, gestational age at birth and the course of Doppler indices between inclusion and birth. Special attention was paid to possible changes in Doppler indices that occurred any time after inclusion, resulting in two possible developmental subgroups: one with normal PI values at inclusion that remained normal (normal-to-normal), and one with normal values at inclusion that became abnormal any time after inclusion (normal-to-abnormal). The following co-variables were evaluated in all models: gender, parity, maternal age, BMI, and smoking.

RESULTS

A total of 43 women were included in the study. Mean gestational age at inclusion was 34.5 (SD 2.6) weeks of pregnancy. Baseline patient and pregnancy outcome characteristics are shown in Table 1. The mean gestational age at birth was 38.2 weeks and mean birth weight was 2374 g. At birth, 17 infants had a weight <2.3rd centile, 10 had a weight between the 2.3rd and 5th centiles, and 16 had a weight >5th centile. The latter group included 11 cases weighing more than the 10th centile at birth (range 10th - to 52nd centile). There was no case of perinatal mortality; 13 infants had at least one adverse outcome measure. None of the variables presented in Table 1, including the adverse outcome measures, differed statistically across the three birth weight groups, except birth weight (Z-score) as expected (data not shown). The total numbers of biometric and Doppler measurements, the mean numbers per fetus, and the gestational ages at first and final scans are presented in Appendix I.

Table 1: *Baseline patient and outcome of pregnancy characteristics*

Variable	Total group (n=43)
Parental characteristics	
Maternal age (y); M (SD); R	31 (5); 21 – 42
Multipara; n (%)	22/43 (51%)
Smoking (y); n (%)	13/43 (30%)
Maternal height (cm); M (SD); R	167 (7); 153 – 184
Maternal BMI (kg/m2); M (SD); R	23.5 (5.7); 16.6 – 43.1
Paternal height (cm); M (SD); R	181 (7); 162 - 195
Maternal education (high); n (%)	21/42 (50%)
Paternal education (high); n (%)	18/41 (44%)
Neonatal characteristics	
Antenatal corticosteroids (y); n (%)	6/42 (14%)
GA at birth (wk); M (SD); R	38.2 (1.5); 34.3 – 41.5
Birth weight (g); M (SD); R	2374 (447); 1550 - 3160
BW Z-score; M (SD); R	-1.77 (0.76); -3.50 to 0.06
Gender (male); n (%)	14/43 (33%)
Apgar 1'; M (SD); R	8.3 (1.3); 2 – 9
Apgar 5'; M (SD); R	9.3 (0.8); 7 – 10
Apgar 1' (<7); n (%)	2/43 (5%)
Apgar 5' (<7); n (%)	0/43 (0%)
Asphyxia (pH < 7.05); n (%)	1/34 (3%)
Perinatal mortality; n (%)	0/43 (0%)
Obstetric intervention for fetal distress; n (%)	10/43 (23%)
Admission to NICU (%)	4/43 (9%)
Poor Composite Score; n (%)	13/43 (30%)

M: mean, SD: Standard Deviation, R: Range. n: Number, %: Percentage. NICU: neonatal intensive care unit. GA: gestational age, BW: birth weight

There was a good association between the degree of fetal smallness assessed by the FAC/EFW Z-score at inclusion and birth weight Z-score (R=0.44, p<0.0001; Figure 1). The FAC/EFW Z-score was also associated with the composite outcome score, with favorable outcome being more often present for higher FAC/EFW Z-scores (Figure 2).

Figure 1. *Relationship between fetal smallness at inclusion and birth weight Z-score*

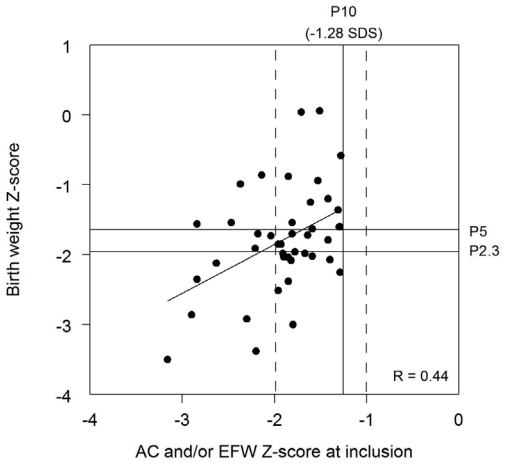
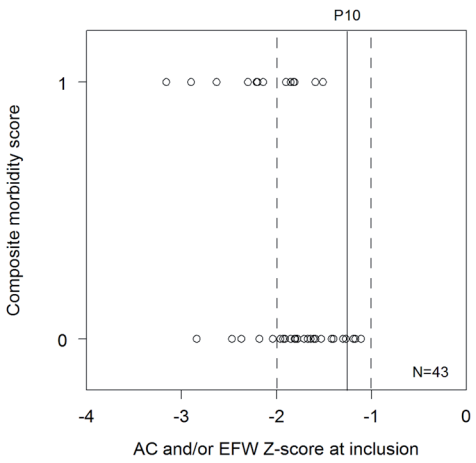


Figure 2. *Relationship between fetal smallness at inclusion and composite outcome score*



In Table 2 the relationship is shown between ultrasound variables at inclusion and outcome of pregnancy. The composite score of adverse outcome was significantly predicted by the FAC/EFW Z-score, but none of the Doppler indices, nor any of the confounding variables was related to outcome.

Table 2. *Prediction model for Composite Outcome measures using ultrasound measurements made at inclusion (logistic regression)*

Variable	Model		
	Beta (SE)	OR (95% CI)	Significance
Poor Composite score		N=43; Nagelkerke R2: 0.171	
Intercept	-4.15 (1.59)		0.016
FAC-EFW Z-score	-1.70 (0.78)	0.18; 0.04 – 0.84	0.029
Co-variable	No effect		
Doppler index (any)	No effect		

Confounders tested: gender, parity, smoking

Table 3 and 4 present a prediction model for composite morbidity score and the course of Doppler indices between inclusion and birth. Only few predictors (maternal age, smoking, birth weight) had a slight, non-significant, effect on the composite neonatal morbidity score, while gender, parity, GA at birth, and BMI had not (Model 1; Tables 3 and 4). The model improved considerably by addition of either the dichotomized changes with time in Z-scores of the CPR or ductus venosus PI as main effects ($\beta = 2.74$ (SE 1.00), $p<0.01$; and $\beta = 1.76$ (SE 0.83), $p<0.05$, respectively; not shown in Tables 3 and 4). Regarding CPR there were 16 cases in which the ratio changed from normal at intake to abnormal with time and 25 cases which remained normal, for DV this concerned 12 cases and 28 cases respectively. For both Doppler changes we found significant interaction effects with GA at birth, birth weight (only for CPR), and BW Z-score as shown in Tables 3 and 4, Models 2 through 4, respectively. The differential effects for both subgroups are presented in Figure 3. If the Doppler indices that were normal at inclusion remained unaltered until delivery (normal-normal subgroup), the probability of neonatal morbidity was relatively low and decreased (slightly) with advancing gestation at birth, birth weight or its Z-score. On the other hand, the chance of neonatal problems increased dramatically in cases in which abnormal values of the CPR (≤P5) or DV PI (≥P95) occurred after inclusion (normal-abnormal subgroup; Figure 3).

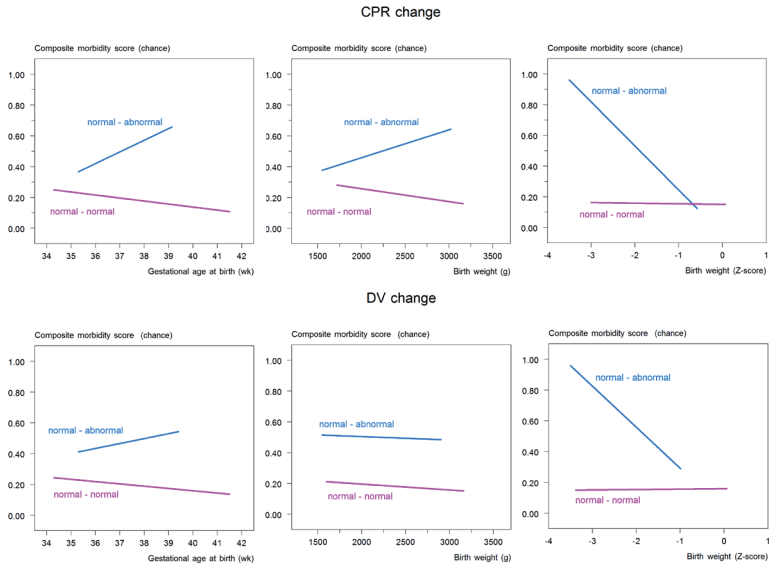
Table 3 *Prediction model for Composite morbidity score without (Model 1) and with Doppler indices CPR Z-score (Models 2 through 4). Additional predictors tested and found non-significant: gender, parity, and maternal BMI. Logistic regression analysis*

Variable	Model 1 (N=43)			Model 2 (N=41)			Model 3 (N=41)			Model 4 (N=41)		
	Beta (SE)	OR (95% CI)	*P*	Beta (SE)	OR (95% CI)	*P*	Beta (SE)	OR (95% CI)	*P*	Beta (SE)	OR (95% CI)	*P*
Composite morbidity and CPR Z-score												
Constant	-2.77 (3.60)		0.44	-8.10 (3.35)		0.016	-6.29 (2.78)		0.024	-8.45 (3.56)		0.018
Maternal age	0.16 (0.09)	1.17; 0.99 – 1.39	0.061	0.19 (0.09)	1.21; 1.01 – 1.46	0.041	0.15 (0.08)	1.16; 0.99 – 1.36	0.06	0.20 (0.10)	1.22; 1.01 –1.49	0.046
Smoking	1.69 (0.93)	5.42; 0.87 – 33.59	0.069	---		n.s.	---		n.s.	---		n.s.
GA at birth (wk)	---		n.s.	---		n.s.	---		n.s.	---		n.s.
Birth weight (kg)	-1.62 (0.91)	0.20; 0.03 – 1.19	0.076	---		n.s.	---		n.s.	---		n.s.
CPR Z-score change by GA at birth				0.07 (0.03)	1.07; 1.02 – 1.13	0.007						
CPR Z-score change by Birth weight							0.80 (0.36)	2.21; 1.09 – 4.50	0.028			
CPR Z-score change by BW Z-score										-1.37 (0.48)	0.25; 0.10 – 0.65	0.004

Table 4 *Prediction model for Composite morbidity score without (Model 1) and with Doppler indices DV Z-score (Models 2 through 4). Additional predictors tested and found non-significant: gender, parity, and maternal BMI. Logistic regression analysis.*

Variable	Model 1 (N=43)			Model 2 (N=40)			Model 3 (N=40)			Model 4 (N=40)		
	Beta (SE)	OR (95% CI)	*P*	Beta (SE)	OR (95% CI)	*P*	Beta (SE)	OR (95% CI)	*P*	Beta (SE)	OR (95% CI)	*P*
Composite morbidityand DV Z-score												
Constant	-2.77 (3.60)		0.44	-5.75 (2.61)		0.028	-5.21 (2.47)		0.035	-6.27 (2.88)		0.029
Maternal age	0.16 (0.09)	1.17; 0.99 – 1.39	0.061	0.13 (0.08)	1.14; 0.98 – 1.32	0.086	0.12 (0.07)	1.13;0.98 – 1.30	0.096	0.14	1.15;0.98 – 1.35	0.095
Smoking	1.69 (0.93)	5.42;0.87 – 33.59	0.069	---		n.s.	---		n.s.	-0.08		
GA at birth (wk)	---		n.s.	---		n.s.	---		n.s.	---		n.s.
Birth weight (kg)	-1.62 (0.91)	0.20; 0.03 – 1.19	0.076	---		n.s.	---		n.s.	---		n.s.
DV Z-score change by GA at birth				0.044 (0.022)	1.05; 1.01 – 1.09	0.041				---		n.s.
DV Z-score change by Birth weight							0.49(0.34)	1.64;0.84 – 3.22	0.15			
DV Z-score change by BW Z-score										-1.18 (0.47)	0.31; 0.12 – 0.77	0.012

Figure 3. *Differential effect on the chance of having morbidity (Composite morbidity score between fetuses with unaltered CPR or DV Z-scores over time and those showing abnormal Z-scores after inclusion (adjusted for co-variables)*



COMMENT

This is a small but detailed study on the predictive value of Doppler parameters in near term SGA fetuses at intake and during follow-up, in relation to neonatal composite morbidity. We found that none of the single Doppler measurements at intake was associated with neonatal outcome, but changes from normal to abnormal Doppler values were related to impaired outcome, with the change in CPR and DV as the most promising parameter to identify the SGA fetus at risk. However, their predictive value was limited, which may have been due to the small study population and relatively mild morbidity. Our measurements of fetal size were far from perfect, given the fact that over 20% of included SGA infants had a birth weight > 10th centile, but that is in line with literature.[30]

It appears that the value of Doppler indices for prediction of adverse outcome can be found within the performance of longitudinal measurements and detection of changes to abnormal values. The cerebro-placental ratio provides information on both the UA and the MCA and may detect, therefore, more subtle changes. However, a single CPR measurement does not seem useful. This finding is supported by a recent large study conducted in the UK in an unselected population of over 6000 singleton pregnancies.[31] A single CPR measurement was performed between 35-37 weeks' gestation and showed no predictive value regarding cesarean section for fetal distress, umbilical artery pH at birth, or Apgar score. A smaller low risk population study showed that reduced CPR immediately prior

to delivery was associated with an increased risk of delivery by emergency cesarean section, however there was no association with adverse neonatal outcome.[32] Several studies in "high risk" populations did show correlations of CPR with adverse neonatal outcome. In over 200 term SGA fetuses who were assessed repeatedly, an abnormal CPR was associated with an increased rate of cesarean delivery for fetal distress in labor,[15] emphasizing the need for longitudinal measurements. In another high risk population of term fetuses, pH at delivery was lower in cases with an abnormal CPR, both in SGA and normally grown fetuses.[33]

Changes in Ductus Venosus PI from normal to abnormal values also showed a higher probability for an adverse outcome. This was somewhat unexpected since abnormal DV is usually known to be a late sign of fetal deterioration mostly present in severe and early growth restriction.[34,35] Unfortunately for term SGA populations, no large trial data on DV exist.

A strength of this study is the longitudinal design. This design made it possible to prospectively collect longitudinal data of patients by performing multiple Doppler velocimetry measurements. By doing so we were able to observe the longitudinal trend of Doppler measurements in the last trimester of pregnancy. However, several limitations of this study need to be mentioned. First, our population was relatively small and the rate of perinatal morbidity was low as expected and there were no perinatal deaths. Therefore a composite measure of adverse outcome was used. Secondly, another limitation is that we did not perform all measurements at the same GA for all participants. Next to this longitudinal measurements of the DV and uterine artery were underrepresented (Appendix 1). Finally, the clinical applicability may be complicated as the performance of Doppler measurements near term may require more expertise, especially regarding Ductus Venosus measurement.

CONCLUSION

In a small group of (near) term SGA fetuses, a change in CPR and DV from normal to abnormal values showed a relationship to adverse neonatal outcome. Single measurements of Doppler indices at intake were not associated with neonatal adverse outcome. Identification of the near term fetus at risk for adverse outcome remains challenging. Integrated risk models, based on large study populations including maternal characteristics, fetal characteristics, Doppler measurements of the maternal and feto-placental circulation and fetal growth assessment, are necessary to determine optimal clinical management. Models must be first exhaustively tested in the population to which they will be applied, to obviate the risk of unnecessary intervention.

Appendix: *Overview of biometric and Doppler measurements in the total group (N=43). R : range.*

Variable	Total number of measurements (n)	Number of measurements; Mean (SD); Range	Gestational age for scan at inclusion (weeks); Mean (SD); Range	Gestational age at final scan (weeks); Mean (SD); Range
Abdominal circumference	121	3.3 (1.6); 1-7	33.8 (0.9); R 32.0 – 36.0	36.8 (1.4); 34.2 – 40.2
Head circumference	108	2.9 (1.6); 1-7	33.9 (0.9); R 32.0 – 36.0	36.6 (1.2); 34.2 – 39.3
Femur length	118	3.2 (1.6); 1-7	33.8 (0.9); R 32.0 – 36.0	36.8 (1.4); 34.2 – 40.2
EFW	117	2.7 (1.1); 1-5	33.8 (0.9); R 32.0 – 36.0	36.8 (1.4); 34.2 – 40.2
Umbilical artery	136	3.3 (1.8); 1-8	34.5 (1.4); R 32.6 – 36.0	37.3 (1.3); 34.2 – 39.3
MCA	117	2.9 (2.0); 0-8	35.0 (1.4); R 32.6 – 36.0	37.7 (1.1); 34.6 – 39.3
Ductus venosus	82	2.0 (1.6); 0-6	35.3 (1.1); R 33.7 – 36.0	37.9 (1.0); 36.3 – 39.3
Uterine artery	33	1.2 (0.6); 0-3	35.6 (1.2); R 33.3 – 37.0	38.1 (0.9); 36.4 – 39.3

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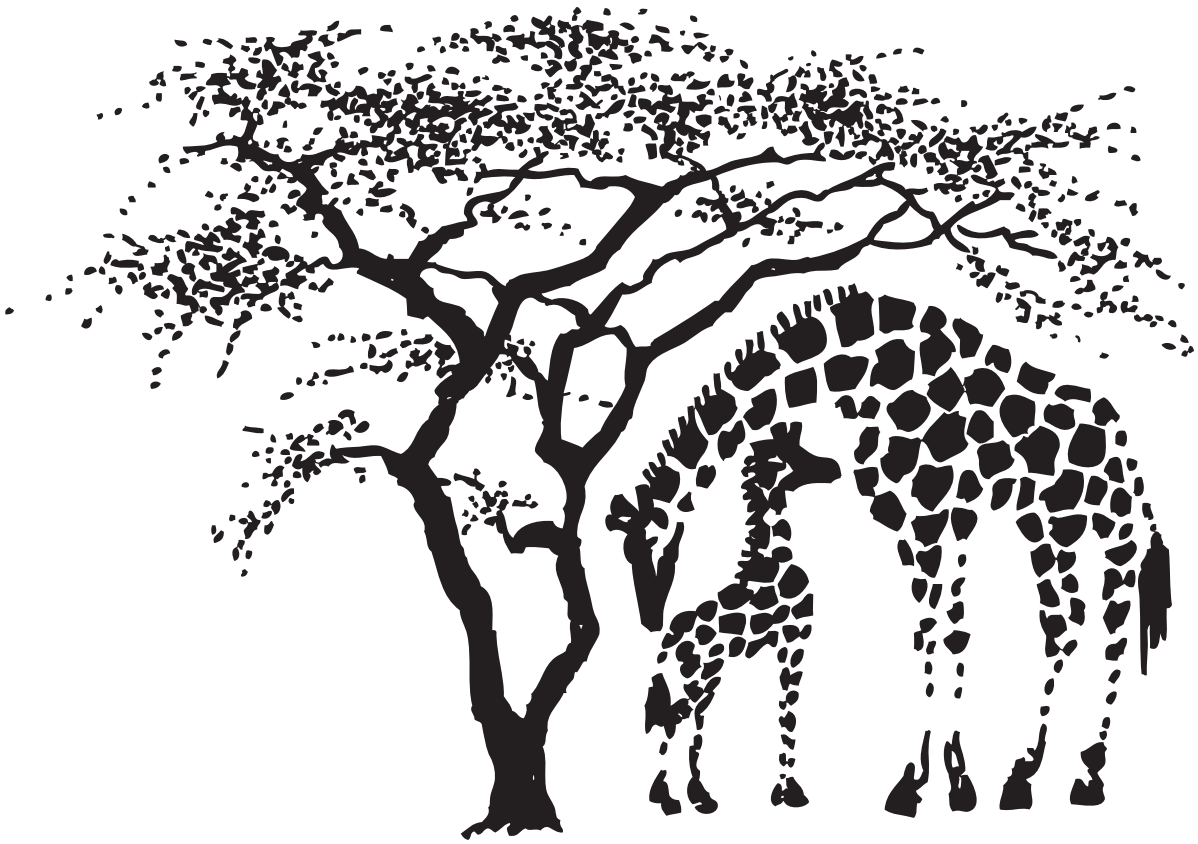

Chapter 6

Maternal cardiovascular risk factors in women with preterm intrauterine growth restriction

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ABSTRACT

Objective To study postpartum cardiovascular risk factors after pregnancies complicated by preterm intra uterine growth restriction with the presence or absence of concomitant pregnancy-associated hypertension.

Methods We assessed postpartum cardiovascular risk factors among a cohort of 157 women with severe intra uterine growth restriction, with and without maternal hypertensive disease, that resulted in delivery before 34 weeks of pregnancy, in comparison to 70 women who delivered one or more appropriately grown infants at term.

Results We found a similar profile of cardiovascular risk factors among women with a history of normotensive and hypertensive intra uterine growth restriction, with higher BMI, increased postpartum levels of fasting blood glucose and lipids compared with controls, with the exception of high blood pressure. These results were independent of age, BMI, interval between index pregnancy and assessment and smoking.

Conclusions Women with a history of preterm intra uterine growth restriction, with or without maternal hypertensive disorder, have an altered cardiovascular risk profile several months after pregnancy with increased levels of modifiable cardiovascular risk factors. Formerly preterm intra uterine growth restriction women should be considered for follow-up and management of cardiovascular risk factors, similar to women with a history of hypertensive pregnancy complications.

INTRODUCTION

Previous studies of women with a history of placental disorders in pregnancy, including preeclampsia, placental abruption and intrauterine growth restriction (IUGR), have revealed an increased prevalence of cardiovascular (CV) disease risk factors after delivery.[1-6] Common risk factors that have been shown to contribute to both CV and placental disorders include chronic hypertension, dyslipidemia, components of the insulin resistance syndrome and inflammatory mediators.[7,8] Pregnancies complicated by IUGR have been associated with an increased maternal risk of ischemic heart disease and CV mortality later in life.[9-13] However, impaired fetal growth is often accompanied by maternal hypertensive disease, i.e. either by chronic hypertension, preeclampsia or pregnancy-induced hypertension. Therefore, it is unclear whether preterm IUGR can be considered as an independent indicator of long-term CV risk, and whether this risk difference can be explained by a higher prevalence of CV risk factors postpartum.

In this study, we prospectively assessed postpartum CV risk factors in a cohort of women with severe preterm IUGR resulting in delivery before 34 weeks of pregnancy, in comparison to women who delivered one or more normal-size infants at term. Further, we compared differences in CV risk factor levels between uncomplicated pregnancies and IUGR pregnancies with and without concomitant maternal hypertensive disease. We hypothesized that the prevalence of postpartum CV risk factors after pregnancies complicated by preterm IUGR would be dependent on the presence or absence of concomitant pregnancy-associated hypertension.

METHODS

Study population

For this study, we used data of an on-going prospective cohort study of women with a singleton pregnancy, who delivered before 34 weeks of pregnancy due to severe placental disorders at a tertiary referral maternity unit based at the University Medical Center Utrecht, The Netherlands. IUGR was diagnosed if infants were small for gestational age, i.e. with a birth weight below the 10th centile based on the most recent Dutch population charts, in the absence of any apparent fetal conditions or congenital abnormalities, and had one or more of the following signs of severe placental insufficiency in pregnancy: abnormal umbilical artery (pulsatility index >95th centile) and/or reduced amniotic fluid volume.[14] If women had IUGR in more than one pregnancy, the most recent pregnancy prior to the date of assessment was defined as the index pregnancy. Infants with known chromosomal abnormalities were excluded. Women in the control group were recruited from the same population as cases. These women experienced only uncomplicated pregnancies and were selected and asked to participate by two low-risk collaborating primary care antenatal clinics within the same geographic area. Control subjects were recruited and enrolled by the same research team, using the same inclusion protocol and were subject to identical sample handling and laboratory procedures

as the cases. All women had already stopped breastfeeding and were asked not to use any vitamin supplements or folic acid for at least 6 weeks before screening. Further details on patient selection, inclusion criteria and sample collection have been published elsewhere.[2,3,15] This study was approved by the Institutional Review Board of the University Medical Center Utrecht, and participants provided written informed consent.

Women with a history of IUGR were divided into 2 groups: (1) normotensive IUGR, i.e. those women who had a normal blood pressure throughout pregnancy and had no signs of preeclampsia or the hemolysis-, elevated liver enzymes and low platelets (HELLP)- syndrome; (2) hypertensive IUGR, i.e. those women with IUGR complicated by pregnancy-induced hypertension, preeclampsia or signs of HELLP-syndrome. Maternal hypertensive disease was defined as pregnancy-induced hypertension, pre-eclampsia, or HELLP syndrome. Pregnancy-induced hypertension was defined as a diastolic blood pressure above 90 mm Hg and/or a systolic blood pressure above 140 mm Hg, measured on at least 2 separate occasions with a minimum 4-hour interval, after 20 weeks gestation. Pre-eclampsia was defined as the combination of pregnancy-induced hypertension and significant proteinuria in the second half of pregnancy, according to the definition proposed by the International Society for the Study of Hypertension in Pregnancy.[16] Proteinuria was diagnosed as either more than 300 mg total protein in a 24-hour urine collection sample or 2+ or more at dipstick urinalysis. HELLP-syndrome was defined using previously published criteria for a combination of thrombocytopenia (less than 100 platelets per 10^9/L), elevated plasma levels of aspartate aminotransferase or alanine aminotransferase of more than 70 U/L, and/or signs of hemolysis (as defined by elevated plasma levels of lactate dehydrogenase above 600 U/L, or fragmented erythrocytes on blood film), and was considered part of the preeclampsia syndrome.[17,18]

Metabolic syndrome was defined according to the International Diabetes Foundation as body mass index (BMI) >30 kg/m2 and ≥2 of the following: triglycerides ≥1.7 mmol/L, high-density lipoprotein cholesterol <1.3 mmol/L, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and fasting plasma glucose levels ≥5.6 mmol/L.[19] The cutoff points total cholesterol >6.2mmol/L, low-density lipoprotein cholesterol >1.8, and high-sensitive C-reactive protein (hsCRP) >2.0 mg/mL were based on the Adult Treatment Panel III guidelines and Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[20,21]

Risk assessment

We performed CV risk assessment for all women at least three months after delivery. At enrollment, demographic, general medical, and obstetric data were recorded, and fasting blood samples were obtained for detection of metabolic, inflammatory, and lipid risk factors. Information on the presence of diabetes mellitus, smoking status and height were obtained by self-report, and maternal weight was measured on the day of the interview. Blood pressure was measured by the auscultatory method using an aneroid sphygmomanometer in sitting position. Diastolic blood pressure values were determined using the fifth Korotkoff sound.[22] Where appropriate, cuff sizes were adjusted to arm

circumference. The mean value of two separate measurements 30 minutes apart was used for analysis. Fasting venous blood samples were collected and immediately sent off for analysis of lipid markers, glucose, high sensitive C-reactive protein (hsCRP) and triglyceride levels by standard operating procedures, performed in a single, certified Clinical Chemistry Laboratory based at the University Medical Center Utrecht. A detailed description of measurements and laboratory procedures was previously published elsewhere.[23,24] Briefly, fasting total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, hsCRP and glucose were determined using a Vitros950 dry-chemistry analyzer (Johnson & Johnson, Rochester, NY). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The Homeostatic Model Assessment (HOMA2) score was used to calculate the level of insulin resistance (IR). The HOMA2-IR index was obtained by the program HOMA Calculator v2.2.3.[25,26] Within-run variation coefficients were <5% for all determinants. Technicians were blinded for outcome.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS, version 20.0, Armonk, NY). To account for missing data a previously validated multiple imputation (10x) method was applied using observed patient characteristics.[27,28] In the original data set, the average missing rate per variable was 7% for IUGR groups and 10% for controls. In brief, missing data were imputed using a logistic regression model that included the following variables: maternal age, maternal height, maternal weight, chronic hypertension, diabetes, current smoking, multiparity, interval between index pregnancy and assessment, group, blood pressure, glucose, insulin, hsCRP, triglycerides and cholesterol levels. Clinical and outcome variables were expressed as means and standard deviation, or number and percentage where appropriate, and comparisons were made between groups by using ANOVA and Chi Square test, respectively. Generalized linear models were used to compare means between the reference group, hypertensive IUGR and non-hypertensive IUGR adjusted for maternal age, BMI, smoking and interval between index pregnancy and assessment. To correct for multiple testing a Bonferroni correction was applied, P values <0.017 were considered to indicate statistical significance. For the not normally distributed data, the models were re-run with log transformation, as this did not affect the results, the raw data results were displayed.

RESULTS

Subject and index pregnancy characteristics are displayed in Table 1. BMI was higher in both IUGR groups and there were more smokers in the normotensive IUGR group compared to the control group. Gestational age and birth weight was lower in IUGR index pregnancies. Intervals between pregnancy and assessment were longer for the IUGR groups. Table 2 shows the subject characteristics at cardiovascular risk assessment of women with previous hypertensive IUGR [N=115] and non-hypertensive IUGR [N=42], compared to the control group [N=70]. After adjustment for age, smoking, interval between index pregnancy and assessment and BMI, both IUGR groups had higher levels of

Table 1. *Subject characteristics at cardiovascular risk assessment and characteristics of index pregnancy*

Parameter	Group 1	Group 2	Group 3	1 vs 2	1 vs 3	2 vs 3
	Controls	Hypertensive IUGR	Normotensive IUGR			
	n=70	n=115	n=42	p value	p value	p value
Characteristics at risk assessment						
Age	33 (4.32)	32 (4.98)	31 (4.24)	0.307	0.027	0.258
Body Mass Index, kg/m2	22.9 (2.85)	26.3 (4.55)	26.0 (6.29)	<0.001*	0.002*	0.944
Smoking, %	13 (19)	29 (25)	18 (43)	0.343	0.007*	0.033
Diabetes Mellitus, %	0	0	0	NA	NA	NA
Hypertension, %	0	39 (34)	2 (5)	<0.001*	0.067	<0.001*
Multiparous at exam, %	26 (37)	41 (36)	18 (43)	0.838	0.549	0.409
Interval between index pregnancy and assessment (years)	2.2 (3.07)	0.9 (1.31)	1 (1.43)	<0.001*	0.007*	0.951
Index pregnancy outcome						
Gestational age at delivery (days)	283 (7.85)	206 (16.88)	204 (16.88)	<0.001*	<0.001*	0.881
Birth weight (grams)	3685 (434.71)	765 (272.57)	590 (224.02)	<0.001*	<0.001*	0.009*
Birth weight centile	59.8 (26.43)	5 (2.89)	2.7 (2.88)	<0.001*	<0.001*	0.668
Infant sex, male, %	32 (46)	69 (60)	26 (62)	0.072	0.112	0.829
Multiparous at index pregnancy, %	26 (37)	38 (33)	18 (43)	0.57	0.549	0.256
Hypertensive disorder in pregnancy, %	0 (0)	115 (100)	0	NA	NA	NA
Pregnancy induced hypertension, %	0 (0)	20 (17)	0	NA	NA	NA
Pre-eclampsia, %	0 (0)	95 (83)	0	NA	NA	NA

Data are presented as means and standard deviation, or number and percentage.
** Level of significance p<0.017*

Table 2. *Determinants of cardiovascular risk in non-pregnant women with a previous pregnancy complicated by intrauterine growth restriction*

Parameter	Group 1	Group 2	Group 3	1 vs 2	1 vs 3	2 vs 3
	Controls	Hypertensive IUGR	Normotensive IUGR			
	n=70	n=115	n=42	p value	p value	p value
Fasting blood glucose mmol/L	4.12 (1.10)	5.29 (1.12)	5.09 (0.97)	<0.001*	<0.001*	0.275
Fasting insulin uIU/L	10.76 (8.37)	10.58 (5.60)	10.23 (5.73)	0.883	0.671	0.735
HOMA 2 IR	1.30 (0.97)	1.38 (0.70)	1.318 (0.71)	0.599	0.913	0.640
Total Cholesterol mmol/L	3.83 (1.20)	5.24 (1.09)	4.70 (1.10)	<0.001*	<0.001*	0.006*
HDL Cholesterol mmol/L	1.14 (0.36)	1.35 (0.33)	1.40 (0.34)	<0.001*	<0.001*	0.453
LDL Cholesterol mmol/L	2.11 (1.08)	3.27 (0.97)	2.80 (0.98)	<0.001*	0.001*	0.007*
Triglycerides mmol/L	1.26 (0.86)	1.35(0.81)	1.10 (0.82)	0.492	0.332	0.082
CRP mg/L	6.00 (12.81)	5.00 (12.29)	5.85 (15.21)	0.534	0.952	0.712
Systolic blood pressure mm Hg	114.87 (15.39)	123.39 (14.49)	120.41 (23.19)	<0.001*	0.174	0.453
Diastolic blood pressure mm Hg	75.02 (11.14)	79.13 (12.18)	75.24 (11.07)	0.023	0.921	0.033

Adjusted for age, BMI, smoking and interval between pregnancy and assessment .
Data are presented as means and standard deviation.
HDL, high-density lipoprotein; HOMA 2 IR, Homeostatic Model Assessment 2 Insulin Resistance; hsCRP, high sensitive C-reactive protein; and LDL, low-density lipoprotein.
**Level of significance p<0.017*

fasting blood glucose, higher total, LDL and HDL cholesterol compared with controls with a history of one or more term deliveries of non-IUGR infants. Mean postpartum systolic blood pressure levels were only higher at follow-up compared with controls in women with a combination of IUGR and pregnancy-associated hypertensive disease. Between IUGR groups total cholesterol and LDL cholesterol was significantly higher in the hypertensive IUGR group.

The prevalence of characteristics of metabolic syndrome did not differ between both IUGR groups (Table 3). A BMI > 30 was present in 18-19% in the IUGR groups, compared with 3% in the control group. High LDL levels occurred in 99% of the hypertensive IUGR group and 90% of the normotensive IUGR group. The prevalence of a high systolic and diastolic blood pressure and high total cholesterol was higher for the hypertensive IUGR group compared to controls.

Table 3: *Cutoff Values Used in Metabolic Syndrome, ATP III Guidelines and JUPITER Trial in IUGR groups and controls*

Parameter	Group 1	Group 2	Group 3	1 vs 2	1 vs 3	2 vs 3
	Controls	Hypertensive IUGR	Normotensive IUGR			
	n=70	n=115	n=42	p value	p value	p value
Metabolic syndrome						
Body Mass Index >30 kg/m2	2 (3)	21 (18)	8 (19)	<0.001*	0.016*	0.856
Systolic blood pressure> 130 mmHg	4 (6)	28 (24)	7 (17)	0.001*	0.173	0.478
Diastolic blood pressure >85 mmHg	4 (6)	25 (22)	4 (10)	0.006*	0.458	0.138
Fasting blood glucose > 5.6 mmol/L	4 (6)	16 (14)	4 (10)	0.089	0.444	0.548
Triglycerides > 1.7 mmol/L	9 (13)	26 (23)	5 (12)	0.087	0.925	0.115
LDL Cholesterol > 1.8 mmol/L	42 (60)	114 (99)	38 (90)	<0.001*	<0.001*	0.064
ATP III guidelines and JUPITER trial						
HDL Cholesterol <1.29 mmol/L	46 (66)	58 (50)	22 (52)	0.056	0.152	0.943
Total Cholesterol > 6.21 mmol/L	3 (4)	19 (17)	3 (7)	0.004*	0.516	0.089
hsCRP >2mg/ml	35 (50)	73 (63)	28 (67)	0.288	0.310	0.810

*Data are presented as number and percentage. HDL, high-density lipoprotein; hsCRP, high sensitive C-reactive protein; and LDL, low-density lipoprotein. *Level of significance p<0.017*

DISCUSSION

In this study, we show that women with an IUGR pregnancy that necessitates delivery before 34 weeks gestational age have high levels of common CV risk factors postpartum, when compared with control women with uneventful pregnancies who delivered an appropriate-size infant at term. Both women with a history of normotensive IUGR and women with a history of hypertensive IUGR appear to have a higher prevalence of CV risk factors postpartum, with the exception of high blood pressure which is only higher in women with a history of hypertensive IUGR. The observed difference in CV risk factors was independent of maternal age, BMI, interval between index pregnancy and assessment and smoking. This suggests that underlying maternal CV risk factors are not only found in women with a history of hypertensive disorders of pregnancy, but are also associated with severe IUGR (i.e. IUGR that requires early delivery) in those women who do not develop any hypertension during the course of pregnancy.

HDL- cholesterol levels were lower in the control group compared with both IUGR groups. As HDL cholesterol is shown to be inversely related to the CVD risk in previous epidemiological studies, it remains difficult to explain this finding.[19,29-31] However this finding is consistent with previous studies on CVD risk after delivery in women with a history of placental disorders in pregnancy.[2,3] We can only

speculate that perhaps the higher HDL levels in the IUGR groups (temporarily) protect them against early atherogenesis, despite alterations in other CVD parameters.

Our findings are consistent with previous studies that demonstrated an increased long-term risk of CV mortality or morbidity in women with a history of 1 or more IUGR pregnancies.[9-11] Long-term risk of CV disease after IUGR appears mediated by the presence or absence of pregnancy-associated hypertension, with women who experience both IUGR and maternal hypertension during pregnancy seem to have the highest risk (3.3-fold versus 1.8-fold, respectively).[13] Findings from our study suggest that a high prevalence of common CV risk factors already present shortly after delivery, may be important drivers of these associations. Limited data exist on the prevalence of CV risk factors after IUGR pregnancies, with variable intervals between delivery and assessment of CV risk factors. Both IUGR and preeclampsia have been associated with a number of elevated CV risk markers measured in the first few years postpartum including higher fasting glucose,[3,4,32] abnormal lipid profile[3] and (pre)hypertension.[3,33] However, none of these studies were stratified for women with a combination of IUGR and maternal hypertensive pregnancy complications, compared with women with IUGR without hypertensive disease. These findings have also been confirmed at long-term follow-up, e.g. in the study by Catov and colleagues who investigated CV risk profiles of women with an age between 70-79 years with a previous delivery of an infant with a birth weight below 2500 grams. In this study, mothers who delivered a low birth weight infant had lower BMI, but higher abdominal circumference and higher systolic blood pressure as compared with women who delivered normal-size infants after exclusion of pregnancies complicated by hypertensive disease.[34] Lipid levels, fasting glucose and CRP levels did not differ between women with previous normal or low birth weight pregnancies. The same group assessed the CV risk profile at 8 years after delivery of a small for gestational age infant (<10th centile).[35] Again, pregnancies with concomitant hypertensive disorder were excluded. In their study, levels of LDL cholesterol, triglycerides and diastolic blood pressures remained higher in women with previous preterm SGA, compared with women who delivered appropriate for gestational age infants at term, thus suggesting that our results may well be predictive of long-term CV risk that already presents itself shortly after delivery.

A strength of this study is the prospective design and stratification of a cohort of women with severe IUGR pregnancy into subgroups with or without maternal hypertension. However, some limitations of this study need to be mentioned. First, as no data on CV risk profile before pregnancy were available, it is not possible to assess whether or not CV risk factors were already present prior to pregnancy, or changed as a result of pregnancy. Second, we found a difference in mean duration of interval between the pregnancy and CV risk factor assessment between groups, therefore results were adjusted for interval between delivery and assessment. For calculation of birth weight centiles we used the most recent Dutch references curves by parity, sex and ethnic background, although these are high quality reference curves,[14] comparison across populations worldwide could be complicated. Finally, the HOMA2 IR score was used as an index of insulin resistance. This method may be inferior compared to the "gold standard" of insulin clamps or oral glucose tolerance test, unfortunately these

data were not available. However the HOMA model is a widely used validated model for assessment of insulin resistance, and the HOMA2 IR score was used to account for a more accurate index of insulin resistance.[26,36]

CONCLUSION

In this study, we identified several modifiable CV risk factors both in women with hypertensive IUGR, as well as in women with normotensive IUGR. As opposed to the now widely accepted advice to consider CV risk factor assessment postpartum in women with a history of pre-eclampsia or pregnancy-induced hypertension,[37,38] this study provides important evidence that women with a history of preterm IUGR, who are not affected by maternal hypertensive disease, may also benefit from CV risk factor assessment and risk reduction strategies. However, future research is required, including data on the CV risk profile of women prior to their pregnancy, to find optimal risk reduction strategies and further evaluation of the clinical and cost- effectiveness of these strategies is necessary before incorporation in clinical practice is possible.

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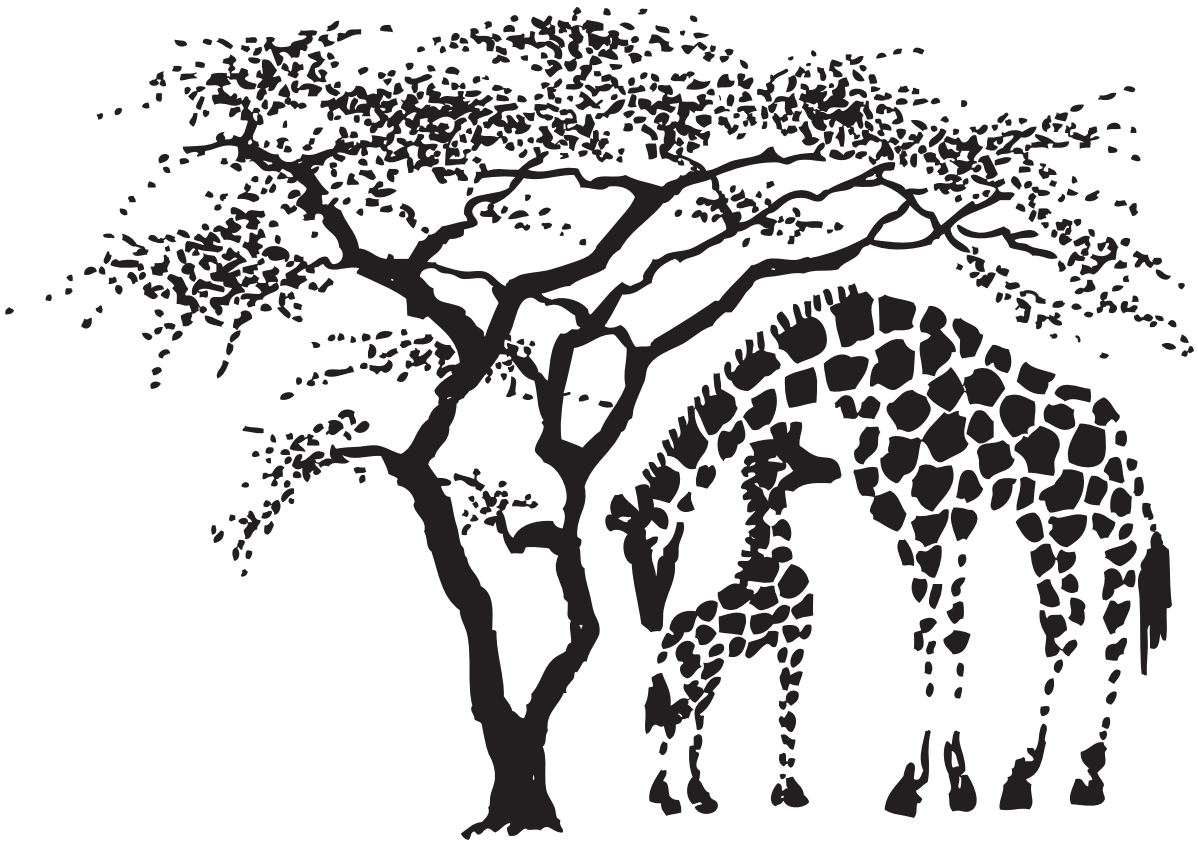
Part II

Risk assessment during labor; monitoring uterine contractions using electromyography



Chapter 7

Uterine electromyography for identification of first-stage labor arrest in term nulliparous women with spontaneous onset of labor

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Am J Obstet Gynecol. 2013 Sep;209(3):232

ABSTRACT

Objective We sought to study whether uterine electromyography (EMG) can identify inefficient contractions leading to first-stage labor arrest followed by cesarean delivery in term nulliparous women with spontaneous onset of labor.

Study Design EMG was recorded during spontaneous labor in 119 nulliparous women with singleton term pregnancies in cephalic position. Electrical activity of the myometrium during contractions was characterized by its power density spectrum (PDS).

Results Mean PDS peak frequency in women undergoing cesarean delivery for first-stage labor arrest was significantly higher (0.55 Hz), than in women delivering vaginally without (0.49 Hz) or with (0.51 Hz) augmentation of labor (P = .001 and P = .01, respectively). Augmentation of labor increased the mean PDS frequency when comparing contractions before and after start of augmentation. This increase was only significant in women eventually delivering vaginally.

Conclusion Contraction characteristics measured by uterine EMG correlate with progression of labor and are influenced by labor augmentation.

INTRODUCTION

Worldwide cesarean delivery (CD) rates increase rapidly.[1] The majority of intrapartum CD (about 47%) are performed for failure to progress in term nulliparous women with a fetus in cephalic position.[2] Effective treatment strategies to address the problem of labor arrest are needed to reduce or at least stabilize the CD rate. Paradoxically, the widespread use of uterotonic drugs does not seem to be the answer to the problem. Comparison between a historic cohort and modern practice has shown that the length of labor has increased during the last 50 years, while the proportion of women receiving uterotonic drugs has increased several fold, even when controlling for factors such as maternal age and body mass index.[3] These data stress the importance of studies on the normal process and progress of labor and on prognostic factors regarding the efficacy of uterotonic medication. The challenge is to identify which labors will respond to oxytocin and which would benefit from other, not-yet-defined interventions. Current monitoring techniques of uterine contractility, either by external tocography or by intrauterine pressure catheters, have not been shown to improve outcomes.[4] However, in the last 15 years several groups have revived interest in uterine electromyography (EMG), a noninvasive technique enabling measurement of electrical activity through the maternal abdominal surface, developed 70 years ago.[5-9] In case of threatened preterm labor, EMG identifies patients delivering at short term more accurately than other current methods.[10-13] We hypothesized that the findings in preterm labor could be translated into the possibility to differentiate between normal and protracted labor at term. The objective of this study was to investigate whether uterine EMG can differentiate between inefficient contractions resulting in a CD for first-stage labor arrest, and efficient contractions (with or without labor augmentation) leading to a vaginal delivery in term nulliparous women with a spontaneous onset of labor.

MATERIALS AND METHODS

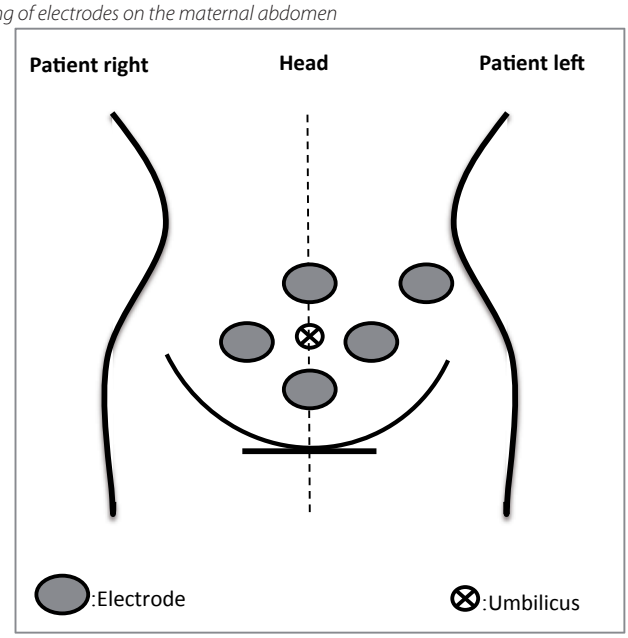
A prospective multicenter observational study was conducted in 3 centers in The Netherlands from August 2009 through May 2011. The inclusion criteria were singleton pregnancies in cephalic position (gestational age ≥37 weeks and ≤42 weeks) admitted to the labor ward for spontaneous labor. Exclusion criteria were suspected congenital or chromosomal abnormalities. The study was approved by the institutional medical ethical committees of the participating hospitals. Patients who were eligible for participation were approached consecutively. After informed consent was obtained, measurements of uterine activity were performed using EMG as recorded noninvasively from the maternal abdominal surface. EMG recordings started from the onset of labor or during first stage of labor upon arrival at the labor ward until delivery. There was no predefined time frame for registration duration and EMG recordings were conducted for as long as possible after inclusion. Registrations were analyzed post hoc. All participating centers belong to a network of teaching hospitals taking

part in the same residency program in obstetrics and gynecology. They follow a similar clinical policy inspired by the active management of labor approach.[14] According to this common policy, onset of active labor was defined as: painful regular contractions ≥2/10 minutes and ruptured membranes or cervical effacement ≥75% and/or cervical dilation ≥2 cm. Progress of labor was monitored with the use of cervical examinations performed at least every 2 hours, or more frequently when indicated. The diagnosis of labor arrest was made by the clinician using the following criteria: patient in active labor (according to the definition outlined previously) with no increase in dilation for at least 2 hours. Protracted labor was defined as a rate of cervical dilation ≤1 cm/h. In both cases oxytocin augmentation was started. A CD for labor arrest was generally performed if labor arrest persisted despite augmentation of labor with oxytocin during an additional 2 hours.[15,16] Maternal, neonatal, and labor characteristics were collected from the patient's charts.

Uterine activity registration and analysis

Uterine activity was monitored using a portable maternal/fetal heart rate/EMG recorder (AN24, Monica Healthcare Ltd, Nottingham, United Kingdom) through 5 disposable electrodes that were positioned on the maternal abdomen in a standardized manner. The electrodes were positioned in the following way: 2 electrodes vertically along the midline, approximately 3-5 cm on both sides of the umbilicus; and 2 electrodes horizontally at the level of the umbilicus and symmetrical with respect to it, about 3-10 cm from the umbilicus. Finally, a (ground) electrode was placed on the left flank (Figure 1).

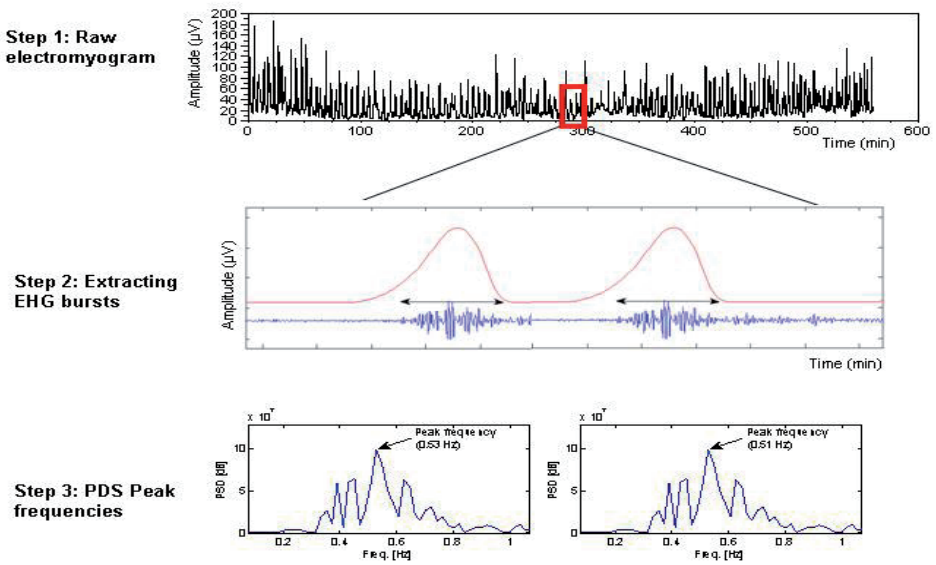
Figure 1. *Positioning of electrodes on the maternal abdomen*



Skin preparation before electrode placement ensured that skin impedance was <5 kΩ in all recordings. The raw abdominal EMG was recorded at 300 Hz and filtered in the 0.34- to 1-Hz bandwidth to obtain the uterine EMG. This procedure is similar to that reported by others in term of electrode placement and signal filtering.[11-13] Filtering in the 0.34- to 1-Hz bandwidth aims at removing heart rate artefacts >1 Hz and respiration artefacts <0.34 Hz. However, in contrast with the works cited previously, we developed an algorithm to identify contractions and compute the power density spectrum (PDS) due to the large number of contractions to be analyzed. This algorithm has been tested and described previously by comparing it against intrauterine pressure catheter measurements.[17]

PDS analysis was performed on each contraction and the peak frequency was used as a contraction characteristic to be linked with clinical outcomes. The signal processing steps are illustrated in Figure 2. This method of analysis has been one of the most predictive EMG parameters in both human and animal studies for prediction of true labor.[7,10,12,13,18,19] The investigators who analyzed the data were not blinded to the labor and delivery data. However, the numerical data of the EMG signal prevented subjective interpretation.

Figure 2. *EMG signal processing steps*



Step 1: Raw EMG as recorded from the maternal abdomen during labor. Step 2: EMG extraction; Red line indicates uterine activity; Blue line represents an electrical burst/contraction. Step 3: For each burst/contraction the peak frequency was calculated with PDS analysis. Figure was provided with permission granted by Monica Healthcare Ltd. Nottingham, UK

Statistical analysis

Data analysis was performed using software (SPSS, version 20.0; IBM Corp, Armonk, NY). The number of inclusions was estimated beforehand at 250 patients to result in around 10 CD for first-stage labor arrest, based on an expected rate of 4%. This was chosen such that in a univariate regression analysis the influence of 1 contraction parameter could be analyzed. It was difficult beforehand to estimate the degree of intercorrelation and intracorrelation due to the nested structure of the data and hence to perform a more precise power analysis. The study was terminated prematurely because 14 cases of CD for first-stage arrest had already been included.

The cohort was divided in different groups depending on the outcome. Patients with a CD for reasons other than first-stage labor arrest were excluded from analysis. Groups were defined as: group 1, women who delivered vaginally without labor augmentation; group 2, women who received labor augmentation because of protracted labor and who delivered vaginally; and group 3, women with a CD for first-stage labor arrest. The effect of labor augmentation on the mean PDS peak frequency was studied by a subanalysis of the contractions before (group a) and after (group b) administration of oxytocin. Due to the nested structure of the data with multiple measurements per subject, linear mixed models were used to evaluate the difference in peak depolarization frequencies between the different groups. Intraclass correlation coefficients were calculated, to compare the variance of contraction characteristics within subjects to the variance between subjects. The following confounders were added to the model: maternal age, body mass index, gestational age, birth weight, cervical dilation, and epidural analgesia. The choice of these confounders was based on literature on confounders of labor outcome.[20-22] Interactions between the confounders and the different groups were studied. A Bonferroni correction was applied to the subanalysis because of multiple testing, by adjusting the level of significance to $P < .005$.

RESULTS

A total of 124 women were included, of whom 105 women delivered vaginally either spontaneously or instrumentally; 14 women delivered by CD during the first stage of labor because of arrest of dilation; another 5 women had a CD because of fetal distress (n = 2) or second-stage labor arrest (n = 3) (Figure 3 flowchart). A total of 119 women were selected for analysis. Group 1 consisted of 32 women, group 2 of 73 women, and group 3 of 14 women. Table 1 shows the characteristics of the 3 groups. Table 2 displays the number of contractions, median peak frequency, and interquartile range per centimeter of cervical dilation for each group. In all groups the PDS peak frequency increased with increasing dilatation. The highest PDS values occurred in the CD group. In groups 2 and 3 all women received augmentation with oxytocin. The mean rate of cervical dilation in the hour before augmentation was 0.14 cm/h and the average cervical dilation at onset of oxytocin was 4.5 cm.

Table 1. *Subject characteristics group 1-3.*

Characteristics	Group 1 (n=32)	Group 2 (n=73)	Group 3 (n=14)
	mean (min-max)/number (%)	mean (min-max)/number (%)	mean (min-max)/number (%)
Maternal			
Age mother	32 (24-42)	31 (19-40)	32 (26-39)
BMI	26 (19-40)	27 (21-38)	29 (18-42)
Gestational age (days)	279 (259-292)	280 (261-293)	285 (268-296)
Labor			
Cervical dilatation at admission (cm)	6 (1-9)	5 (0.5-9)	5 (2-8)
Duration rupture of membranes (hrs)	10 (2-34)	15 (3-69)	15 (5-26)
Duration labor	8 (3-23)	12 (3-22)	15 (9-26)
Labor augmentation (oxytocin)	0 (0%)	73 (100%)	14 (100%)
AROM (artificial rupture of membranes)	17 (53%)	38 (52%)	6 (43%)
Epidural analgesia	12 (38%)	61 (84%)	12 (86%)
Indication transfer			
Maternal[a]	13 (41%)	17 (23%)	-
Fetal[b]	12 (37.5%)	17 (23%)	6 (43%)
Labor arrest	4 (12.5%)	15 (21%)	4 (28.5%)
Analgesia request	3 (9%)	24 (33%)	4 (28.5%)
Registration Uterine activity			
Duration registration (min)	219 (48-543)	363 (30-928)	370 (133-824)
Number of contractions measured (First stage)	79 (20-218)	142 (14-377)	143 (38-296)
Total number of contractions measured	2537	10333	1996
Without oxytocin	2537	2282	220
With oxytocin	-	8051	1776
Neonatal			
Female	17 (53%)	32 (44%)	7 (50%)
Birth weight	3405 (2330-4280)	3500 (2395-4560)	3848 (3400-4460)
Apgar 1 min[c]	9 (4-10)	9 (3-10)	9 (3-10)
Apgar 5 min[c]	10 (7-10)	10 (8-10)	10 (9-10)
pH art	7.19 (7.02-7.30)	7.23 (7.05-7.35)	7.3 (7.23-7.37)

AROM, Artificial rupture of membranes; BMI, body mass index;
group 1, vaginal delivery without oxytocin; group 2, vaginal delivery with oxytocin; group 3, cesarean delivery for first-stage labor arrest.
[a]Main maternal indications: diabetes, hypertensive disorders, maternal disease;[b]Main fetal indications: growth restriction, meconium, oligohydramnios;[c] Displayed in median (minimum- maximum).

Figure 3. *Flowchart delivery mode*

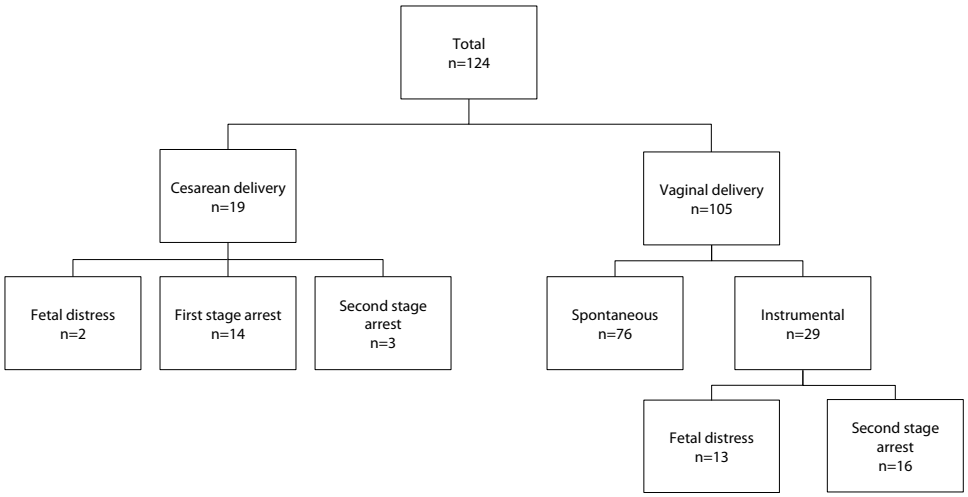


Table 2. *Contraction characteristics by cervical dilation*

Vaginal delivery without labor augmentation			
Cervical dilation	Number of contractions	Median PDS PF (Hz)	IQR
0-2cm	48	0.45	0.39-0.51
2-4cm	131	0.49	0.41 - 0.55
4-6cm	324	0.49	0.43- 0.57
6-8cm	677	0.49	0.41-0.57
8-10cm	1357	0.51	0.45-0.59
Vaginal delivery with labor augmentation[a]			
Cervical dilation	Number of contractions	Median PDS PF (Hz)	IQR
0-2cm	28	0.41	0.39-0.45
2-4cm	537	0.45	0.39-0.53
4-6cm	1423	0.49	0.43-0.57
6-8cm	2033	0.51	0.45-0.59
8-10cm	4030	0.53	0.47-0.59
Cesarean delivery for first stage labor arrest			
Cervical dilation	Number of contractions	Median PDS PF (Hz)	IQR
0-2cm	5	0.39	0.35-0.46
2-4cm	386	0.55	0.49-0.63
4-6cm	834	0.55	0.47-0.63
6-8cm	583	0.59	0.49-0.64
8-10cm	188	0.55	0.43-0.66

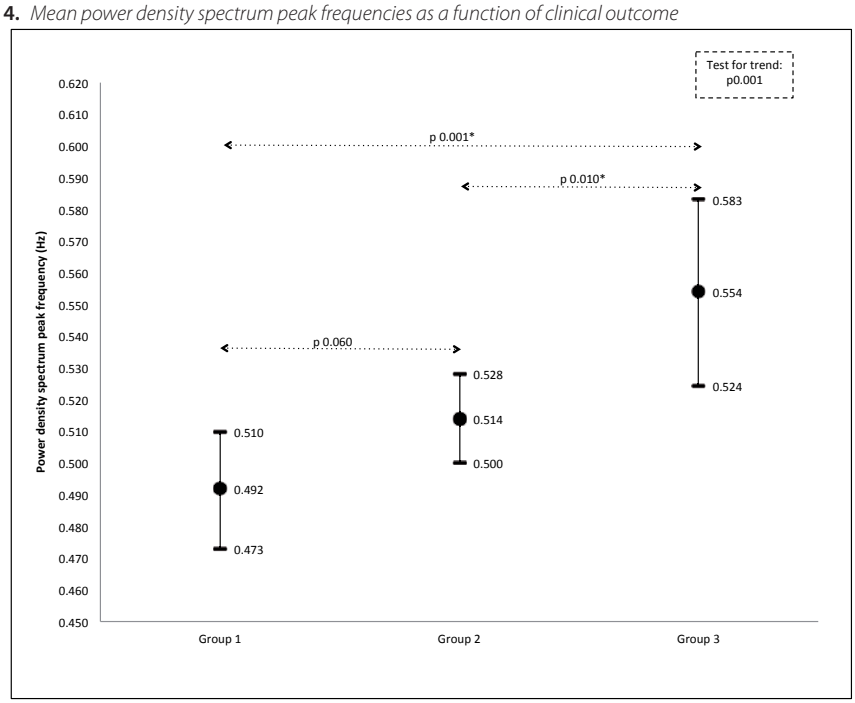
Power density spectrum (PDS); Peak frequency (PF); Interquartile range (IQR)

[a] Contractions after starting oxytocine

Similarly labor arrest or very slow cervical dilation despite augmentation occurred in all cases in which a CD for first-stage labor arrest was performed (mean cervical dilation in the last 2 hours with augmentation was 0.16 cm/h). The mean cervical dilation at CD was 6 cm.

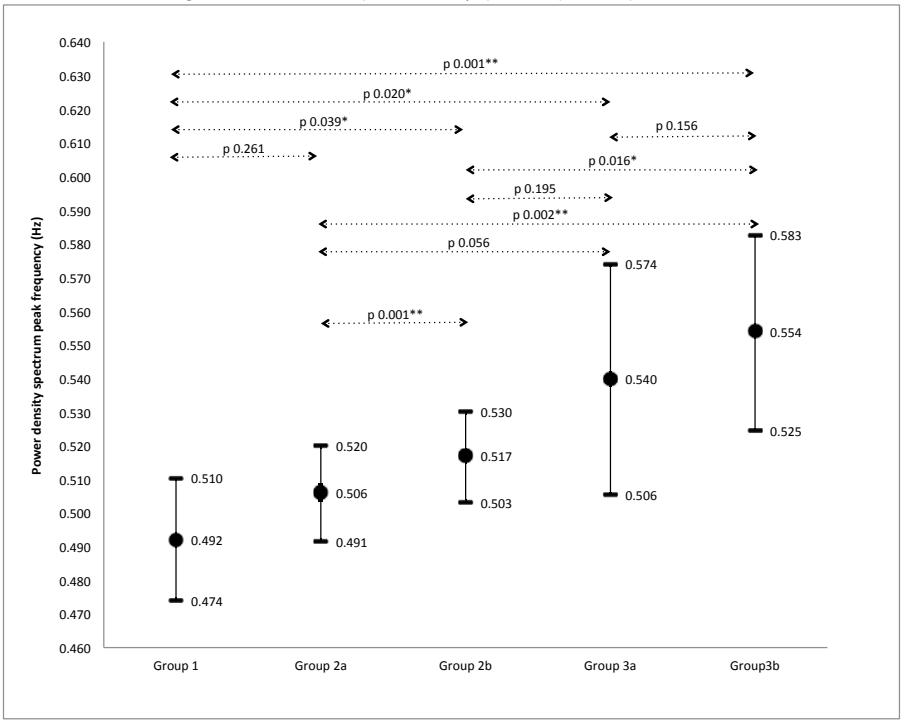
Figure 4 shows the mean peak frequencies with 95% confidence intervals (CIs) of groups 1, 2, and 3, with P values for differences between the groups. Interactions between the confounders and the groups showed no effect modification. In women delivering vaginally without or with augmentation (groups 1 and 2) the PDS peak frequency was significantly lower than in those with a CD for first-stage labor arrest (group 3). Of all confounders added to the model, only cervical dilation had a significant effect (P = .000), by increasing PDS peak frequency with 0.008 Hz (95% CI, 0.007–0.009) per centimeter dilation.

Figure 4. *Mean power density spectrum peak frequencies as a function of clinical outcome*



*Mean power density spectrum peak frequencies for groups 1-3, with 5-95% confidence intervals and p values, calculated with linear mixed model analysis. Test for trend analysis p 0.001. * Significant (p<0.05)*

Figure 5. *Effect of labor augmentation on mean power density spectrum peak frequencies*



Mean power density spectrum peak frequencies for groups 1-3b, with 5-95% confidence intervals and p values, calculated with linear mixed model analysis.
**Significant before correction (p<0.05). ** Significant after Bonferroni correction (p<0.005)*

The results of the subanalysis of the contractions before and after oxytocin administration are displayed in Figure 5. The number of contractions measured is shown in Table 1.

In the women who eventually delivered vaginally after augmentation (group 2), the PDS peak frequency before the start of oxytocin (group 2a) was slightly higher (nonsignificant) than in the women delivering vaginally without augmentation (group 1). In these women the PDS peak frequency increased significantly after the start of oxytocin (group 2b). In the women delivering by CD for first-stage arrest the PDS peak frequency before oxytocin administration was nonsignificantly higher (after Bonferroni correction) than in group 1 (P = .020) and group 2a (P = .056), ie, as compared to women who delivered vaginally without augmentation and in those before the start of oxytocin who subsequently responded to oxytocin. In group 3 the increase in PDS peak frequency after the start of oxytocin was not significant, but the number of contractions considered in group 3a was limited (Table 1). Again, of all confounders, only cervical dilation had a significant effect (P = .000), by increasing PDS peak frequency with 0.007 Hz (95% CI, 0.006–0.008) per centimeter dilation.

COMMENT

This study showed that the PDS peak frequency of contractions leading to CD despite augmentation was significantly different from that of contractions in women delivering vaginally with or without protracted labor. Augmentation increased the mean PDS peak frequency when comparing contractions before and after start of oxytocin. This increase was only significant in women who eventually delivered vaginally. In women who delivered vaginally after augmentation, the contractions before augmentation were similar to those of women not needing augmentation, whereby PDS values increased significantly after the start of oxytocin. In women eventually having a CD, PDS values were already increased before augmentation (nonsignificant) and further increased thereafter.

Previous studies on EMG in the context of preterm labor have shown that PDS values increased in women at risk for delivery at short term.[11-13] PDS values in the latter group were comparable to those observed by us in the group of women delivering vaginally without augmentation. The increase in PDS values in preterm threatened labor has been explained by an accelerated development of gap junctions resulting in an increased synchronization of myocyte activity.[7,11,12,18] The fact that augmentation with oxytocin also increased PDS values (this study) might be explained by the same mechanism. In this context, it is interesting to note that tocolysis with nifedipine in case of preterm contractions has been shown to lower PDS values.[23] There seems, however, to be a limit beyond which an increase in PDS peak frequency is not efficient anymore. This may reflect an increase in lactic acidosis due to a prolonged exposition to oxytocin as has been shown in other studies.[24] Women who do not respond to augmentation seem to have higher PDS values even before starting augmentation, perhaps reflecting the presence of a certain degree of lactic acidosis. It would be of great interest to study the relationship between intrapartum EMG and in vitro analysis of myometrium contractility to test this hypothesis. If our results were to be replicated and correlated to lactic acidosis, one may argue that a temporary arrest of contractions using a tocolytic drug may restore adequate metabolization. Similarly, dextrose administration might improve uterine contractility and shorten the duration of labor in such cases.[25]

Finally, the evidence that early and high-dose oxytocin augmentation rather than late and/or low-dose augmentation shortens the duration of labor,[26] also suggests that augmentation is more effective if given before impaired metabolization of the myometrium.

One of the challenges in current obstetrics is to prevent the first CD to subsequently prevent later fetal and maternal morbidity. Most of the CDs in this cohort were performed because of first-stage labor arrest (14 of 19 CD). Considering the high rate of augmentation in our cohort and in general obstetrical practice, uterotonics alone are not an efficient strategy. The results reported here need to be replicated before alternative treatment strategies can be studied but they point toward a more selective use of uterotonics and open the way for testing of alternative strategies in a selected group of patients who beforehand have a low susceptibility of responding to augmentation.

Comparison of EMG with conventional registration methods has shown that EMG during labor shows a strong correlation with the invasive gold standard intrauterine pressure monitoring.[17,27,28] EMG also performs much better than external tocodynamometry, which does not correlate well with intrauterine pressure recording.[29]

This is the first study using EMG to measure PDS peak frequencies in protracted labor in term nulliparous women with a spontaneous onset. It is also the first study to distinguish between contraction characteristics before and after start of augmentation. Comparison with previous studies is therefore indirect. As mentioned earlier, the PDS values measured in women delivering vaginally without augmentation were comparable to those measured in women at high risk of preterm labor in other studies.[11-13] Euliano et al[30] used EMG in a different way but in a similar population and with a similar research question. They showed that the spatial propagation of contractions differed between patients delivering vaginally and patients delivering by CD because of labor arrest. It would be interesting to see whether secondary analysis of their data focused on the frequency content of the contractions yielded similar results as those described by us. Unfortunately we can not replicate their analysis as the distance between the electrodes was only specified in a general way and was not measured accurately.

A limitation of our study is the limited number of patients with a CD for first-stage labor arrest. Division of the group for subanalysis of the effect of augmentation on contraction characteristics also resulted in small numbers of contractions (n = 220). Subsequently the interpretation of the data becomes more speculative. The intracase variance in contractions characteristics was, however, much larger than the intercase variance. This suggests limited dependence between contractions due to clustering and implies that a linear mixed model with a larger number of confounders could be used than would have been possible based on the number of cases solely. The linear mixed model analysis enabled us to respect the repeated measures structure in time of the data and to analyze the effect of possible confounders. Another limitation of this study is the high rate of protracted labor (70%). This largely reflects the context of Dutch obstetrical care in which low-risk pregnant women deliver under the care of the midwife or general practitioner, and high-risk women deliver under the care of the obstetrician. The study population therefore represents a selected, high-risk population, in which risk factors for protracted labor such as increased maternal age, diabetes, and obesity are more prevalent. Nationwide data on the rate of labor augmentation in term nulliparous women delivering under the care of the gynecologist are comparable: 59% in 2011 and 64% in the region of the participating centers.[31] The same holds for the high incidence of CD (15%) and vaginal instrumental delivery (23%). Again these figures are comparable to nationwide data, with an incidence of 13% for CD and 28% for vaginal instrumental delivery, respectively.[31]

The strength of this study is that it is to date the largest prospective study on EMG in labor. It includes a homogeneous population, solely nulliparous women, cervical assessment at set times, and a standard augmentation protocol. Next to that, this is the first study in which the effect of augmenta-

tion on contraction characteristics was studied by comparing contractions before and after the start of oxytocin administration.

The next step would be to replicate the current findings in a larger study powered to detect the differences between contractions before augmentation in women delivering vaginally and in women undergoing a CD for labor arrest. An additional aspect would be to couple intrapartum recordings to in vitro analysis to test the hypothesis of a link between increase in PDS peak frequency and lactic acidosis and impaired in vitro contractility. If the results are replicated and a threshold above which labor augmentation is likely to fail can be identified, a randomized controlled trial could be designed testing alternative strategies for these patients.

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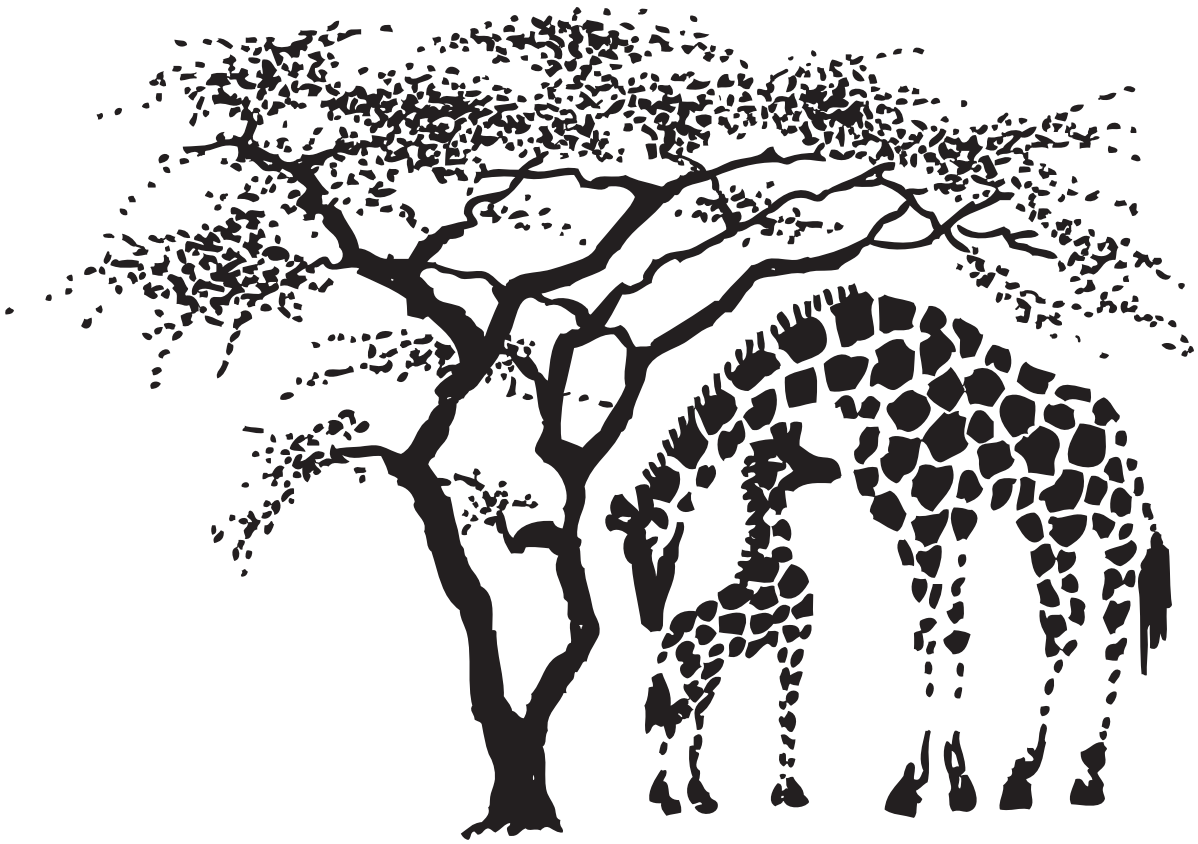

Chapter 8

Identification of first stage labor arrest by electromyography in term nulliparous women after induction of labor

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Revised version submitted to Acta Obstetricia et Gynecologica Scandinavica

ABSTRACT

Introduction Worldwide induction and cesarean delivery (CD) rates have increased rapidly, with consequences for subsequent pregnancies. The majority of intra-partum CDs are performed for failure to progress, typically in nulliparous women at term. Current uterine registration techniques fail to identify inefficient contractions leading to first stage labor arrest. An alternative technique, uterine electromyography (EMG) has been shown to identify inefficient contractions leading to first stage arrest of labor in nulliparous women with spontaneous onset of labor at term. The objective of this study was to determine whether this finding can be reproduced in induction of labor.

Material and methods Uterine activity was measured in 141 nulliparous women with singleton term pregnancies and a fetus in cephalic position during induced labor. Electrical activity of the myometrium during contractions was characterized by its power density spectrum (PDS).

Results No significant differences were found in contraction characteristics between women with induced labor delivering vaginally with or without oxytocin and women with arrested labor with subsequent cesarean delivery.

Conclusion Uterine EMG shows no correlation with progression of labor in induced labor, which is in contrast to spontaneous labor.

INTRODUCTION

Induction of labor is a common obstetrical intervention. Over the last two decades induction rates have increased rapidly in developed countries. In the United States the induction rate increased from 9,5% in 1990 to 23,2 % in 2014.[1] Concurrently cesarean delivery (CD) rates have also increased rapidly over the last years.[2] In some countries one out of three nulliparous women has a CD nowadays, whereby almost half of these CD's are performed because of failure to progress.[3,4] Induction of labor does not seem to increase the rate of CD compared to expectant management for certain indications,[5-8] but these results have to be interpreted in the context of a high background rate of CD and conflicting results of retrospective studies comparing inductions with spontaneous labor.[3,4]

The use of uterotonics is a standard component of most labor inductions. The clinician faced with protracted labor or labor arrest has few other therapeutic options than to increase the rate of uterotonic administration. The high rate of CD for labor arrest shows that this strategy is only partially successful. The identification of patients who are likely not to respond to uterotonics and for which alternative strategies could be devised could be one way of trying to reduce CD rates. In this context renewed interest has gone towards uterine electromyography (EMG), a technique developed seven decades ago.[9-13] This non-invasive method enables to measure the electrical changes occurring when myocytes depolarize during a contraction, through the maternal abdomen. Changes in cell excitability and coupling by gap junctions required for effective contractions that lead to delivery are reflected in changes of several EMG parameters.[14] EMG during labor shows a good correlation with the invasive 'gold' standard of intra-uterine pressure monitoring.[15-17] In case of preterm contractions EMG may help to identify true labor more accurately than current methods.[14,18,19] A study by our group in women with spontaneous onset of labor, showed that contraction characteristics measured by EMG, correlate with progression of labor and are influenced by labor augmentation.[20] We hypothesized that the findings in preterm labor and spontaneous onset of labor could be used to identify inefficient contractions leading to an arrest of first stage labor at term, in induced labor. The objective of this study was to investigate whether uterine electromyography (EMG) can identify inefficient contractions leading to first stage labor arrest followed by CD, in term nulliparous women after induction of labor.

MATERIAL AND METHODS

A prospective multicenter observational study was conducted in three centres in the Netherlands from August 2009 to May 2011. The inclusion criteria were singleton pregnancies in cephalic position (gestational age ≥ 37 weeks and ≤ 42 weeks) admitted to the labor ward for induction of labor. Exclusion criteria were suspected congenital or chromosomal abnormalities. The study was approved on July 6 2009 by the institutional medical ethical committees of the participating hospitals, (number of ethical approval 08-265). Patients who were eligible for participation were approached consecutively.

After informed consent was obtained, measurements of uterine activity were performed using EMG as recorded non-invasively from the maternal abdominal surface. EMG-recordings started from the onset of labor, or during first stage of labor until delivery. There was no predefined time frame for registration duration and EMG recordings were conducted for as long as possible after inclusion. Registrations were analysed post hoc.

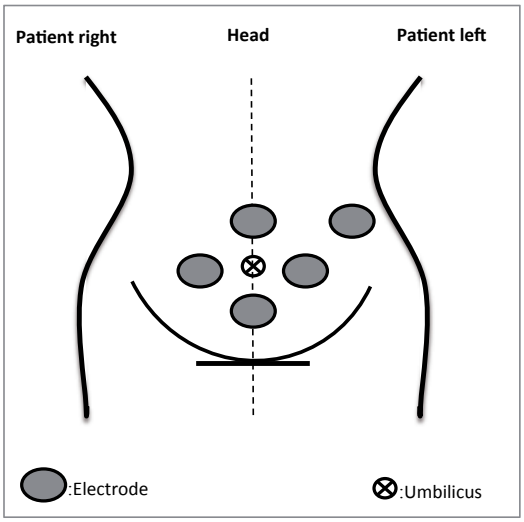
All participating centers belong to a network of teaching hospitals taking part in the same residency program in obstetrics and gynaecology. They follow a similar clinical policy inspired by the "active management of labor" approach.

The method of induction was based on the Bishop score assessed by the clinician at admission. As a rule, a Bishop score lower than six led to priming with vaginal prostaglandin E2 gel. Once ripe, whether after priming or not, membranes were artificially ruptured. An oxytocin drip was started when this did not lead to the appearance of regular contractions within one hour. Active labor was defined as: painful regular contractions ≥ 2/10 minutes and ruptured membranes or cervical effacement ≥75% and/or cervical dilation ≥2cm. Progress of labor was monitored with the use of cervical examinations performed at least every two hours, or more frequently when indicated. As a rule oxytocin was titrated to obtain 4 to 5 contractions per 10 minutes. The diagnosis of labor arrest was made by the clinician using the following criteria: patient in active labor (according to the definition outlined previously) with no increase in dilation for at least 2 hours and optimalized uterine contractions. Protracted labor was defined as a rate of cervical dilation less than or equal to 1cm/hour. A CD for labor arrest was generally performed if labor arrest persisted despite optimal administration of oxytocin during at least two hours.[21,22]

Uterine activity registration and analysis

Uterine activity was monitored using the portable AN24 Maternal Heart Rate/Fetal Heart Rate/EMG recorder (AN24, Monica Healthcare Ltd. Nottingham, UK) through five disposable electrodes that were positioned on the maternal abdomen in a standardized manner. The electrodes were positioned in the following way: two electrodes vertically along the midline, approximately 3 to 5 cm on both sides of the umbilicus, two electrodes horizontally at the level of the umbilicus and symmetrical with respect to it, about 3 to 10cm from the umbilicus. Finally, a (ground) electrode was placed on the left flank. (Figure 1) Skin preparation before electrode placing ensured that skin impedance was below 5 kΩ in all recordings. The raw abdominal electromyogram was recorded at 300 Hz and filtered in the 0.34 – 1 Hz bandwidth to obtain the uterine EMG. This procedure is similar to that reported by others in term of electrode placement and signal filtering.[18,19,23] Filtering in the 0.34-1 Hz bandwidth aims at removing heart rate artefacts above 1Hz and respiration artefacts below 0.34Hz. The signal obtained was treated using an own algorithm to identify each contraction and compute its peak frequency using a power density spectral analysis. This algorithm has been tested and described previously by comparing it against intra-uterine pressure catheter measurements.[15] Power density spectral (PDS) analysis was performed on each contraction and the peak frequency (PF), was used as a contraction characteristic

Figure 1. *Positioning of electrodes on the maternal abdomen*



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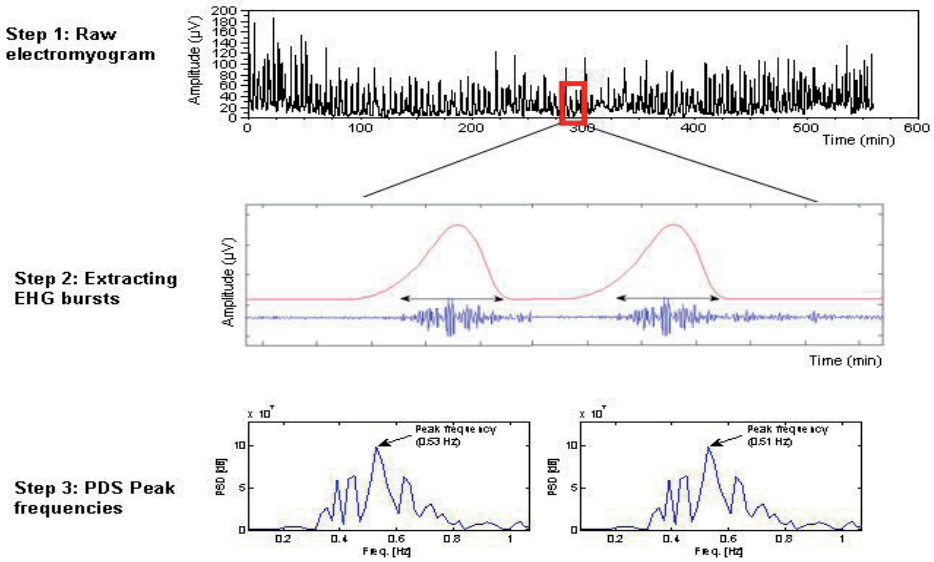
to be linked with clinical outcomes. The signal processing steps are illustrated in Figure 2. This method of analysis has been one of the most predictive EMG parameters in both human and animal studies for prediction of true labor.[12,14,19,24,25] In short, power spectrum analysis converts temporal information, the amplitude of the electrical signal over time during a contraction, to frequency information, the range of frequencies at which myocyte depolarization takes place. Because all myocytes do not depolarize at the same time this leads to a range, e.g. spectrum, of frequencies. The frequency at which most myocytes depolarize is the peak depolarization frequency. Roughly speaking this peak frequency is around once every two seconds (0.5Hz). Changes in cell excitability and coupling lead to changes in this peak frequency. The relation between these changes and clinical outcomes is analysed in this study. The investigators who analyzed the data were not blinded to the labor and delivery data. However, the numerical data of the EMG signal prevented subjective interpretation.

Figure 2. *EMG signal processing steps*



Step 1: Raw EMG as recorded from the maternal abdomen during labor. Step 2: EMG extraction; Red line indicates uterine activity; Blue line represents an electrical burst/contraction. Step 3: For each burst/contraction the peak frequency was calculated with PDS analysis.
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Statistical analysis

Data analysis was performed in SPSS (version 20.0). The sample size was chosen according to the rule of thumb that for measurement of 1 parameter (the peak frequency) 10 cases are necessary in a univariate regression analysis. It was difficult to estimate beforehand the degree of inter and intra-correlation due to the nested structure of the data and hence to perform a more precise power analysis. At the moment of designing the study, in 2009, the rate of cesarean delivery in The Netherlands in induced labor was estimated to be around 12%.[6] With a conservative estimation that 50% of those cesarean sections were performed because of first stage labor arrest we needed a minimal sample size of 150 inclusions. The study was not powered for those cases that did not require oxytocin during the active phase of labor. This sub-analysis was mainly performed as a proof of concept to try to understand the influence of oxytocin on the parameter studied based on findings in spontaneous labor.

The cohort was divided in different groups depending on the outcome. Patients with a CD for other reasons than first stage labor arrest were excluded from analysis. Groups were defined as; group 1: women who delivered vaginally without the use of oxytocin i.e. either because adequate contractions appeared after priming or artificial ruptures of membranes, group 2: women in which labor was induced with oxytocin with or without priming beforehand and delivered vaginally, group 3: women

with a CD for first stage labor arrest. For further analysis groups 1, 2 and 3 were compared to a reference group, obtained from a cohort described previously, consisting of women with spontaneous onset of labor with vaginal delivery without oxytocin administration (group 4).[20] Because of multiple testing, a Bonferroni correction was applied by adjusting the level of significance to $p< 0.008$.

Due to the nested structure of the data with multiple measurements per subject, linear mixed models were used to evaluate the difference in peak depolarisation frequencies between the different groups. Intra class correlation coefficients were calculated, to compare the variance of contraction characteristics within subjects to the variance between subjects. The following confounders were added to the model; maternal age, body mass index, gestational age, birth weight, priming, cervical dilation and epidural analgesia. We chose to perform a statistical test on the mean value of the peak frequency using the cervical dilation as confounder in the mixed linear model to respect the nested structure of the data rather than comparing the groups for each centimeters of dilation. The choice of these confounders was based on literature on confounders of labor outcome.[26-28] Interactions between the confounders and the different groups were studied.

RESULTS

A total of 155 women were included, 123 women delivered vaginally either spontaneously or instrumentally: in 10 of them no oxytocin administered (group 1) and in 113 oxtocin was used (group 2). Thirty two women delivered by CD. Of the 32 CD's 18 were performed for first stage labor arrest (group 3). The other 14 were performed because of suspected fetal distress (n=5) or second stage labor arrest (n=9) and were excluded from analysis. See flowchart in figure 3. Thirty seven percent of

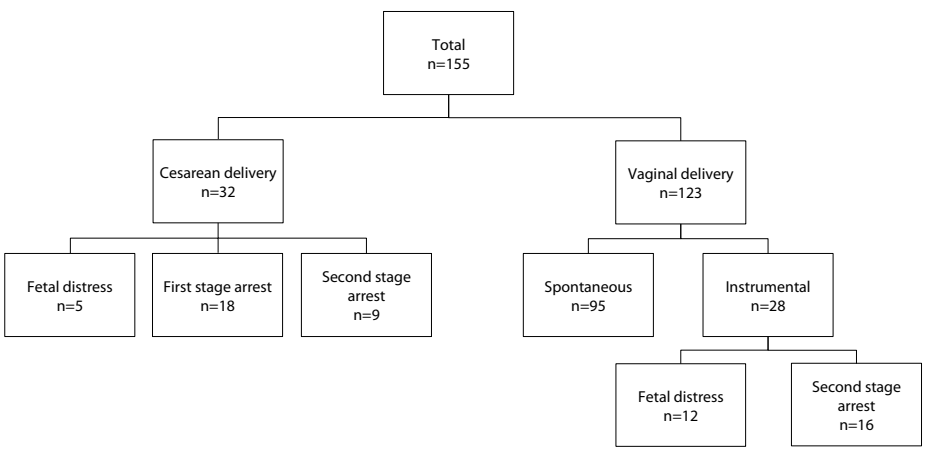


Figure 3. *Flowchart inclusions and delivery mode*

Table 1. *Baseline characteristics*

Characteristics	Group 1 (n=10)	Group 2 (n=113)	Group 3 (n=18)	Group 4 (n=32)
	mean (min-max)/ number (%)	mean (min-max)/ number (%)	mean (min-max)/ number (%)	mean (min-max)/ number (%)
Maternal				
Age mother	31 (23-40)	30 (20-46)	32 (25-42)	32 (24-42)
Body mass index	28 (22-36)	29 (18-48)	30 (23-38)	26 (19-40)
Gestational age (days)	280 (266-293)	279 (257-296)	289 (266-296)	279 (259-292)
Labor				
Duration rupture of membranes (hours)	7 (2-14)	19 (2-100)	17 (9-68)	10 (2-34)
Duration labor (hours)	6 (2-12)	8 (2-22)	13 (2-18)	8 (3-23)
Priming	7 (70%)	35 (31%)	10 (56%)	-
Oxytocin	-	113 (100%)	18 (100%)	0 (0%)
Artificial rupture of membranes	8 (80%)	83 (73%)	13 (72%)	17 (53%)
Epidural analgesia	2 (20%	67 (59%)	16 (89%)	12 (38%)
Indication for induction				
*Maternal**	4 (40%)	53 (47%)	4 (22%)	-
*Fetal***	6 (60%)	40 (35%)	13 (72%)	-
Prelabor rupture of membranes	0 (0%)	20 (18%)	1 (6%)	-
Registration Uterine activity				
Duration registration first stage (min)	309 (68-641)	471 (99-1302)	602 (119-999)	219 (48-543)
Number of contractions measured (First stage)	107 (30-223)	96 (17-302)	229 (26-366)	79 (20-218)
Total number of contractions measured	1009	16050	3959	2537
Without oxytocin	1009 (100%)	842 (5%)	185 (5%)	2537
With oxytocin	-	15208 (95%)	3774 (95%)	-
Neonatal				
Female	6 (60%)	67 (59%)	9 (50%)	17 (53%)
Birth weight	3231 (2730-3710)	3384 (2320-4800)	3998 (2650-4960)	3405 (2330-4280)
Apgar 1 min***	9 (7-10)	9 (5-10)	9 (7-10)	9 (4-10)
Apgar 5 min***	10 (9-10)	10 (6-10)	10 (9-10)	10 (7-10)
pH art	7.24 (7.17-7.31)	7.22 (7.02-7.38)	7.27 (7.20-7.32)	7.19 (7.02-7.30)

Group 1: Vaginal delivery without oxytocin Group 2: Vaginal delivery with oyxtocin Group 3: CD for first stage labor arrest, Group 4: Spontaneous onset of labor vaginal delivery without oxytocin

** Main maternal indications: Hypertensive disorders, Diabetes, maternal disease **Main fetal indications: Serotinity, Decreased fetal movement, Oligohydramnios*

****Displayed in median (min-max)*

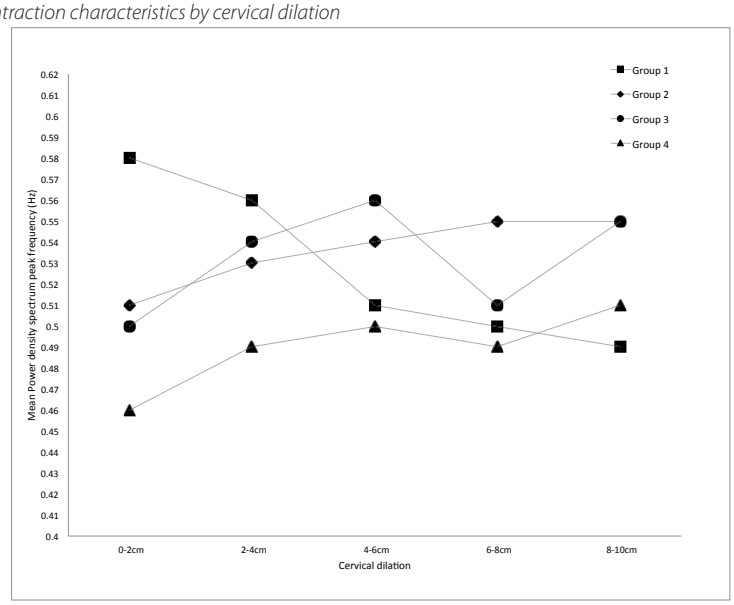
the women were primed and in 60% epidural analgesia was given. Group 4 with a spontaneous onset of labor consisted of 32 women. This group has been described at length in a previous publication[20] and was included here for comparison. Table 1 shows the characteristics of the different groups. Labor arrest or inadequate progression of cervical dilation despite oxytocin occurred in all cases where a CD for first stage labor arrest was performed (mean cervical dilation in the last 2 hours before CD was 0 cm/hour). The mean cervical dilation at CD was 7 cm (range 3-9cm). Table 2 presents the number of contractions, mean peak frequency and standard deviation (SD) per centimeter cervical dilation,

Table 2. *Contraction characteristics by cervical dilation*

Group 1: Vaginal delivery without oxytocin (induction)			
Cervical dilation	**Number of contractions**	**Mean PDS PF (Hz)**	**SD**
0-2cm	158	0.58	0.11
2-4cm	76	0.56	0.09
4-6cm	219	0.51	0.12
6-8cm	168	0.50	0.12
8-10cm	462	0.49	0.10
Group 2: Vaginal delivery with oxytocin (induction)			
Cervical dilation	**Number of contractions**	**Mean PDS PF (Hz)**	**SD**
0-2cm	2102	0.51	0.11
2-4cm	4161	0.53	0.10
4-6cm	2711	0.54	0.10
6-8cm	2579	0.55	0.11
8-10cm	5096	0.55	0.11
Group 3: Cesarean delivery for first stage labor arrest (induction)			
Cervical dilation	**Number of contractions**	**Mean PDS PF (Hz)**	**SD**
0-2cm	476	0.50	0.11
2-4cm	698	0.54	0.11
4-6cm	1159	0.56	0.11
6-8cm	1041	0.51	0.10
8-10cm	585	0.55	0.11
Group 4: Vaginal delivery without labor augmentation (spontaneous onset of labor)			
Cervical dilation	**Number of contractions**	**Mean PDS PF (Hz)**	**SD**
0-2cm	48	0.46	0.10
2-4cm	131	0.49	0.11
4-6cm	324	0.50	0.10
6-8cm	677	0.49	0.10
8-10cm	1357	0.51	0.10

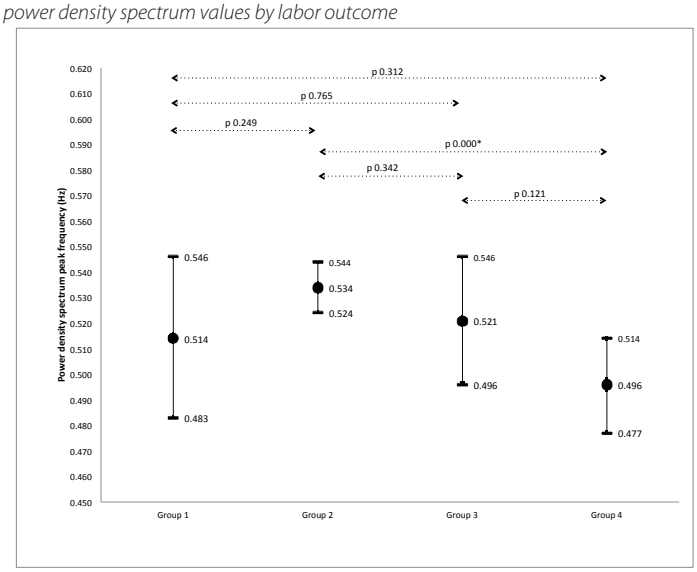
PDS: Power Density Spectrum; PF: Peak Frequency; IQR: Inter Quartile Range

Figure 4. *Contraction characteristics by cervical dilation*



Mean power density spectrum peak frequencies by cervical dilation.

Figure 5: *Mean power density spectrum values by labor outcome*



Mean PDS peak frequencies for groups 1-4 with 5-95% confidence intervals and P values, calculated with linear mixed model analysis. Group 1: induced labor, vaginal delivery without oxytocin, group 2: induced labor, vaginal delivery with oxytocin, group 3: induced labor, CD for first stage labor arrest, Group 4: spontaneous onset of labor, vaginal delivery without oxytocin.

** Significant after Bonferroni correction (p= <0.008)*

for each group. Figure 4 displays the distribution of mean peak frequency as a function of cervical dilation. In group 1 PDS values decreased with increasing dilation. For all other groups PF values increased with increasing dilation. In group 3 there was a drop in mean PF peak frequency at 6-8 cm dilation, where after it increased again for 8-10 cm. The group with spontaneous onset of labor (4) had the lowest PF values. The mixed linear model showed no effect modification in the interaction between confounders. Figure 5 shows the mean peak frequencies with 95% confidence intervals of groups 1-4 with p values for differences between the groups. There was a trend towards a higher mean peak frequency in all induced groups (1-3) compared to the group representing spontaneous labor without oxytocin augmentation, group 4. However this was only significant between group 2 and 4. Overall there were no differences between the different subgroups after induction of labor. The difference found between women eventually undergoing a cesarean delivery because of first stage arrest found in spontaneous labor could not be replicated in induced labor.

DISCUSSION

This study showed no significantly differences in contraction's peak depolarization frequency between women with induced labor delivering vaginally with or without oxytocin and women with arrested labor for which a CD was performed. Women with induced labor and vaginal delivery with oxytocin had a significant higher PF value than women with spontaneous onset of labor with vaginal delivery without oxytocin.

These findings are in contrast with results published recently by our group on the differences between efficient and inefficient contractions in a group of term nulliparous women with spontaneous onset of labor.[20] In that study it was shown that peak frequencies increased significantly when oxytocin was started and differed significantly between women delivering vaginally without oxytocin and CD for first stage labor arrest. This effect was not found in the present study. We have suggested that an increased level of peak frequencies in women undergoing a CD because of first stage labor arrest after spontaneous onset of labor might be a reflection of impaired myometrium function because of lactic acidosis.[20,29] Increased amniotic fluid lactate has been found to be an independent predictor of a labor disorder and CD in spontaneous onset of labor.[30] This hypothesis could not be confirmed in the group of women with labor induction. A possible explanation for this discrepancy might be the fact that almost all induced women received oxytocin as part of the induction scheme and not because of protracted labor. In other words, where our previous study compared the effect of oxytocin on labor protraction disorders, the current study tried to identify labor arrest in a background of generalized oxytocin use. Earlier we have shown that in spontaneous labor, oxytocin increased the value of the peak frequency, even if the women went on to deliver vaginally. It might be that the effect of oxytocin in labor induction is so prominent that additional changes due to protraction disorders are not visible anymore.

It is interesting to note that the peak frequency value of women who delivered vaginally without oxytocin, either after priming or artificial rupture of membranes, was lower than in the other groups. This difference, however, was not significant and should be replicated in larger groups. The fact that the peak frequency value decreased with cervical dilation in this group is also contrary to previous findings in spontaneous labor. Whether this is an effect of priming (70% are primed in this group) or due to the small group size has to be determined in a larger group. However, at this point, uterine EMG cannot guide the clinician towards a differentiated approach of labor protraction disorders in induced labor once oxytocin has been started to induce contractions. Its usefulness seems restricted to labor protraction disorders after a spontaneous onset of labor.

The objective of this study was to look at a novel parameter in a clinical context. First stage labor arrest in nulliparous women remains a difficult problem to address with few effective strategies except active management of labor. Our study was too small and not designed to address issues of conventional contraction characteristics such as intra-uterine pressure. This has been the subject of larger trials before with no impact on clinical outcomes. A recent subgroup analysis of the IUPC trial did show that the group with low Montevideo units was more likely to end up with a cesarean delivery[31] but rightly underlines that despite this knowledge there is little that can be done in practice to increase Montevideo units in those patients. The uterine activity of each woman eventually undergoing a cesarean section because of first stage labor arrest included in the study was optimalized as far as clinically possible according to standard protocols on labor arrest. Augmentation of labor in the few cases with "spontaneous" labor after priming or AROM and oxytocin levels in those induced were aimed at reaching 4 to 5 contractions per 10 minutes in the active phase of labor. The decision to perform a cesarean section due to first stage labor arrest was based on arrested labor for more than 2 hours given optimal uterine activity according to active management of labor. In other words, although the aim of the study was not to compare power density spectrum analysis with other methods of characterizing uterine activity, the failure to find a relation between the peak frequency and progress of labor is not due to underlying inadequate uterine activity in terms of frequency or duration at least as far as possible within a clinical context.

The results of our study should be seen as a complementary analysis searching for additional parameters to characterize inadequate uterine activity, ideally visible at an early stage. Whether this is the case remains unclear given the discrepancies between results in spontaneous and induced labor. The trends observed are, however, similar to the extent that a confirmation study with larger groups seems indicated (n=10 and n=18 respectively).

A limitation of this study was the low number of women in group 1 and 3, (n=10 and n=18 respectively). Nevertheless, in these groups over 1000 and 4000 contractions could be recorded and analysed respectively. The mixed linear model enabled us to add the most important confounders to our model. One confounder lacking was the position of the fetal head. Other aspects that might be of importance in this complex process are the velocity and direction of electrical activity. Euliano et al studied the spatiotemporal patterns of uterine electrical activity and found a significant correlation

between upward movement of the center of uterine activity (fundal dominance) and labor progress.[32] In prediction of preterm delivery EMG propagation velocity was significantly higher in patients in preterm and term labor compared with patients not in labor. In our study we were not able to take these aspects of electrical activity in account.

The strength of this study is that to our knowledge it is to-date the largest prospective study on EMG in induced labor. Another strength is the homogeneous population; solely nulliparous women, cervical assessment at set times (every 2 hours, or more when indicated) and a standard induction protocol. All women included were treated according to an active management of labor approach with optimalization of uterine activity and consistent definition of first stage labor arrest.

In conclusion, EMG showed no correlation with progression of labor in induced labor, which is in contrast to the identification of inefficient contractions leading to an arrest of first stage term labor in spontaneous onset of labor. Studies with larger sample sizes and with assessment of other EMG parameters are necessary to try to identify first stage labor arrest in an early stage in women with induced labor.

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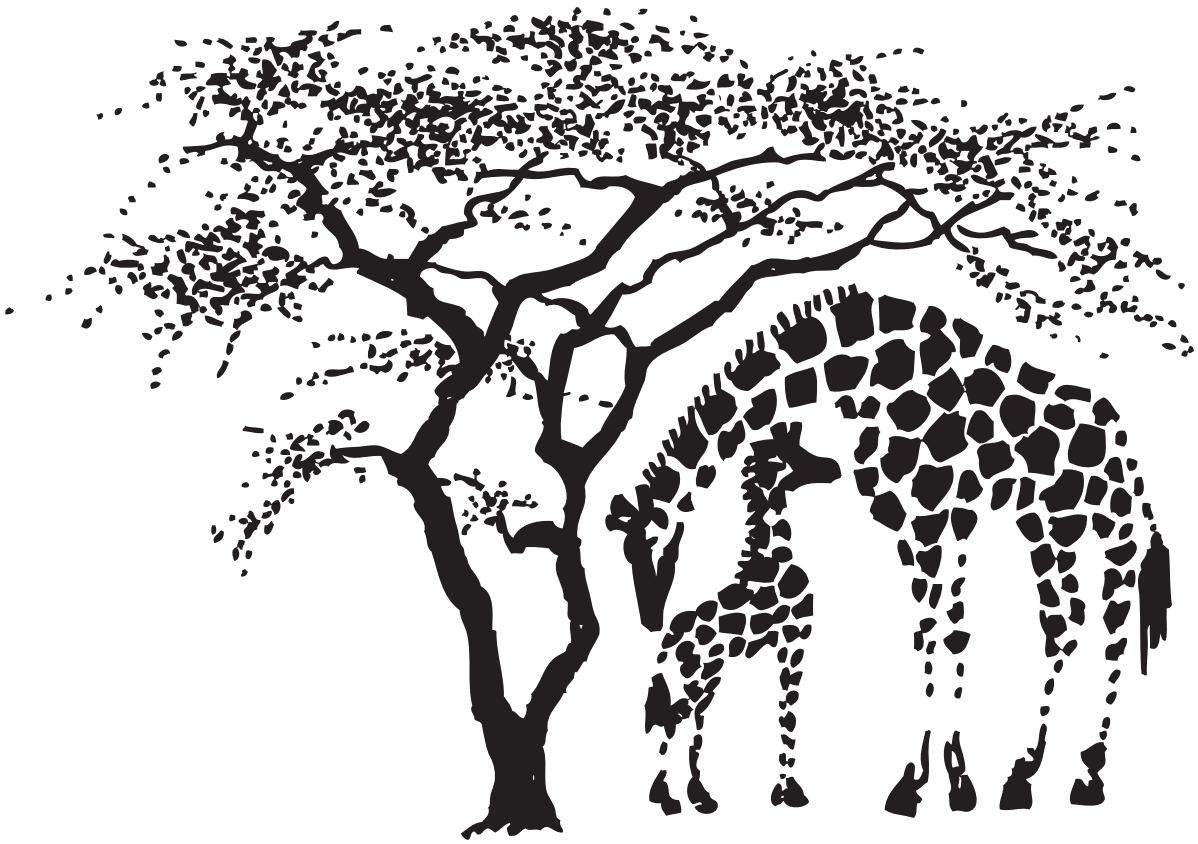

Chapter 9

Summary and General discussion

This thesis focuses on risk assessment during pregnancy and labor. Part 1 of this thesis describes risk assessment during pregnancy concentrating on fetal growth in relation to perinatal morbidity, perinatal mortality and implications for maternal health. Part 2 of this thesis focuses on risk assessment during labor by studying a new technique, electromyography, to monitor contractions for identification of inefficient contractions leading to first stage labor arrest followed by cesarean delivery in term nulliparous women. Both parts will be discussed separately.

PART I

Optimal fetal growth

Normal fetal growth is usually defined as an estimated fetal weight between the 10th and 90th centile based on population specific birth weight centiles corrected for gestational age at delivery, parity and fetal sex. So-called customized growth charts also correct for maternal ethnicity, weight and length.[1] Such definitions are based on the fact that both impaired and excessive fetal growth result in an increased risk of perinatal morbidity and mortality. Indeed, in small for gestational age (SGA) fetuses, defined as a birth weight below the 10th centile, there is an increased risk of intra-uterine fetal death across all gestational ages[2,3] compared with non-SGA fetuses, with the highest risk in infants with a birth weight below the 3rd centile.[4] Large for gestational age (> 90th centile, macrosomic) fetuses are at risk of labor complications and thus also of increased perinatal morbidity and mortality.[5,6] However, with a focus on too small or too big it may be forgotten that the majority of perinatal (and especially antepartum) deaths occur in fetuses with a 'normal' weight. Moreover, the use of population based fetal growth charts assumes that optimal size at birth for outcome is at the 50th centile. In the Chapters 2 and 3 we studied optimal birth weight for gestation for perinatal survival in both singletons and twins, by using nationwide data from the Netherlands Perinatal Registry. Altogether we included over 1 million non-malformed singletons born after 28 weeks of gestation and over 40.000 twins.

Fetal growth/size and short term perinatal survival in singletons (Chapter 2)

Perinatal mortality related to fetal growth according to gestational age and birth weight was studied in singleton pregnancies delivered between 2002 and 2008. 64% of all perinatal deaths occurred in infants with a weight between the 10th and 90th centile. Highest mortality occurred in infants with a weight < 2.3rd centile. Lowest perinatal mortality was found in infants with a birth weight between the 80th and 84th centiles for the population and this held for all gestational ages at delivery. Lowest antepartum mortality occurred in infants with a weight around the 95th centile and lowest intrapartum and neonatal mortality at a weight around the 80-84th centile. So, from an immediate survival perspective, optimal fetal growth requires a birth weight between the 80th and 84th centiles for the population. Median birth weight in the population is, by definition, substantially lower than these centiles, implying that the majority of fetuses exhibit some form of constraint on growth. This finding

is consistent with adaptations that have evolved in humans in conjunction with a large head and bipedalism, to reduce the risk of obstructed delivery.[7,8]

Several studies have found similar results. A study conducted in Newcastle in the United Kingdom, using Z-scores for distribution of birth weight showed that the lowest stillbirth rate and infant mortality occurred in infants with a Z-score of +1, both between 1961-1980 and 1981-2000, a period over which the overall stillbirth rate fell in that region of the UK from 23·4 to 4·7 per 1000, respectively.[9] In a larger nationwide study in Norway lowest mortality was found for a birth weight Z-score between +1 and +2.[10] Similar results were recently published from Australia[11] and Scotland.[12] In the latter study regarding 780.000 births, lowest antenatal mortality occurred in fetuses with a birth weight in between the 90-97th centile in both cases with unknown cause of death and death related to antenatal haemorrhage or maternal hypertensive disease. Only in case of maternal diseases, including diabetes, the stillbirth rate was lowest in fetuses with a weight around the 20th centile. Data on cerebral palsy are also in line with the mortality figures since the lowest prevalence of cerebral palsy by Z-score of weight for gestation was found in infants with a Z-score of +1.[13]

These studies indicate that optimal fetal weight for intact perinatal survival occurs at a much higher centile than the 50th centile. In fact perinatal mortality of fetuses with a weight at the 50th centile is 34% higher than in that of fetuses weighing in between the 80th and 84th centile.[14] The lower 'optimal weight' for intrapartum and neonatal survival (80-84th centile), as compared to that of antepartum survival (90-95th centile), may be explained by intrapartum complications in infants at the highest birth weight centiles. Regarding antepartum survival it may be concluded that 'the bigger the better'[10] and that most infants have a birth weight below optimal for perinatal survival, which seems illogical in evolutionary perspective. However, mothers also have to survive and the relatively small pelvis associated with bipedalism and the large human fetal head constitute major obstacles for uncomplicated childbirth. It may therefore well be that maternal factors restrain fetal growth that is below optimal for perinatal survival. In other words, a conflict between mother and fetus with a compromise as a result. Given the fact that during the whole existence of mankind women have looked after their offspring, such a compromise may have resulted in a net benefit for the infants at the end. In developing countries this can nowadays still be seen in the very poor survival of children whose mother has died during or directly after childbirth.[15,16]

These data also nicely fit with recent Doppler findings of blood flow redistribution to the fetal brain. In a large cohort of third trimester fetuses it was shown that the cerebroplacental ratio (CPR) increased progressively with increasing fetal weight centiles whereby signs of redistribution were only consistently absent in case of an estimated fetal weight >90th centile.[17] The association between CPR and weight centiles has recently been confirmed in another study.[18]

Fetal growth and long term survival

The data of this thesis also fit remarkably well with those on long-term adult cardiovascular and metabolic health risks, which are lowest in cases with a birth weight around the 90th centile. The

high birth weight (centile) favorable for perinatal survival is also associated with reduced risk of later non-communicable disease. Studies on the Developmental Origins of Health and Disease (DOHaD) concept have shown that birth weight is inversely related in a graded manner to risk of later cardiovascular and cerebrovascular death[19-22] and to impaired glucose tolerance and Type 2 diabetes.[23] Thus, in historical studies in the UK lowest risks of adult cardiovascular disease (CVD) were found in infants weighing around 4 kg at birth, approximately the 90th centile at 40 weeks of gestation.[19,21] A high birth weight, indicative of absence of intra uterine growth restraint and resulting in a low perinatal mortality is, therefore, also favourable for long-term health.

Optimal fetal growth in twins (Chapter 3)

We performed a similar study in 41.068 twins, delivered after 28 weeks of gestation between 2002 and 2008. In twins fetal growth is a more complex process than in singletons and zygosity and chorionicity have important influences. Monochorionic twins have additional risks for mortality and morbidity due to twin related pathologies, such as the twin-to-twin transfusion syndrome (TTTS) resulting in haemodynamic inbalance influence on growth.[24-28] In twins after 30 weeks gestation fetal weight is lower than in singletons and this is likely to be due to inadequate maternal cardiovascular adaptation or non-optimal placental location and/or perfusion.[29-31] Chapter 3 shows that from an immediate survival perspective, optimal birth weight for all twins requires a birth weight between the 10-50th centile. However, after stratification for estimated data on zygosity using the Weinberg rule[32] this only held for the monozygotic twins. Optimal birth weight for dizygotic twins was comparable to that of singletons at around the 90th centile. This implies that the monozygotic twins, with high mortality rates at both low and high birth weight centiles which are possibly related to TTTS, cause the difference in optimal fetal weight between singletons and twins. As discussed before for singletons it is postulated that maternal constraint occurs to compromise between maternal and fetal survival. In twins fetal growth also seems to be generally constrained below optimal for perinatal survival and we hypothesize that this is due to the maternal constraint process and inadequate maternal cardiovascular adaptation and suboptimal placental perfusion. It should be noted that for this thesis, data on zygosity could only be obtained by estimation using the Weinberg rule, although the validity of this rule's assumptions has never been conclusively verified, nor rejected,[33] large population based studies with information on zygosity are necessary to find optimal risk reduction strategies.

Perinatal mortality in twins versus singletons (Chapter 4)

Based on large registry data in Western countries (PERISTAT) a twin pregnancy has a crude 2-3 fold increased perinatal mortality risk compared to singletons.[34] Twin pregnancies are therefore classified as high-risk pregnancies and managed accordingly; for twin pregnancies more frequent routine check- ups and ultrasound investigations are advised by national guidelines throughout the world. We studied 1.502.120 singletons and 51.658 twins born between 2002 and 2010 after 28 weeks of gestation, we found that overall perinatal mortality was higher in twins than in singletons (6.6/1000 vs

4.1/1000). However, when taking into account differences in gestational age at delivery, antepartum mortality was significantly lower during the preterm period in twins than in singletons. This is supported by previous (smaller) studies.[35-37] Differences in parity, fetal sex and socioeconomic status did not explain the observed differences in outcome. Although further detailed information on cause of death and maternal and fetal characteristics were not studied in this thesis we hypothesize that the overall higher mortality rate in twins is most likely caused by the high preterm birth rate and not by a higher mortality rate for gestation, apart from term pregnancies. For many thus far uncomplicated twin pregnancies, preterm delivery seems part of a 'natural' process due to uterine overdistention as the causative mechanism without other pathologies. In contrast, for singletons many of the preterm deliveries are associated with pathologies such as preeclampsia, IUGR and placental abruption.[38,39] We also hypothesize that the difference in preterm mortality might be due to the closer monitoring of twins during pregnancy, which indirectly suggests a need for closer monitoring of singleton pregnancies.

Clinical implications, identification (Chapter 5)

Early stillbirths are generally SGA.[3] So, at early gestation identification of SGA fetuses remains of utmost importance. This is facilitated by the fact that early fetal growth restriction is usually associated with maternal hypertensive disease.[40,41] After approximately 32 weeks of gestation the majority of stillbirths concern appropriate- for gestation infants and most of these women do not have a hypertensive disease.[3,14] Identification of these apparently normally grown fetuses at risk for stillbirth is currently one of the challenges in obstetrics. On the other hand, also in the third trimester of pregnancy SGA fetuses have the highest risk of dying antenatally. So, identification of third trimester SGA infants remains important since mortality may be reduced when these fetuses have been identified as being small.[42,43] The diagnosis of SGA relies on fetal biometry, but Doppler ultrasound is the fundamental tool to evaluate the cause and further management of the subgroup suspected of being growth restricted. Hemodynamic changes related to placental dysfunction involve the umbilical artery (UA), the middle cerebral artery (MCA) and the maternal uterine artery (UtA). Poorer placentation may result in a higher blood-flow resistance of the UA, with as a result decreasing the blood-flow resistance of the MCA as a fetal adaptation. Theoretically one would expect to find these changes with Doppler measurements, however when placental dysfunction is less severe and occurs later on in pregnancy, these changes might be more subtle and therefore more difficult to detect.[44-46] In Chapter 5 we studied the potential of diagnostic antenatal ultrasound Doppler parameters to identify (near) term small for gestational age fetuses at risk for short term adverse neonatal outcomes. Longitudinal data from the obstetric departments of the UMC Utrecht and UMC Groningen were prospectively obtained from 43 SGA fetuses. We found that none of the single Doppler measurements at intake showed a correlation with neonatal outcome, but changes from normal to abnormal with time were related to impaired outcome, with the cerebroplacental ratio (CPR) and ductus venosus (DV) as the best parameter to identify the SGA fetus at risk. However, their predictive value was limited, possibly due to the small

study population and relatively mild morbidity. The CPR is the ratio between umbilical artery Doppler and middle cerebral artery Doppler. The advantage of using this ratio is that more subtle changes may be detected, by combining information from both UA and MCA. Apparently a single measurement does not seem to identify fetuses at risk for impaired outcome, but the value of CPR in term SGA pregnancies lies within longitudinal following the course of CPR values with time. This is supported by a recent study where, in an unselected population of 6000 fetuses that were assessed with a single measurement at around 36 weeks of gestation, no predictive value of the CPR was found regarding cesarean section for fetal distress, umbilical artery pH at birth, or Apgar score.[18] However, in a high risk population of term fetuses, pH at delivery was lower in cases with an abnormal CPR, both in SGA and normally grown fetuses.[47] Similarly, a reduced CPR immediately prior to delivery has been shown to be associated with an increased risk of delivery by emergency cesarean section.[48] In studies in SGA term fetuses that were assessed repeatedly, a reduced CPR was associated with a poorer outcome than in cases with a normal ratio.[49] This suggests that the CPR might be useful in high risk fetuses, and/or directly before delivery and/or when measured longitudinally. A single measurement some time before delivery and/or before the occurrence of fetal hypoxaemia does not seem to be useful.

Changes in ductus venosus PI from normal to abnormal values also showed a relationship to adverse neonatal outcome. In our near term SGA population this was somewhat unexpected since abnormal DV is usually known to be a late sign of fetal deterioration mostly present in severe and early growth restriction.[50,51] Unfortunately for term SGA populations, no large trial data on DV for prediction of adverse neonatal outcome exist.

Identification of fetuses at risk for intrauterine death remains difficult. On the one hand SGA fetuses have to be identified and on the other hand a larger group of apparently normally grown fetuses at risk of dying in utero should be identified. This will require integrated risk models, including maternal characteristics (BMI, age, socio-economic situation), Doppler measurements of the maternal and feto-placental circulation, fetal growth assessment, and measurement of biochemical markers of placental function. Most likely a contingent screening is required (e.g. to identify decreasing fetal growth velocity). Models must be first exhaustively tested in the population to which they will be applied, to obviate the risk of unnecessary intervention.

Fetal growth and maternal health (Chapter 6)

In addition to fetal complications, impaired fetal growth also seems to have implications for maternal cardiovascular health. The process of fetal growth is influenced by maternal, fetal and placental factors. Maternal cardiovascular adaptation with optimal placental perfusion is necessary to allow fetal growth. If this adaptation is suboptimal, impaired fetal growth occurs resulting in intra-uterine growth restriction. One could say that pregnancy can be viewed as the "ultimate stress test" for the cardiovascular system, revealing underlying cardiovascular pathology that may cause cardiovascular morbidity or mortality later on in life. Placental disorders such as preeclampsia and IUGR are associated with an increased prevalence of maternal cardiovascular (CV) disease risk factors after delivery.[52-57] This is most

likely due to common risk factors including chronic hypertension, dyslipidemia, components of the insulin resistance syndrome and inflammatory mediators.[58,59] IUGR is often accompanied by other placental disorders such as preeclampsia or pregnancy induced hypertension, which makes it more difficult to find out if IUGR is an independent indicator for cardiovascular morbidity and mortality.

In Chapter 6 we have shown that women with a history of preterm intra uterine growth restriction, with or without maternal hypertensive disorder, have an altered cardiovascular risk profile several months after pregnancy with increased levels of modifiable cardiovascular risk factors. It has been shown that cardiovascular disease is largely preventable by early modification of cardiovascular disease risk factors.[60] Preeclampsia, pregnancy induced hypertension and gestational diabetes have already been acknowledged as independent risk factors by the American Heart Association (AHA).[61] Chapter 6 provides evidence that women with a history of preterm IUGR, with or without a concomitant hypertensive disorder might also benefit from cardiovascular risk factor assessment and preventive interventions. However, this needs to be investigated further before wide implementation since a recent meta-analysis showed that published studies on this relationship are few and of moderate quality at best, and that delivery of a small for gestational age infant was related to an increased risk of developing or dying from overall cardiovascular disease (RR 1.66).[62] The authors considered this to be only a moderately increased risk (RR <2) and disrecommended specific follow up (level B evidence). Thus, more research of better quality is required to assess the clinical and cost- effectiveness of these strategies before they can be incorporated in clinical practice.

PART 2

Electromyography and identification of first stage labor arrest

As discussed in Part 1 of this thesis risk assessment in the intra uterine period of a child is imperative. During the process of leaving the intra uterine environment, also known as birth, identification of risk groups remains vital for both mother and child. The rate of cesarean deliveries and inductions of labor has increased rapidly over the last years.[63,64] First stage labor arrest accounts for almost half of all cesarean deliveries.[65,66] Failure to progress during labor is often caused by inefficient uterine contractions. Uterotonics are widely used for augmentation and induction of labor, however if uterotonics fail to stimulate progression of labor, clinicians are faced with limited other therapeutic options. Current uterine monitoring techniques fail to identify inefficient contractions and patients who are not likely to respond to uterotonics.[67] Early identification of these groups could provide a basis for alternative strategies with reduction of cesarean delivery rates. In the Chapters 7 and 8 we measured the uterine electrical activity (uterine electromyography; EMG), with non-invasive electrodes placed on the maternal abdomen the investigate whether with this technique inefficient contractions resulting in labor arrest and cesarean delivery may be detected and to assess the effect of oxytocin. We developed an algorithm to identify contractions and compute the power density spectrum (PDS). PDS analysis was

performed on each contraction and the peak frequency was used as a contraction characteristic to be linked with clinical outcomes.

Electromyography and spontaneous onset of labor (Chapter 7)

Chapter 7 shows that for nulliparous women with a singleton pregnancy in cephalic position contraction characteristics measured by uterine EMG correlate with progression of labor. Mean PDS peak frequency in women undergoing cesarean delivery for first-stage labor arrest was significantly higher than in women delivering vaginally without or with augmentation of labor. Augmentation increased the mean PDS peak frequency in women who eventually delivered vaginally. In women who delivered vaginally after augmentation, the contractions before augmentation were similar to those of women not needing augmentation, whereby PDS values increased significantly after the start of oxytocin. For the women who did not respond to augmentation by uterotonics, PDS values were already higher before starting uterotonics, and increased after augmentation. In studies on preterm labor increases in PDS values were also found and this increase was described to be due to accelerated development of gap junctions, resulting in an increased synchronization of myocyte activity.[68-71] There seems however to be a limit beyond which an increase in PDS values is not efficient anymore, possibly reflecting an increase in lactic acidosis due to prolonged exposition to uterotonics.[72] Increased amniotic fluid lactate has been found to be an independent predictor of a labor disorder and cesarean delivery in women with a spontaneous onset of labor.[73] We hypothesize that this mechanism could also have been the same for the women in our study with increased PDS values and cesarean delivery for first stage labor arrest. For this group, conventional augmentation strategies with uterotonics do not seem to result in progression of labor.

Electromyography and induced labor (Chapter 8)

As induced labor is different from spontaneous labor in many ways, this group was studied separately. No significant differences were found in contraction characteristics between women with induced labor delivering vaginally with or without oxytocin and women who had a cesarean delivery for arrested labor. We theorize that the effect of oxytocin in labor induction might be so prominent that additional changes due to protraction disorders are not visible anymore. This thesis shows that EMG is not able to identify inefficient contractions leading to first stage labor arrest followed by CD, in term nulliparous women after induction of labor.

Future directions for research and clinical practice

For the obstetrician in the labor ward there are two challenges related to first stage labor arrest. The first challenge is to timely identify women with inefficient contractions and to identify the group that is not likely to respond to uterotonics. The next challenge after identification is the lack of alternative therapeutic options where consequently a cesarean delivery is the only option.

For spontaneous onset of labor this thesis shows that EMG could help the clinician identify women at risk for cesarean delivery with a poor response to conventional augmentation. However therapeutical options are still lacking. The first step to obtain more information on the mechanism behind PDS values and protraction of labor would be to conduct an in vitro analysis of myometrium contractility to test the hypothesis of the effect of lactic acidosis. If a correlation would be found, one could argue that a temporary arrest of contractions using a tocolytic drug may restore adequate metabolization. With more information on these mechanisms targeted therapeutically options can be studied.

MAIN CONCLUSIONS OF THIS THESIS AND RECOMMENDATIONS

Part 1

Main conclusions

- For singletons from an immediate survival perspective, optimal fetal growth requires a birth weight between the 80th and 84th centiles for the population. For antenatal survival a fetal weight around the 95th centile is optimal.
- For twins from an immediate survival perspective, optimal birth weight requires a birth weight between the 10-50th centile. After stratification for estimated data on zygosity optimal birth weight for dizygotic twins was comparable to that of singletons and around the 90th centile.
- Overall perinatal mortality is higher in twins than in singletons. However, when taking into account differences in gestational age at delivery, antepartum mortality was significantly lower during the preterm period in twins than in singletons. The later may, among other reasons, be due to a better surveillance of twin pregnancies
- For prediction of adverse neonatal outcome of near term small for gestational age fetuses changes from normal to abnormal Doppler parameters with time were related to impaired outcome, with the cerebro-placental ratio and ductus venosus as the best parameter to identify the SGA fetus at risk. This implies longitudinal monitoring of these variables. A single measurement was not related to outcome.
- Women with a history of preterm intra uterine growth restriction, with or without maternal hypertensive disorder, have an altered cardiovascular risk profile several months after pregnancy with increased levels of modifiable cardiovascular risk factors.

Recommendations for future research and clinical practice

- When developing risk scores for perinatal mortality not only fetal weights < 10th centile should be included, but so should a graded, more sophisticated, risk-centile distribution.
- Large population based studies should point out if intensified antepartum surveillance of all singleton pregnancies will lower perinatal mortality rates.

- For identification of term SGA fetuses at risk longitudinal ultrasound measurements are required with special attention for changes from normal to abnormal values.
- Women with a history of preterm intra uterine growth restriction might benefit form follow-up and management of cardiovascular risk factors. High-quality prospective studies are needed to elucidate this.

Part 2

Main conclusions

- For term nulliparous women with a singleton pregnancy in cephalic position and spontaneous onset of labor, contraction characteristics measured by uterine electromyography correlate with progression of labor.
- In women with spontaneous onset of labor delivering vaginally, augmentation of labor altered contraction characteristics measured by electromyography when comparing contractions before and after start of augmentation. In these women electromyography may help in identifying women at risk of labor arrest.
- Uterine electromyography shows no correlation with progression of labor in induced labor in nulliparous women with singleton term pregnancies and a fetus in cephalic position.

Recommendations for future research and clinical practice

- For spontaneous onset of labor, electromyography could help the clinician identify women at risk for cesarean delivery with a poor response to conventional augmentation.
- The first step to obtain more information on the mechanism behind altered electromyography values and protraction of labor would be to conduct an in vitro analysis of myometrium contractility to test the hypothesis of the effect of lactic acidosis.
- After information on the mechanism is obtained targeted therapeutically options can be studied.

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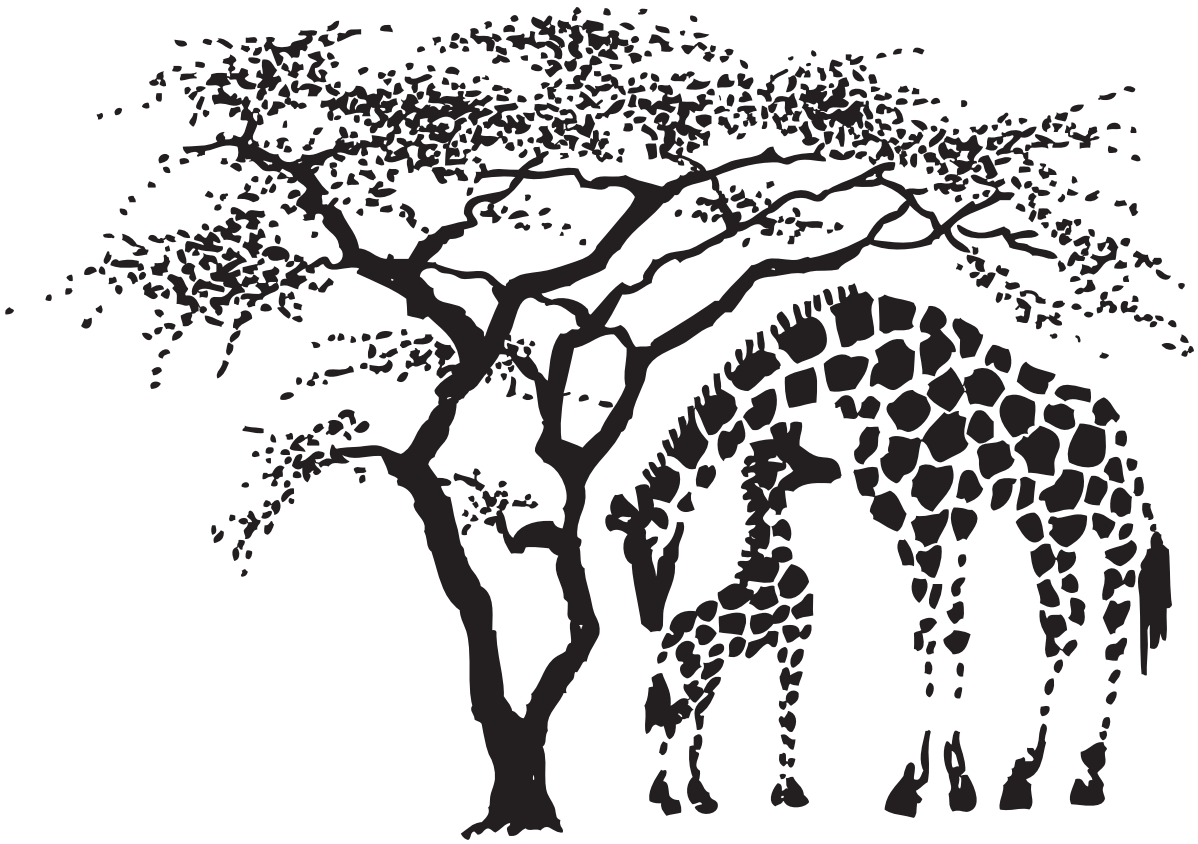

Chapter 10

Dutch summary

(Nederlandse samenvatting)

Dit proefschrift richt zich op identificatie van risicogroepen tijdens de zwangerschap en de bevalling. Deel 1 van dit proefschrift beschrijft de foetale groei tijdens de zwangerschap in relatie tot perinatale morbiditeit en sterfte en gezondheidsrisico's voor de moeder. Deel 2 van dit proefschrift richt zich op de risicoselectie tijdens de baring, waar elektromyografie, een nieuwe techniek voor het meten van weeën- activiteit tijdens de bevalling, wordt onderzocht. Hierbij wordt specifiek gekeken of deze nieuwe techniek in staat is om inefficiënte weeën, met als gevolg een niet vorderende baring, te identificeren.

DEEL 1

In hoofdstuk 2 en 3 is de relatie tussen geboortegewichtspercentielen, zwangerschapsduur en perinatale sterfte onderzocht in zowel eenling- als tweelingzwangerschappen. Beide retrospectieve cohort studies zijn gebaseerd op de landelijke perinatale registratie (Perined)[1] gegevens van 1.170.534 eenlingen en 4.1090 tweeling kinderen geboren na 28 weken zwangerschapsduur in Nederland tussen 2002-2008. De geboortegewichtspercentiel geeft de verdeling aan van geboortegewichten bij een bepaalde zwangerschapsduur in een populatie, rekening houdend met het geslacht van het kind en pariteit van de moeder. Voor zowel eenlingen als tweelingen werd de hoogste sterfte gevonden voor kinderen met een geboortegewicht onder de 5de percentiel. De laagste sterfte werd bij eenlingen gevonden bij een gewicht tussen de 80-84ste percentiel. Het gemiddelde geboortegewicht (de 50ste percentiel) in de populatie is aanzienlijk lager dan de laatstgenoemde percentielen, wat impliceert dat de meeste foetussen een geboortegewicht hebben dat lager is dan het optimale gewicht voor perinatale overleving. Vanuit evolutionair perspectief lijkt dit niet logisch, echter de overlevingskans van de moeder speelt ook een rol in dit proces. Een te groot hoofd van de foetus in verhouding tot een relatief klein bekken van de moeder kan grote belemmeringen vormen voor een bevalling. De hypothese is dat maternale factoren de foetale groei beperken tot een "suboptimaal" geboortegewicht voor de foetus. Met andere woorden, een conflict tussen moeder en foetus met als resultaat een compromis.

Vervolgens laat hoofdstuk 3 zien dat voor alle tweelingen samen het optimale geboortegewicht lager ligt dan bij eenlingen, namelijk tussen de 10-50ste percentiel. Na stratificatie voor zygositeit, dat wil zeggen onderscheid tussen een- en twee-eiige tweelingen, (met geschatte gegevens) bleken de laagste sterftecijfers voor twee-eiige tweelingen vergelijkbaar te zijn met eenlingen, namelijk rond de 90ste percentiel. Bij eeneiige tweelingen lag het optimale geboortegewicht lager en werd de laagste perinatale sterfte gevonden bij een geboortegewicht tussen de 10-50ste percentiel. Bij een-eiige tweelingen was zowel bij lage als hoge gewichtspercentielen de sterfte hoger, wat zeer waarschijnlijk te maken heeft met een specifiek probleem bij deze tweelingen, bloedvatverbindingen tussen de beide circulaties. Helaas was het bij deze analyses niet mogelijk te stratificeren naar chorioniciteit.

Met uitzondering van specifieke complicaties bij eeneiige tweelingen, lijkt het fenomeen van optimale groei voor perinatale overleving bij een foetaal gewicht rond de 90e gewichtspercentiel, dus universeel en dit is ook in andere populaties gevonden.[2-5] Deze perinatale gegevens komen ook overeen met de lange termijn levensverwachting van deze kinderen: bij een hoog geboortegewicht is de kans om op latere leeftijd op hart- en vaatziekten en/of diabetes te ontwikkelen verlaagd.[6-9] Met andere woorden, optimale foetale groei, lage kans op sterfte voor en na de bevalling en een betere prognose voor de rest van het leven.

In hoofdstuk 4 werd de perinatale sterfte in relatie tot de zwangerschapsduur bij tweelingen vergeleken met deze van eenlingzwangerschappen, gebaseerd op de landelijke Perinatale Registratie (Perined) gegevens in Nederland van 2002-2010. In deze retrospectieve cohort studie werden 1.502.120 eenlingen met 51.658 tweelingen, geboren na 28 weken zwangerschapsduur, met elkaar vergeleken. De totale perinatale sterfte was hoger bij tweelingen dan bij eenlingen, echter tijdens de preterme periode (voor 37 weken zwangerschapsduur) was de perinatale sterfte vele malen lager bij tweelingen dan bij eenling zwangerschappen. Onze hypothese is dat dit gedeeltelijk verklaard kan worden door het feit dat tweelingzwangerschappen vaker en nauwer gecontroleerd en bewaakt worden tijdens de zwangerschap en bevalling. Dit suggereert indirect dat er een noodzaak bestaat voor een meer nauwlettende bewaking van eenlingzwangerschappen.

Uit hoofdstuk 2 en 3 van dit proefschrift blijkt dat de hoogste perinatale sterfte wordt gevonden bij kinderen met een extreem laag geboortegewicht voor de zwangerschapsduur (<5de percentiel). Intra-uteriene identificatie van deze "hoog risico" foetussen is daarom van groot belang. Echografische metingen van de foetale groei en van bloedstroomprofielen in de vaten (Doppler metingen) zijn een essentieel instrument voor dit identificatie proces, maar in de a terme periode (na 37 weken zwangerschapsduur) slagen de meeste van deze instrumenten er niet in om de hoog-risico foetus te identificeren. In hoofdstuk 5 werd in een populatie van 43 a terme foetussen, met een groei onder de 10de percentiel, onderzocht wat de potentie van diagnostische echo parameters is om foetussen met een verhoogd risico op een negatieve neonatale uitkomst te identificeren. De beste voorspeller voor een slechte neonatale uitkomst was een verandering van normale naar abnormale waarden bij longitudinale Doppler metingen van de cerebro-placentaire ratio, (de verhouding tussen de doorstroming in de navelstreng en de middelste hersenslagader) en de ductus venosus. Voor elke parameter gold dat een eenmalige Doppler meting geen voorspellend vermogen had. Omdat deze uitkomsten op kleine aantallen gebaseerd zijn, bestaat er een noodzaak om dit verder uit te zoeken in grotere studie populaties.

Naast foetale complicaties, lijkt een afwijkende groei van de foetus ook implicaties te hebben voor de cardiovasculaire gezondheid van de moeder. Andere placentaire aandoeningen zoals pre-eclampsie en abruptio placentae (placenta loslating) worden geassocieerd met een verhoogde prevalentie van cardiovasculaire risicofactoren enkele maanden na de bevalling.[10-15] Hoofdstuk 6 beschrijft het cardiovasculaire risico profiel bij vrouwen die een zwangerschap doorgemaakt hebben met ernstige vroege (vóór 34 weken zwangerschapsduur) intra-uteriene groeirestrictie (IUGR), met stratificatie

voor hypertensieve ziekte bij de moeder. In deze prospectieve cohort studie werden 157 vrouwen met een zwangerschap met IUGR, waarvan 42 vrouwen zonder en 115 vrouwen met bijkomende hypertensieve aandoening, vergeleken met 70 vrouwen met een ongecompliceerde zwangerschap. Vrouwen met een voorgeschiedenis van preterme intra-uteriene groeirestictie, met of zonder een maternale hypertensieve aandoening, blijken enkele maanden na de zwangerschap een veranderd cardiovasculair risicoprofiel te hebben met verhoogde aanpasbare cardiovasculaire risicofactoren. Dit zou betekenen dat deze vrouwen zouden kunnen profiteren van zowel het vervolgen van de cardiovasculaire risicofactoren als preventieve interventies. Om de daadwerkelijke ziektewinst en kosteneffectiviteit van deze strategieën te beoordelen en alvorens deze in de praktijk te gebruiken, is vervolgonderzoek in grotere populaties noodzakelijk.

DEEL 2

Tijdens het proces van de baring blijft voor zowel moeder als kind de identificatie van risicogroepen van vitaal belang. In de afgelopen jaren is het percentage keizersneden wereldwijd fors gestegen.[16] Een groot deel van deze keizersneden wordt verricht wegens het niet vorderen van de baring. Conventionele technieken voor registratie van weeënactiviteit tijdens de baring slagen er niet in om uitkomsten voor moeder en kind te verbeteren.[17] Elektromyografie (EMG) is een nieuwe niet-invasieve techniek om weeënactiviteit tijdens de baring te meten. Bij vrouwen met een dreigende vroeggeboorte lijkt het EMG de vrouwen die ook daadwerkelijk te vroeg gaan bevallen, nauwkeuriger te identificeren dan de conventionele technieken.[18-21] In hoofdstuk 7 wordt onderzocht of het EMG in staat is om inefficiënte weeën te identificeren bij vrouwen bij wie de bevalling spontaan op gang is gekomen. In een prospectief multicenter onderzoek werd bij 119 nullipara met een a terme eenling zwangerschap met een kind in hoofdligging de weeënactiviteit middels het EMG gemeten. Hieruit blijkt dat contractie karakteristieken gemeten met het EMG goed correleren met de progressie van de baring. Ook blijkt dat EMG karakteristieken beïnvloed worden door het weeën-stimulerende middel oxytocine.

Omdat een baring die spontaan op gang komt substantieel anders is dan een baring die ingeleid wordt, hebben we deze laatste groep (n=141) apart bestudeerd in hoofdstuk 8. De resultaten laten zien dat bij vrouwen met een eenlingzwangerschap en een kind in hoofdligging bij wie de baring is ingeleid, het EMG geen correlatie laat zien met de voortgang van de baring. Vooralsnog lijkt er dus alleen een rol weggelegd voor het EMG bij vrouwen bij wie de baring spontaan op gang komt.

Belangrijkste conclusies van dit proefschrift

Deel 1

– Voor eenlingen ligt het optimale geboorte gewicht voor perinatale overleving tussen de 80-84ste percentiel. Het gemiddelde geboortegewicht (de 50ste percentiel) in de populatie is aanzienlijk

lager dan deze percentielen, wat impliceert dat de meeste foetussen enige vorm van groeibeperking vertonen. Gedacht wordt dat maternale factoren de foetale groei beperken om mechanische baringsbelemmeringen te voorkomen.

- In het algemeen is de totale perinatale sterfte hoger bij tweelingen dan bij eenlingen, echter tijdens de preterme periode is deze juist lager bij tweelingen. Mogelijk wordt dit veroorzaakt door nauwlettendere controles van tweelingzwangerschappen. Dit suggereert indirect dat eenlingzwangerschappen vaker gecontroleerd moeten worden. Grote populatie studies moeten verricht worden om te onderzoeken of meer intensieve controles van eenlingzwangerschappen uiteindelijk tot een lagere perinatale sterfte leidt.
- De hoogste perinatale sterfte wordt gevonden bij kinderen met een extreem laag geboortegewicht voor de zwangerschapsduur. Intra-uteriene identificatie van deze "hoog risico" foetussen is moeilijk in de a terme periode. Longitudinale metingen van de cerebro-placentaire ratio met verandering van normale naar abnormale waarden lijkt vooralsnog het beste instrument hiervoor. Omdat deze uitkomsten op kleine aantallen gebaseerd zijn, bestaat er een noodzaak om dit verder uit te zoeken in grotere studie populaties.
- Het achterblijven van de foetale groei is naast foetale sterfte ook geassocieerd met een verhoogd risico op cardiovasculaire aandoeningen bij de moeder postpartum. Aangezien deze riscofactoren reversibel zijn vaak, lijkt winst te behalen bij preventieve interventies. Vervolgonderzoek is nodig om de ziektewinst en kosteneffectiviteit te bepalen.

Deel 2

- Contractie karakteristieken gemeten met elektromyografie correleren goed met de progressie van de baring bij nullipara die spontaan in bevalling zijn geraakt. In de praktijk zou in deze groep het EMG kunnen helpen bij het identificeren van vrouwen met een verhoogd risico op een keizersnede wegens het niet vorderen van de baring.
- Bij nullipara bij wie de bevalling ingeleid wordt vertoont het elektromyografie geen correlatie met de progressie van de baring. Voorlopig lijkt er geen rol weggelegd voor EMG in deze groep.

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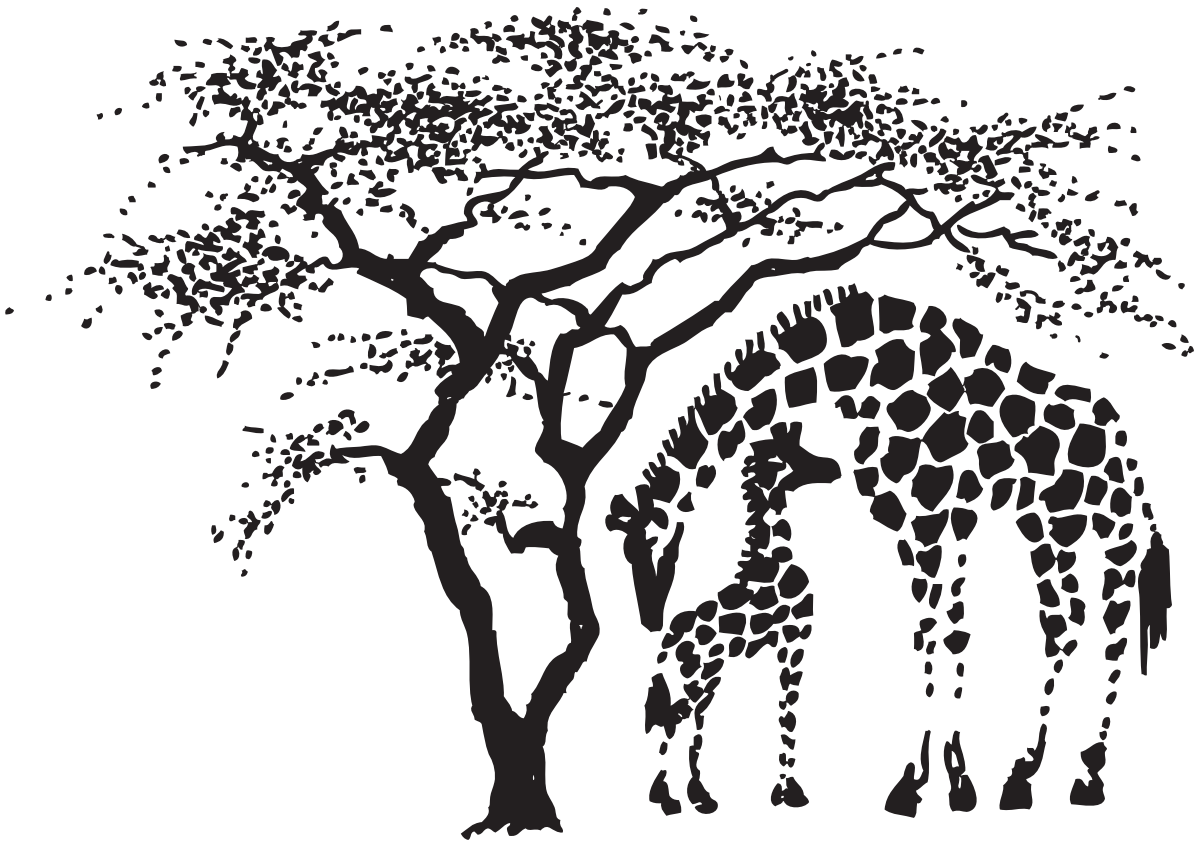

Chapter 11

List of Publications

Curriculum Vitae

Acknowledgements
(Dankwoord)

LIST OF PUBLICATIONS

1. Graatsma EM, Mulder EJ, Vasak B, Lobmaier SM, Pildner von Steinburg S, Schneider KT, Schmidt G, Visser GH. Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by fetal growth restriction. *J Matern Fetal Neonatal Med*. 2012 Dec;25(12):2517-22.

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CURRICULUM VITAE

Blanka Vasak was born on October 23rd 1985 in Nairobi Kenya. She grew up with her parents Slavek and Annetje and her brother Alan. She spent her younger years in Nairobi, and later moved to Yemen where she attended Sana'a International School. After this she moved to Wassenaar, where she graduated from Adelbert College in 2003. Blanka studied medicine at the University of Utrecht from 2003-2010. It was after performing her first delivery during one of her internships that her interest in obstetrics and gynaecology was sparked. Blanka's profound love for Africa inspired her to do internships in tropical medicine in Namanyere Tanzania and Oshakati Namibia where this interest developed further. During medical school Blanka worked on a research paper with Margo Graatsma which later resulted in her attaining a PhD position with prof. dr. G.H.A. Visser. Blanka's career started in St. Antonius Hospital where she worked as a resident from 2010-2012. In 2012 the official PhD trajectory started under supervision of prof. dr. G.H.A. Visser and prof. dr. A. Franx at the University Medical Center Utrecht. In 2014 she started her official OBGYN training, first in Diakonessenhuis Utrecht and in 2015 she returned to the University Medical Center Utrecht where she is currently working.

ACKNOWLEDGEMENTS (DANKWOORD)

Tranen van blijdschap, het boek is af!

Dit proefschrift zou nooit tot stand zijn gekomen zonder de hulp van een groot aantal mensen, ik wil iedereen bedanken die hierbij betrokken is geweest. Daarnaast wil ik graag een aantal mensen in het bijzonder bedanken.

Allereerst wil ik alle vrouwen bedanken die belangeloos hebben deelgenomen aan de studies beschreven in dit proefschrift. Zonder jullie had dit proefschrift niet bestaan.

Professor G.H.A. Visser, geachte promotor, beste Gerard, uw eindeloze enthousiasme en passie voor het vak en het onderzoek zijn ongeëvenaard. Uw unieke gave om van een olifant een mug te maken heeft mij in deze avontuurlijke reis staande gehouden. Van uw optimistische insteek en kritische blik op het onderzoek heb ik heel veel geleerd. Motiveren kunt u ook als geen ander, uw bevlogenheid werkt aanstekelijk en de kleine dingen zoals "Hartstikke goed" of "Prachtig" waren van onschatbare waarde. Daarnaast was laagdrempelig overleg altijd mogelijk, vanuit elke uithoek van de wereld kwam er snel reactie en kwamen de stukken steeds een beetje minder rood terug. Ik vond het een absolute eer om één van uw laatste promovendi te mogen zijn. Grazie Mille!

Professor A. Franx, geachte promotor en opleider, beste Arie, ik kan mij ons eerste telefoongesprek nog goed herinneren. Het onderzoek naar elektromyografie viel niet meer binnen de speerpunten, het idee wat stond om verder te gaan op dit onderwerp was niet meer mogelijk. Desondanks heb jij mij de kans gegeven op een ander onderwerp toch te kunnen starten aan mijn promotie traject. Ik wil je bedanken voor deze kans. Daarnaast heeft jouw daadkrachtige aanpak en begeleiding ervoor gezorgd dat het mij is gelukt mijn opleiding met het promotietraject te kunnen combineren.

Geachte prof. dr. M.L. Bots, prof. dr. K.W.M. Bloemenkamp, prof. dr. S.G. Oei, prof. dr. J.J.H.M. Erwich en prof. dr. F. van Bel, hartelijk dank dat u zitting hebt willen nemen in mijn beoordelingscommissie.

Dr. S.V Koenen, beste copromotor, beste Steven, toen bleek dat ik niet verder kon op het EMG onderwerp, kwam Gerard op het idee om verder te gaan op jullie eerdere PRN-analyses. Jij was meteen enthousiast om hier mee aan de slag te gaan. Jouw kritische blik was zeer waardevol in het opzetten en uitwerken van dit hele proces.

Dr. B.C. Jacod, beste copromotor, beste Benoit, toen ik bij jou en Margo als student begon bij de MAPLE-studie had ik nooit gedacht dat dit het resultaat zou zijn. Het EMG-onderwerp had de nodige uitdagingen, hierbij kwam jouw technische achtergrond altijd goed van pas. Ook bij het analyseren

van de EMG-data heb ik veel van jou geleerd. Ik heb bewondering voor jouw carrièrepad en ik wil je graag bedanken voor je begeleiding bij het begin van mijn pad.

Dr. M.P.H. Koster, lieve Wendy, jouw grote aandeel in dit proefschrift verdient een eervolle vermelding hier. Altijd even laagdrempelig en bereid om mee te denken, ik zou niet weten hoe ik alle statistische en Excel uitdagingen had kunnen oplossen zonder jouw hulp. Daarnaast heb ik genoten van jouw vriendschap, humor en gezelligheid bij al onze "extra-curriculaire" activiteiten. Ze hebben goud binnengehaald daar in Rotterdam!

Dr. E.J.H. Mulder, beste Edu, wat heb je mij ontzettend geholpen in de laatste fase van dit proefschrift. Ondanks het feit dat mijn last-minute noodkreet een abrupt einde van jouw welverdiende vakantie of een weekend doorwerken voor jou betekende, stond je voor me klaar. Ik ben je ontzettend dankbaar hiervoor.

Aan alle co-auteurs, bedankt voor de fijne samenwerking en het tot stand brengen van dit proefschrift. Beste René, bedankt voor de hulp bij de MAPLE-analyses, het is uniek hoe goed jij moeilijke statistische analyses begrijpelijk kunt maken voor een promovendus. Dear Mark, it was an honor working with you. Your willingness to collaborate and your enthusiastic thought provoking additions to our papers were inspiring. Beste Lou, bedankt voor je hulp bij de echo's voor de SAFARI-studie. Beste Chantal, bedankt voor de fijne samenwerking en alle hulp bij de PRN-analyses en de dataverzameling. Jessica en Sophie, fijn dat jullie hebben geholpen bij de PRN- en SAFARI-analyses.

Lieve Margo, ik had nooit gedacht dat mijn wetenschapsstage bij jou zou leiden tot mijn carrière in de gynaecologie. Bedankt dat je hebt geholpen om dit mogelijk te maken voor mij. Ontzettend leuk dat we ook nog even samen hebben mogen werken in het WKZ en dat we elkaar vast nog regelmatig tegen zullen komen.

Beste collega's van het St. Antonius Ziekenhuis, het Diakonessenhuis, het WKZ en het UMC, op elke plek heb ik mij thuis gevoeld dankzij jullie. Lieve collega AIOS wat een feestje om onderdeel te zijn van dit cluster. In het bijzonder wil ik mijn collega's bedanken die in de laatste fase van mijn proefschrift hebben meegeleefd en begrip hadden voor mijn verminderde reserves op werk. Jet, na een top onderzoekstijd, werken we nu ook gezellig samen als collega's, wat bof ik met jou.

Lieve Journal club, ik kan geen leukere groep bedenken om je onderzoekstijd mee door te brengen. Ik denk met heel veel plezier terug aan deze dagen. De BLAJA tours tripjes naar Milano, Cambridge, Londen en San Francisco waren de slagroom op de onderzoekstaart. Jannie, als mede tour operator mag jij natuurlijk niet ontbreken, de reisbrochure in elkaar zetten was al de helft van het plezier. Bedankt voor jullie gezelligheid. En Daph, nu op naar jouw boek!

Lieve Maggy, bedankt dat ik mijn door jouw ontworpen geboortekaartje voor de omslag mocht gebruiken.

Lieve Ro, Jacky, Lijn, Chiel, Quit, Maik, Joris en Jur, iedereen is zijn eigen weg gegaan en toch blijft het altijd als vanouds als we elkaar zien bij de "life events" of voor een gewone borrel. Dit koester ik.

Lieve Boefjes, jullie hebben mijn eerste baan als ANIOS in het Anton nog leuker gemaakt. Van memorabele skireisjes tot jaarwisselingen en weekendjes Londen. Dat er nog vele mogen volgen!

Lieve Bruutjes, onze lustrumreis naar Portugal bevestigde maar weer eens dat we zelfs na twaalf jaar nog ontzettend veel plezier met elkaar kunnen maken. Loesje, nu het boek af is, heb ik eindelijk weer tijd om gezellig af te spreken. Lieve Val, jouw steun en interesse in alles wat ik doe, betekent veel voor mij, ik ben erg benieuwd naar jullie kleine meisje.

Lieve Tollies, altijd heerlijk thuis komen in een warm bad bij jullie. Fong, jouw eindeloze en positieve energie houdt het lekker levendig. Ems, wat is het fijn om eindeloos te discussiëren zonder het ooit eens te worden en toch zoveel gemeen te hebben met elkaar. You are awesome!

Lieve Ro, wat heb ik veel bewondering voor jouw positieve kijk op het leven en je doorzettingsvermogen. Je bent een groot voorbeeld voor mij.

Lieve Didy, ik geniet enorm van onze spontane afspraken als ik even thuis ben in Wassenaar. En wat maakt Puck het leven mooi!

Lieve Daltons, wat bof ik toch met zulke lieve vriendinnetjes. Onze tripjes naar Barcelona zijn heilig en ieder jaar weer een feestje. Soof, met een goed glas wijn onze bizarre banen bespreken zet de dingen vaak weer meer in perspectief voor mij. Lottie, jouw verhuizing naar San Fran was wel even slikken, maar gelukkig gaan we je snel opzoeken! Bedankt voor jullie altijd luisterende oor en onvoorwaardelijke vriendschap. Lieve Lex, het was vriendschap op het eerste gezicht! Wat kan ik lachen met jou, en ook als er tranen zijn sta je altijd voor me klaar. Ik kan me een leven zonder jou niet voorstellen.

Lieve Karst, wat ontzettend leuk dat wij deze mijlpaal op dezelfde dag gaan beleven. Zeker in de laatste fase was het fijn om te kunnen sparren en de laatste dingen samen te regelen. Ik kan niet wachten om deze bijzondere dag samen te vieren.

Lieve paranimfjes! Wat is het toch altijd een feestje met jullie. Always feeling number one als jullie in de buurt zijn. En wat ben ik toch een mazzel..... dat jullie 23 december aan mijn zijde staan!

Lieve Maddy, we go way back (Nairobi Hospital 1985), zonder dat we het wisten! Dat onze wiegjes op dezelfde plek stonden in het mooie Afrika, schepte zelfs jaren later meteen een band. Onze voorliefde voor verkleedfeestjes en Indiaas eten ook. Jouw positieve en warme vibe geeft mij altijd het gevoel dat ik thuis ben. Daarnaast zijn jouw "healing hugs" onmisbaar geworden in mijn leven!

Lieve Fee, ik ken niemand zoals jij. Met een gestrekt been ga jij door het leven en maak je overal een feestje van, ik heb er bewondering voor. Uren kunnen we praten over het leven en die cocktailbar ergens in de tropen, maar ook in moeilijke tijden sta je voor me klaar. Onze Zuid Afrika trip was al fantastisch (what, what), ik kan niet wachten op ons volgende avontuur!

Dear family Vasak, although we live in different countries, whenever we are together it feels like home. Lieve Kor, mijn beide grootvaders heb ik helaas nooit gekend, maar gelukkig heb ik altijd jou gehad. Pap, ik denk dat oma trots zou zijn geweest.

Lieve Alan, je bent mijn leukste broer en bovenal een heel goed mens. You always have my back, en dat is heel fijn om te weten. Mijke vanaf het begin hoorde je er helemaal bij, bedankt voor je hulp bij mijn omslag. En... ontzettend leuk dat ik volgend jaar een neefje krijg! Ik kijk er heel erg naar uit.

Lieve papa en mama, zonder jullie was dit alles nooit gelukt. Jullie eindeloze onvoorwaardelijke liefde heeft er altijd voor gezorgd dat alles mogelijk was. Mijn dankbaarheid voor jullie liefde en steun is niet in woorden uit te drukken.