Prenatal detection of small for gestational age pregnancies

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PRENATAL DETECTION OF SMALL FOR GESTATIONAL AGE PREGNANCIES

door

BART JAN VOSKAMP

op woensdag 21 mei 2014 om 10:00 uur in de Agnietenkapel Oudezijds Voorburgwal 231 Amsterdam

na afloop

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Prenatal detection of small for gestational age pregnancies

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Prenatal detection of small for gestational age pregnancies

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in het openbaar te verdedigen in de Agnietenkapel
op woensdag 21 mei 2014, te 10.00 uur
door

Bart Jan Voskamp

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Chapter 1

General introduction
**Introduction**

**Background and definition**
In an uncomplicated pregnancy, fetal growth is not restricted by placental dysfunction or other adverse environmental factors. As a result, most infants grow (approximately) according to their genetic growth potential and are born with a weight that is considered appropriate for gestation.

It has long been known that very small infants suffer perinatal mortality and neonatal morbidity more often than infants with an average birth weight.\(^1\)\(^2\) This is likely caused by the higher incidence of fetal and maternal pathologic conditions in these pregnancies.

Originally, absolute birth weight was used as a parameter to classify abnormal growth. Since the 1970’s, growth was expressed as weight by gestational age and percentile cut-off values were determined to classify which infants are normally grown and which are not.\(^3\)\(^4\)\(^6\) This allowed classification of subgroups with a higher risk of adverse pregnancy outcome. Infants with a weight below a certain threshold - usually a birth weight below the 2.5\(^{th}\), 5\(^{th}\), or 10\(^{th}\) percentile - are considered Small for gestation (SGA). The group of SGA infants consists of infants that have not reached their growth potential - growth restricted infants - and infants that are constitutionally small. Severity of SGA is associated with the incidence of true growth restriction and adverse outcome.\(^7\)

**Prevalence and etiology**
The prevalence of fetal growth restriction depends on the definition used. If the 10\(^{th}\) percentile is used as a cut-off for SGA, by definition approximately 10% of infants are born small for gestation. However, the exact incidence depends on the population and the reference curves used.

A lot of research has been performed to unravel the pathogenesis of abnormal fetal growth. Multiple risk factors have been identified, and SGA seems to be a multifactorial and heterogeneous adverse outcome of pregnancy. Known factors associated with SGA are of maternal, environmental, fetal and placental origin. These factors are summarized in table 1. Abnormal growth can result from one factor, or from more factors at the same time. Clinical maternal vascular disease secondary to chronic hypertension, renal disease, diabetes mellitus, and collagen vascular disease, especially when complicated by preeclampsia, is the most common cause of impaired fetal growth, accounting for nearly a third of FGR cases.\(^8\)

A distinction is often made between early onset growth restriction and late onset growth restriction.
Early onset (<34 weeks gestation) growth restriction is easier to detect due to better ultrasound accuracy before 36 weeks gestation, because it shows a characteristic sequence of circulatory responses to placental dysfunction\(^9\), and because it often presents itself with maternal morbidity.\(^10\)
Since there are no therapeutic options to treat growth restriction, fetal growth is monitored to allow induction of labor when fetal condition is compromised.

Late onset growth restriction is harder to detect, because of decreased accuracy of ultrasound after 36 weeks gestation\(^11\) and subtler Doppler and biophysical abnormalities. It often remains unrecognized and contributes to over 50% of unanticipated stillbirths at term.\(^12\) If late onset growth restriction is suspected, fetal condition should be monitored and labor can be induced to avert adverse pregnancy outcome.
Impact
SGA (<10th percentile) deliveries are responsible for 20-25% of perinatal death and 2-13% of severe neonatal morbidity.13 The impact of abnormal growth and associated adverse outcome extends beyond the neonatal period and throughout the life of SGA infants. This affects the SGA infants themselves, their families and the rest of society.

History
Until the 1980’s, fetal growth was assessed by abdominal palpation and fundal height measurements, but no diagnostic instruments were available to assess if fetal condition was compromised and delivery had to be pursued. Infant weight appeared at birth and was used to assess the risk of hypoglycemia or hypothermia.14-16

Since the emergence and increased use of ultrasound, reliable pregnancy dating with 1st trimester ultrasound can be performed. Consequently, fetal growth can be assessed in relation to gestational age. Ultrasound also allows assessment of fetal condition through Doppler blood flow velocimetry. Furthermore, cardiotocography has become available to monitor fetal wellbeing before and during labor.

Management
Deteriorating fetal condition is often preceded by suboptimal growth. 17 Therefore, prenatal detection of abnormal growth is an important tool to identify infants at risk of adverse outcome. And although not all SGA infants are growth restricted and fetal condition often remains good until delivery, detection of abnormally grown infants potentially prevents adverse pregnancy outcome. The size of the problem, the complexity of the pathogenesis of abnormal fetal growth, the difficulties in early risk assessment and the impossibility to treat abnormal fetal growth, make abnormal fetal growth a major challenge in clinical obstetric practice and scientific research. On the part of the neonatologists, the improved care of SGA infants during the last decades has led to significant better outcomes on the short and long term. However, on the part of the obstetric caregivers still lies a big challenge to detect SGA infants prenatally to improve pregnancy outcomes.

Abdominal palpation, fundal height measurement and ultrasound are used to detect SGA pregnancies. Although ultrasound is reported to have a higher sensitivity, neither is proven to be effective at detecting SGA fetuses.18 The reported sensitivity of third trimester ultrasound to detect SGA (<10th percentile) in a low risk population is low - between 28% and 46%19-21 -, and routine late pregnancy ultrasound is reported not to be associated with improvements in overall perinatal mortality.22 However, the use of Doppler ultrasound in high-risk pregnancies reduces the risk of perinatal deaths and results in less obstetric interventions.23 Therefore, identifying risk factors for abnormal growth and improvement of abnormal fetal growth detection are issues that might help reduce adverse pregnancy outcome.

Objectives and outline of this thesis
The objective of this thesis is to identify and describe in detail SGA risk factors. We also compare two methods to express fetal growth, and discuss the relation between antenatal SGA detection, timing of delivery and pregnancy outcome in SGA pregnancies.
Table 1. Factors associated with SGA

**Maternal**
- Previous SGA pregnancy\(^{26-28}\)
- Diabetes mellitus\(^{29}\)
- Renal disease\(^{30}\)
- Systemic lupus erythematosus\(^{31}\)
- Bowel disease (Celiac\(^{32}\), Crohn\(^{33}\))
  - Pregnancy-related hypertensive diseases (eg. Chronic hypertension, gestational hypertension, or preeclampsia)\(^{34}\)
  - Thrombophilia\(^{35}\)
  - Age >35\(^{36}\)
- Weight (BMI<20)\(^{37}\)

**Environmental**
- Low socio economic status\(^{38}\)
- Malnutrition\(^{39}\)
- Smoking\(^{40}\)
- Alcohol\(^{41}\)
- Teratogen exposure (eg. Cyclophosphamide, valproic acid, or antithrombotic drugs)
- Infection\(^{42}\) (eg. Malaria, cytomegalovirus, rubella, toxoplasmosis, or syphilis)

**Fetal**
- Aneuploidy\(^{43}\) (eg. Trisomy 13, trisomy 18)
- Structural abnormalities\(^{44}\) (eg. congenital heart disease, or gastroschisis)
- Multiple gestation\(^{45}\)
- IVF conception\(^{46}\)

**Placental**
- Placental disorders\(^{47}\) and umbilical cord abnormalities

**Part 1. SGA risk factors**
In the first part of this thesis we aim to describe in more detail the association between several pregnancy-, maternal- and fetal-characteristics and their influence on the incidence of SGA and adverse pregnancy outcome. In chapter two we assess patterns of recurrence of SGA. Chapter three is a systematic review and meta-analysis on the outcome of fetuses with an isolated single umbilical artery (SUA) diagnosed in the second trimester of pregnancy. Chapter four describes whether - after adjustment for GA at delivery and birth weight percentile- fetal sex is independently associated with perinatal death and neonatal morbidity.

**Part 2. Methods to detect SGA pregnancies and perinatal outcome**
Fetal and neonatal growth-for- gestation are usually expressed in percentiles. However, the use of percentiles also has some disadvantages. In chapter five, birth weight ratio is presented as an alternative to birth weight percentiles in research and clinical practice. In Chapter six we assess the association between fetal sex and abnormal fetal growth using birth weight ratio.
Third-trimester ultrasound is increasingly used to detect pregnancies at risk of SGA. Nevertheless, the majority of SGA infants remain undiagnosed until birth.\textsuperscript{24,25} In chapter seven a study is presented in which we assess if relative growth between the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester improves identification of infants at risk of being born small for gestation in a high-risk population, and if changing cut-off values for follow-up after 3\textsuperscript{rd} trimester ultrasound scan affects SGA detection of term infants.

Part 3. Outcome of SGA pregnancies: Timing of delivery and influence of antenatal SGA detection
The time frame of term delivery between 37 and 42 weeks is considered physiologic. However, it is not known whether this time frame is also optimal for delivery of SGA fetuses. Chapter eight provides insight in the association between timing of delivery in small for gestational age fetuses near term and perinatal outcome. In Chapter nine we describe differences in perinatal outcome and management of labor and delivery between antenatally-detected SGA and not-antenatally-detected SGA infants.
References


Chapter 2

Recurrence of small for gestational age pregnancy:
analysis of first and subsequent singleton pregnancies in The Netherlands

Bart Jan Voskamp, Brenda M. Kazemier, Anita C.J. Ravelli, Jelle Schaaf, Ben Willem J. Mol, Eva Pajkrt

Chapter 2

Abstract

Objective: Small for gestational age (SGA) neonates are at increased risk of adverse pregnancy outcome. Our objective was to study the recurrence rate of SGA in subsequent pregnancies.

Study design: A national cohort study of all women with a structurally normal first and subsequent singleton pregnancy between 1999 and 2007. SGA was defined as birth weight below the 5th percentile for gestation. We compared the incidence and recurrence rate of SGA for women in total and with and without a hypertensive disorder (HTD) in their first pregnancy. Moreover we assessed the association between gestational age at first delivery and SGA recurrence.

Results: We studied 259,481 pregnant women, of which 12,943 (5.0%) had an SGA neonate in their first pregnancy. The risk of SGA in the second pregnancy was higher in women with a previous SGA neonate, than for women without a previous SGA neonate (23% versus 3.4%) (adjusted Odds Ratio (OR) 8.1, 95% Confidence Interval (CI) 7.8-8.5) and present in both women with and without a HTD in pregnancy. In women without a HTD, the increased recurrence risk was independent of the gestational age at delivery in the index pregnancy, whereas in women with a HTD this recurrence risk was only increased when the woman with the index delivery delivered after 32 weeks.

Conclusion: Women with SGA in their first pregnancy have a strongly increased risk of SGA in the subsequent pregnancy and first pregnancy SGA delivers a significant contribution to the total number of second pregnancy SGA cases.
Introduction

Small for Gestational Age (SGA) refers to a fetus or neonate that has failed to achieve a specific biometric or estimated weight threshold by a specific gestational age. SGA neonates are defined as those born with a weight below a certain percentile (p) (p2.5, p5 or p10) for gestational age. SGA neonates are a heterogeneous group comprising fetuses that have failed to achieve their growth potential (fetal growth restriction, FGR) and neonates that are constitutionally small. Thus, not all SGA neonates are growth restricted. The lower the percentile for defining SGA, the higher the likelihood of FGR\textsuperscript{7}. On the other hand, a neonate with growth restriction may not be SGA.

SGA neonates are at increased risk of perinatal mortality and adverse perinatal and health outcome later in life\textsuperscript{2-6}. The explanation that some studies on SGA neonates have shown poor perinatal outcome is likely to be a reflection of the high incidence of true FGR\textsuperscript{7,8}.

Patterns of recurrence of restricted fetal growth are important for patient counseling and adequate care in subsequent pregnancies. Previous studies found a strong tendency of SGA recurrence in subsequent pregnancies (20.1 – 28.7%)\textsuperscript{9,11}. However knowledge gaps persist, particularly in the area of defining etiology-specific risks\textsuperscript{12}. Clinical maternal vascular disease secondary to chronic hypertension, renal disease, diabetes mellitus, and collagen vascular disease, especially when complicated by preeclampsia, is the most common cause of impaired fetal growth, accounting for nearly a third of FGR cases\textsuperscript{13}. Hypertensive disorders during pregnancy thus play an important role in the etiology of SGA. The aim of this study was to assess and describe in detail the SGA incidence and recurrence rate in general and the influence of a hypertensive disorder in the first pregnancy on the recurrence rate and incidence of SGA in the second pregnancy. Moreover we investigated whether SGA recurrence rate depends on the gestational age (GA) of delivery in the first pregnancy.

Methods

Dataset

This study was performed in a nationwide cohort with the use of The Netherlands Perinatal Registry (PRN). The PRN consists of population-based data that contain information on pregnancies, deliveries, and re-admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of newborn neonates\textsuperscript{14,15}. Records are entered in the PRN registry at the child’s level. There is no unique maternal identifier available in the registry to follow-up on outcomes of subsequent pregnancies in the same mother. A longitudinal probabilistic linkage procedure was performed to create a cohort with complete data on first and second deliveries of the same mother. Details on entry, linkage, aggregation, validation and verification of the data are published elsewhere\textsuperscript{16}.

The coverage of the PRN registry is approximately 96% of all deliveries in The Netherlands. It contains pregnancies of ≥22 weeks’ gestation and a birth weight of ≥500 g and is used primarily for an annual assessment of the quality indicators of obstetric care.
Ethical approval
The data in the perinatal registry are anonymous; therefore ethical approval was not needed. The Dutch Perinatal Registry gave their approval for the use of their data for this study (approval number 12.39).

Inclusion and exclusion criteria
From our linked cohort\(^{16}\), we included all women who delivered two subsequent singleton pregnancies (first and second delivery) in The Netherlands between January 1, 1999, and December 31, 2007. We excluded all cases with major congenital anomalies\(^{17}\) and multiple gestations.

Outcome measures
Our primary outcome measure was SGA, defined as a birth weight below the fifth percentile for gestational age. The Dutch reference curves for birth weight by gestational age separate for parity, sex and ethnic background were used.\(^{18}\) Pregnancy dating was performed by last menstrual period (LMP) or ultrasound measurements before 20 weeks of gestation (crown-rump-length (CRL) or head-circumference (HC) measurement). If estimation by ultrasound measurement differed more than 6 days from the last menstrual period, then the ultrasound measurement was considered the dominant one.

Population characteristic and clinical characteristics
We registered demographic and obstetric characteristics including maternal age, parity, ethnicity and (socio-economic status) SES. Maternal age was categorized into <25 years, 25–34 years and ≥ 35 years. Parity was categorized into 0 (first birth), 1 (second birth) and 2+ (third or higher birth). Ethnicity is ascribed by the woman’s care provider. For this study, we differentiated between Western (native Dutch and other Westerners) and non-Western (including different ethnic groups like African/ Surinamese Creole, Surinamese Hindustani, Moroccan and Turkish). The SES score is based on mean income level, the percentage of households with a low income, the percentage of inhabitants without a paid job and the percentage of households with on average a low education in a postal code area.\(^{18}\) The continuous SES score was categorized into a high, middle and low group based on percentile ranges, 25th percentile, middle, 75th percentile).

Cases were analyzed in total and stratified into two groups: women with a hypertensive disorder (HTD) in their first pregnancy and women without an HTD in their first pregnancy. Hypertensive disorders include pregnancy induced hypertension (PIH), preeclampsia (PE), and chronic hypertension. Hypertension was a clinical diagnosis that was made in case of a systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg and or (pre)-eclampsia and or proteinuria.

We also stratified the analysis by gestational age at delivery in the first pregnancy in three groups: very preterm (24\(^{0}\)–31\(^{6}\) weeks’ gestation), late preterm (32\(^{0}\)–36\(^{6}\) weeks’ gestation) and term (37\(^{0}\)–42\(^{6}\) weeks gestation).

Statistics
We compared the recurrence rate and incidence of SGA in the second pregnancy in women with and without SGA in their first pregnancy. For these two groups, we studied demographic and obstetric baseline characteristics.

Univariate analyses were performed with the Student t test and Chi Square test as appropriate to compare baseline characteristics. All statistical tests were 2-sided; a probability value of 0.05 was chosen as the threshold for statistical significance. Logistic regression analyses were performed to
determine the effect of the risk factors on SGA in the second pregnancy expressed as odds ratios (OR) with 95% confidence intervals (CI). In a multivariable analysis we adjusted for maternal age, ethnicity, social-economic status and year of birth.

In addition, we calculated the population-attributive risk (PAR) percentage based on the prevalence (P) and relative risk (RR) \( PAR = \frac{P \times (RR-1)(P+(RR-1)\times (1-P))}{(P+(RR-1)\times (1-P))} \times 100 \) for each factor.\(^9\)

We tested for interaction between SGA and HTD in the first pregnancy and SGA and GA at delivery (in the first pregnancy). If statistically significant (\( P < 0.001 \)), analyses were also performed separately for HTD and non-HTD cases and for three strata of GA at delivery in the first pregnancy.

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

Results

From January 1, 1999 until December 31, 2007 a total of 1,503,996 singleton pregnancies were identified in the PRN database. After application of our inclusion and exclusion criteria 259,481 women (518,962 deliveries) made up our study population.

Baseline characteristics of this cohort are presented in Table 1. In the first pregnancy, 12,943 (4.99%) fetuses had a birth weight below the fifth percentile for gestational age. Hypertensive disorders, low socio-economic-status, younger age, non-Caucasian ethnicity, and preterm birth were more prevalent in women who delivered an SGA neonate in the first pregnancy.

Of the 12,943 women with an SGA neonate in the first pregnancy, 2,996 women (23.2%) had an SGA neonate in the subsequent pregnancy (see figure 1).

<table>
<thead>
<tr>
<th>Table 1. Study population</th>
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<tr>
<td>First pregnancy birth weight (percentile for gestational age)</td>
</tr>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>Maternal characteristics</td>
</tr>
<tr>
<td>Maternal age (mean, SD)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
</tr>
<tr>
<td>Spontaneous onset of labour (%)</td>
</tr>
<tr>
<td>Low social economic status (&lt;p25)</td>
</tr>
<tr>
<td>Hypertensive disorder (%)</td>
</tr>
<tr>
<td>Preterm delivery before 37 weeks GA (%)</td>
</tr>
<tr>
<td>Neonatal characteristics</td>
</tr>
<tr>
<td>Male (%)</td>
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</tbody>
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SD, standard deviation; GA, gestational age
Figure 1. SGA incidence and recurrence

Table 2 shows that SGA and HTD in the first pregnancy, low SES, non-Caucasian ethnicity, and maternal age <25 years all had increased crude odds ratios for SGA in the second pregnancy. The population attributable risk (PAR) of previous SGA was 22.2% and the PAR of HTD in the first pregnancy was 3.7%.

Table 2. Unadjusted odds ratios and PAR % of risk factors for SGA in the second singleton pregnancy in the Netherlands 2000–2007

<table>
<thead>
<tr>
<th>Prevalence of risk factor (%)</th>
<th>SGA in second pregnancy (n=11,478)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Unadjusted OR (95% CI)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>SGA 1st pregnancy</td>
<td>23.15</td>
</tr>
<tr>
<td>HTD 1st pregnancy</td>
<td>5.56</td>
</tr>
<tr>
<td>Low SES</td>
<td>5.81</td>
</tr>
<tr>
<td>Non-western ethnicity</td>
<td>6.89</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>6.89</td>
</tr>
<tr>
<td>25-34</td>
<td>4.21</td>
</tr>
<tr>
<td>≥35</td>
<td>4.34</td>
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</table>

SGA, small for gestational age; HTD, hypertensive disorder; SES, socio economic status; OR, odds-ratio; CI, confidence interval; PAR, population attributable risk; ref, reference

Table 3 shows the unadjusted and adjusted odds ratios of SGA in the first pregnancy on the recurrence risk of SGA. After adjusting for maternal age, ethnicity, SES and year of first delivery, SGA was associated with a significantly increased risk of SGA in a subsequent pregnancy (adjusted Odds Ratio (aOR), 8.1; 95%CI, 7.8-8.5). De novo SGA in the second pregnancy in women with a previous non-SGA neonate in the first pregnancy occurred in 3.4% (n= 8,482) from the total of 12,943 infants with SGA in the first pregnancy.
Table 3 also presents the prevalence, recurrence rate and odds ratios for SGA in the second pregnancy stratified by the presence of an HTD in their first pregnancy because there was interaction between SGA and hypertension (p<0.0001). The risk of SGA recurrence in HTD women was smaller than in non-HTD women (21.0% vs. 23.7%, RR 0.86, 95%CI 0.77-0.95). However, the risk of de novo SGA in the second pregnancy was higher for HTD women than for non-HTD women (4.1% vs. 3.4%, RR 1.22, 95%CI 1.14 – 1.29).

Of the 259,481 first pregnancies, 32,742 (12.6%) had an HTD in the first pregnancy. In the second pregnancy only 16,590 women (6.4%) had an HTD. The risk of SGA was higher in the HTD group than in the non-HTD group both in the first pregnancy (8.7% vs. 4.5%, aOR 2.13, 95%CI 2.04-2.22) and in the second pregnancy (8.3% vs. 4.2%, aOR 2.16, 95%CI 2.03-2.29).

Table 3 finally shows that in women without an HTD in the index pregnancy, the SGA recurrence risk was increased independent of gestational age at delivery in the index pregnancy (aOR 5.1-9.1, p<0.0001). In contrast, in women with an HTD in the index pregnancy, this recurrence risk was only increased when the index delivery had occurred after 32 weeks GA (aOR 4.1-6.9, p<0.0001).
<table>
<thead>
<tr>
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<th>Birth weight ≤&lt;span class=&quot;math&quot;&gt;P_5&lt;/span&gt; recurrence N (%)</th>
<th>De novo birthweight ≤&lt;span class=&quot;math&quot;&gt;P_5&lt;/span&gt; in 2nd pregnancy N (%)</th>
<th>Unadjusted Odds ratio (95% CI)</th>
<th>p-value</th>
<th>Adjusted* Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete cohort first pregnancy SGA (n=12,943), no-SGA (n=246,538)</strong></td>
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<tr>
<td>SGA in second pregnancy</td>
<td>2.996 (23.2)</td>
<td>8.482 (3.4)</td>
<td>8.5 (8.1-8.9)</td>
<td>&lt;0.0001</td>
<td>8.1 (7.8-8.5)</td>
<td>&lt;0.0001</td>
</tr>
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<td><strong>Hypertensive disorder in first pregnancy (SGA (n=2,844), no-SGA (n=29,898))</strong></td>
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<tr>
<td>SGA in second pregnancy</td>
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<tr>
<td>Very preterm delivery:</td>
<td>(GA 24+0 - 31+6 wks)</td>
<td>598 (21.0)</td>
<td>1.223 (4.1)</td>
<td>&lt;0.0001</td>
<td>6.0 (5.4-6.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Late preterm delivery:</td>
<td>(GA 32+0 - 36+6 wks)</td>
<td>115 (24.0)</td>
<td>233 (7.3)</td>
<td>&lt;0.0001</td>
<td>4.1 (3.2-5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Term delivery:</td>
<td>(GA 37+0 - 42+6 wks)</td>
<td>467 (20.6)</td>
<td>895 (3.5)</td>
<td>&lt;0.0001</td>
<td>6.9 (6.1-7.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>No hypertensive disorder in first pregnancy (SGA (n=10,099), no-SGA (n=216,640))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA in second pregnancy</td>
<td>2.398 (23.7)</td>
<td>7.259 (3.4)</td>
<td>9.0 (8.5-9.5)</td>
<td>&lt;0.0001</td>
<td>8.6 (8.2-9.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Very preterm delivery:</td>
<td>(GA 24+0 - 31+6 wks)</td>
<td>29 (23.4)</td>
<td>106 (6.0)</td>
<td>&lt;0.0001</td>
<td>5.1 (3.1-8.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Late preterm delivery:</td>
<td>(GA 32+0 - 36+6 wks)</td>
<td>137 (30.2)</td>
<td>535 (4.3)</td>
<td>&lt;0.0001</td>
<td>9.1 (7.3-11.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Term delivery:</td>
<td>(GA 37+0 - 42+6 wks)</td>
<td>2.332 (23.4)</td>
<td>6.618 (3.3)</td>
<td>&lt;0.0001</td>
<td>8.7 (8.2-9.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SGA, small for gestational age; HTD, hypertensive disorder; OR, odds ratio; CI, confidence interval; SES, socio economic status

*Adjusted for maternal age, SES, ethnicity, and year of first delivery
Discussion

We investigated in the first two subsequent singleton pregnancies the recurrence rate and incidence of SGA in women with and without SGA in their first pregnancy. Moreover, we assessed the influence of a hypertensive disorder in the first pregnancy on the SGA incidence and recurrence risk. The incidences of hypertensive disorders in the first and second pregnancy are in accordance with previous research\textsuperscript{10-26}. Women with SGA in their first pregnancy have a strongly increased risk of SGA in the subsequent pregnancy and first pregnancy SGA delivers a significant contribution to the total number of second pregnancy SGA cases. The risk of SGA, both in the first and second pregnancy is significantly higher in women with an HTD than in women without an HTD.

Similar to previous studies on SGA recurrence, this study has some limitations and possible weaknesses. First, the PRN database does not contain data on how pregnancy dating is performed. Until the introduction of the combined test in 2007 and the first ‘official’ dating protocol in 2011, no uniform pregnancy dating was performed in the Netherlands. Historically, it was common practice to date pregnancies based on LMP. Since the 1980s the use of ultrasound was gradually introduced in obstetric care. During our study period CRL and HC measurements had already increasingly replaced LMP for dating, but no quantitative data are available on how pregnancy was dated in individual cases. Theoretically, the SGA incidence might have been overestimated in pregnancies dated by last menstrual period.\textsuperscript{24} This overestimation however, is probably small and unlikely to have caused bias in our results since the prevalence of SGA in this study is similar to previous reports. Moreover, no differences in distribution are expected between HTD and non-HTD women. By correcting for year of first pregnancy we tried to correct for possible differences in gestational age estimations over the years.

Second, we used SGA as a substitute for fetal growth restriction. Although it has been proven that SGA is a good predictor for adverse neonatal outcome\textsuperscript{2-6}, identification of growth restriction is more accurately performed using the individual growth potential (IGP)\textsuperscript{17} and placental characteristics\textsuperscript{28}. Unfortunately it was not possible to do this, because maternal length and weight, and placental weight and pathology are not registered in the Dutch Perinatal Registry. Therefore the Dutch reference curves for birth weight by gestational age separate for parity, sex and ethnic background were used\textsuperscript{29} and all neonates with major congenital anomalies were excluded. This was the best possible method to distinguish between constitutionally small and FGR fetuses. The use of SGA instead of IGP might be detrimental to the accurate representation of FGR recurrence because a part of SGA neonates may be constitutionally small instead of growth restricted. Therefore it is not certain what proportion of SGA recurrence in non-HTD women is constitutional. We hypothesize that this is only a small proportion for two reasons. (1) The SGA group contains a much smaller proportion of constitutionally small neonates now the SGA cut-off is set at the 5\textsuperscript{th} percentile than when it is set at the 10\textsuperscript{th} percentile.\textsuperscript{1}\textsuperscript{.} (2) A weight change of a few grams causes a much smaller subgroup to shift across an SGA cut-off line when it is set at the 5\textsuperscript{th} percentile than when it is set at the 10\textsuperscript{th} percentile. Consequently the influence of small differences in birth weight on SGA incidence and recurrence rate is likely smaller in this research than in studies with a 10\textsuperscript{th} percentile SGA cut-off.

Finally, SGA incidence and recurrence in very preterm neonates are surprisingly low. A possible explanation is that our weight curves are based on birth weight instead of healthy neonatal weight. There is a well-proven association between spontaneous preterm birth and fetal growth restriction\textsuperscript{30,31}. Therefore very preterm neonates with a birth weight above the 5\textsuperscript{th} centile for gestational age might have a birth weight far below the 5\textsuperscript{th} centile compared to healthy preterm neonates. This could cause an underestimation of SGA neonates in the very preterm group.
Consequently, depending on the gestational age of delivery in the second pregnancy, this might cause an underestimation of SGA recurrence risk and an overestimation of de novo SGA in the second pregnancy in this group. This underestimation of SGA incidence and recurrence rate in very preterm neonates is of less importance in late preterm neonates and of no importance in term neonates. Therefore it is plausible that the results in the latter two groups demonstrate the actual rates of SGA incidence and recurrence.

The main strength of this study is the size and composition of the cohort. Data are derived from a large, well-maintained population-based national perinatal registry (1999-2007). The vast majority of the caregivers contribute to the PRN registry; therefore, it comprises approximately 96% of all pregnancy and birth characteristics in The Netherlands. The 4% missing birth data are due to 1-2% non-reporting general practitioners and 2-3% non-reporting midwives. The limitations of longitudinal linkage are described elsewhere, we found that the longitudinally linked dataset was comparable to the national pregnancy characteristics. Because hypertensive disorders, suspected or diagnosed SGA and threatened preterm delivery are an indication for referral to an obstetrician and the registration by obstetricians is nearly complete (>99%), it is unlikely that we have missed many cases due to non-reporting. The incidence of hypertensive disorders was 12.6% in the first pregnancy and 6.39% in the second pregnancy. This is comparable to incidences reported in previous research.

Previous publications on SGA recurrence have reported corresponding results and conclusions on SGA recurrence\textsuperscript{21-25,32}. However, cohorts were smaller (4,623 up to 152,827 women\textsuperscript{9,11}), less uniform\textsuperscript{11}, or included anomalous fetuses and/or twins.\textsuperscript{11,32} Moreover, due to a different cutoff value for SGA (10\textsuperscript{th} percentile\textsuperscript{9,11} or 2,500g\textsuperscript{32}), reported incidences of SGA were higher in previous studies. As a result, SGA groups in those studies probably contain more constitutionally small instead of growth-restricted neonates. We therefore chose to use the 5\textsuperscript{th} percentile as cutoff for SGA.

The main difference between this study and previous studies is the fact that the association between the presence of an HTD in the first pregnancy and the incidence and recurrence of SGA in subsequent pregnancies has been taken into account. Moreover, to the best of our knowledge this is also the first study to assess the association between GA at delivery of the first pregnancy and SGA incidence and recurrence rate.

The evidence of an increased risk of SGA recurrence in the general population is substantial and consistent.\textsuperscript{9-12} In addition, the PAR (22.7%) shows that first pregnancy SGA account for a considerable proportion of second pregnancy SGA cases. Given the very low incidence of de novo SGA in the second pregnancy, both in the HTD and the non-HTD group, one could state that the risk of SGA is decreased significantly after a previously appropriate for gestational age fetus.

Although we have demonstrated a higher SGA recurrence rate in women with a hypertensive disorder in the first pregnancy, this does not seem clinically relevant because the difference is relatively small (23.7% vs. 21.0%) and the PAR of previous HTD is low (3.7%). This study can be an important aid for clinicians to assess the SGA risk for individual patients and adapt pregnancy care accordingly.

Women with an HTD in the first pregnancy and women who delivered an SGA neonate in the first pregnancy have a strongly increased risk of SGA in the second pregnancy. Prenatal care aims at identifying SGA fetuses before their health is compromised. The 30 weeks scan has been suggested to be of added value for diagnosing FGR. There is no substantial evidence from clinical trials that this examination reduces neonatal morbidity and mortality in a general obstetric population.\textsuperscript{33,34} It is still unclear, if women with a previous SGA, will benefit from a third trimester ultrasound to improve pregnancy outcome. Performing standard growth ultrasounds even in a sub population with an increased risk of SGA remains costly, since 75% of the neonates will be AGA. The role of Uterine
Artery (UA) Doppler measurements in high-risk pregnancies is yet unclear. If performed routinely during the 20 weeks anomaly scan, UA measurements can provide valuable information about the prognosis of fetal growth.\textsuperscript{35} It might help identify low-risk pregnancies among women with an HTD or SGA neonate in the first pregnancy and consequently reduce the number of fetal growth assessments that needs to be performed without compromising sensitivity for diagnosing SGA. More research is needed to establish the potential role of UA ultrasound in these patients.

Once SGA is diagnosed with ultrasound, it is important to identify fetuses at risk for adverse neonatal outcome. Evidence suggests that the use of weekly Doppler ultrasound in high-risk pregnancies reduces the risk of perinatal deaths and results in less obstetric interventions (level A recommendation).\textsuperscript{36}

There is no indication for ultrasound growth assessment as part of standard pregnancy care in non-HTD women and women who delivered an AGA neonate before, because of the low risk of SGA in this group and because there is no evidence that a growth ultrasound improves pregnancy outcome in these women.\textsuperscript{34,35} However, one should realize that there can be numerous other indications that might necessitate ultrasound growth assessment in these women.

Future research should focus on the influence of other etiology specific risks of FGR such as diabetes and preeclampsia and on methods to identify “true high risk” pregnancies antenatally.
References

(5) Pinheiro AR, Salvucci IDM, Aguila MB, Mandarim-de-Lacerda CA. Protein restriction during gestation and/or lactation causes adverse transgenerational effects on biometry and glucose metabolism in F1 and F2 progenies of rats. Clinical Science 2008; 114(5-6):381-392.
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Chapter 3

Relationship of single umbilical artery to fetal growth, aneuploidy and perinatal mortality: systematic review and meta-analysis

Bart Jan Voskamp, Hanneke Fleurke-Rozema, Katrien Oude Rengerink, Rosalinde J.M. Snijders, Catharina M. Bilardo, Ben Willem J. Mol, Eva Pajkrt

Ultrasound Obstetrics and Gynecology, 2013
Abstract

Objective: To review the available literature on outcome of pregnancy when an isolated Single Umbilical Artery (iSU) is diagnosed at the time of the mid-trimester anomaly scan.

Methods: We searched MEDLINE (1951-2012), Embase (1980-2012) and the Cochrane Library (until 2012) for relevant citations reporting on outcome of pregnancies with an iSU seen on ultrasound. Two reviewers extracted data. Where appropriate, we pooled odds-ratios (OR) for the dichotomous outcome measures: small for gestational age (SGA), perinatal mortality and aneuploidy. For birth weight we determined the mean difference with 95% confidence interval (CI).

Results: We identified three cohort studies and four case-control studies reporting on 928 pregnancies with iSU. There was significant heterogeneity between cohort and case-control studies. Compared to fetuses with a three-vessel cord (TVC), fetuses with an iSU were more likely to be SGA (OR 1.6, 95% CI 0.97-2.6, n=489) or suffer perinatal mortality (OR 2.0, 95% CI 0.95-4.2, n=686), although for neither of the outcomes statistical significance was reached. The difference in mean birth weight was 49 grams (3105 versus 3158 grams; 95% CI -154.7 to 52.6, n=407). We found no evidence that iSU fetuses have an increased risk for aneuploidy.

Conclusion: In view of the non-significant association between iSU and fetal growth and perinatal mortality, and in view of the heterogeneity in studies on aneuploidy, we feel that large-scale, prospective cohort-studies are needed for definite conclusions on the appropriate work-up in iSU pregnancies. At present, targeted growth assessment after diagnosis of an iSU should not be routine practice.
Introduction

The umbilical cord normally contains two arteries and one vein. Absence of one of the umbilical arteries is referred to as a single umbilical artery (SUA). The most widely accepted underlying explanations for the cause of a SUA include primary agenesis of one umbilical artery, later thrombotic atrophy of one umbilical artery or persistence of the original single allantoic artery of the body stalk. In literature, the reported incidence of SUA varies from 0.5% at the time of second trimester prenatal ultrasound and in umbilical cord specimens from live born infants to 2.1% in fetal deaths, autopsies or aborted fetuses and 5.9% in a selected population undergoing chorion villus sampling in the first trimester.

There is sufficient evidence in literature that SUA is associated with an increased risk of structural and chromosomal anomalies. Approximately 33% of the fetuses with a SUA have additional structural anomalies, and 10% are affected with aneuploidy. Therefore, in case of a SUA diagnosed at the time of the mid-trimester scan, a targeted ultrasound is warranted to rule out underlying pathology.

In approximately 65% of cases, SUA appears to be an isolated finding. However, in pregnancies with an apparently isolated SUA, aneuploidy or SGA may become apparent later on in pregnancy or at birth. The reported rate with which this occurs varies. As a result there is still no consensus regarding the extent of workup required.

This systematic review summarizes the available literature on the outcome of SUA diagnosed at the mid-trimester ultrasound exam. Our aim is to assess whether sufficient data are available to decide upon the appropriate work-up and pregnancy management.

Methods

We performed a systematic review and meta-analysis according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.

Data sources
We searched Medline (from 1948), Embase (from 1980) and Cochrane until December 2012 to identify papers reporting on SUA. MeSH terms and keywords used were “single umbilical artery [Mesh]” OR “single umbilical arteries[Mesh]” OR “single umbilical artery*[Tiab]” OR “two-vessel cord[Tiab]” OR (“SUA[Tiab]” AND (“foetal[Tiab]” OR “prenatal[Tiab]”)). Reference lists of review articles and eligible primary studies were checked to identify papers not captured by the electronic search.

Eligibility criteria
Randomized controlled trials, cohort studies and case-control studies were considered eligible if they described at least 30 cases of apparently isolated SUA identified with ultrasound, before an average gestational age of 24 completed weeks.

SUA was considered to be isolated if researchers reported that there were no additional structural anomalies, markers for aneuploidy, SGA or hydramnios at the time of the ultrasound exam.

Studies were not included if SUA was first diagnosed at birth or if the study focused on twin pregnancies only.
We included all studies that enabled (re)construction of a 2x2 table with the incidence of the outcome of interest in SUA fetuses and TVC fetuses.

Study selection
Studies were selected in a staged process. First, one reviewer (BV) scrutinized titles and abstracts of all retrieved references to select potentially eligible articles reporting on iSUA in human fetuses diagnosed with ultrasound. We used reference Manager Professional Edition Version 5.1 to collect all articles. Two reviewers (BV and HR) independently further examined eligibility using full text papers. In case of multiple publications of one dataset only the most complete paper was included. Disagreements about eligibility were resolved by consensus. If consensus was not reached a third reviewer (EP) was consulted.

Data extraction
A standardized form was used to extract data for each of the studies included in this review. Study characteristics that were summarized on the form included: data collection period, country of investigation, number of iSUA, study type, study population (high risk, low risk, unselected), method of diagnosis (at mid-trimester or at birth), method and completeness of ascertainment, and gestational age at ultrasound. In addition, method of pregnancy dating, definition of SGA, and ascertainment of karyotype were summarised.

Quantitative data on the outcome variables included rate of SGA and perinatal mortality, median or mean birth weight and frequency of aneuploidy.

Quality assessment
Both reviewers (BV and HR) assessed the methodological quality of eligible studies using the Newcastle-Ottawa Scale (NOS)\textsuperscript{14}, this scale assesses the selection of the study groups; the comparability of the groups; and the ascertainment of iSUA and outcome variables.

Data synthesis
We constructed forest plots using Review Manager 5.0. A forest plot is a graphical display that illustrates the relative strength of effects in multiple quantitative studies addressing the same question. It gives a weighed average of the association between a factor - in this study an iSUA - and the outcome variables.

We determined odds ratios with 95% confidence intervals for the occurrence of SGA, perinatal mortality, and for the rate of aneuploidy in isolated SUA compared to TVC fetuses. For birth weight, we calculated a mean difference in (grams) with 95% confidence interval between SUA and TVC fetuses.

We tested the heterogeneity of results across the studies using the $I^2$ test. If statistical heterogeneity was small ($I^2<30\%$) a Mantel-Haenszel fixed effects model was used. For studies with moderate statistical heterogeneity ($I^2>30\%$), we used a Mantel-Haenszel random effects model. If heterogeneity was too large or if studies showed both positive and negative odds-ratios we did not pool the results. We used funnel plots to check if there were any indications for publication bias.
Results

The search revealed 449 articles, of which 383 studies were excluded after reviewing titles and abstracts, as they did not fulfil the inclusion criteria. The full text of the remaining 66 papers was examined in more detail. Of these, 59 studies did not meet the inclusion criteria, leaving 7 studies for inclusion in the systematic review.\(^\text{1,2,15-19}\) Figure 1 shows the study selection process and reasons for exclusion. The reasons for exclusion of individual studies are listed in appendix S1.

Figure 1. Flow diagram: identification, screening for eligibility and selection of studies

SUA, single umbilical artery

We included three cohort studies and four case-control studies. In these studies 68 to 297 cases of apparently isolated SUA were reported, resulting in an overall number of patients with an ISUA of 982. An overview of these studies is shown in appendix S2. This appendix also shows that one study reported data on SUA in a high-risk population\(^\text{18}\) two studies in a mixed population\(^\text{1,17}\), two studies in an unselected population\(^\text{2,15}\). The incidence of SUA of the population was not described in two studies\(^\text{16,19}\). Average gestational age at SUA diagnosis ranged from 19.0 weeks to 24.3 weeks. Four studies reported on SGA\(^\text{1,15,16,19}\), three on neonatal birth weight\(^\text{15,16,19}\), four on perinatal mortality\(^\text{1,15,17}\), and three on aneuploidy\(^\text{2,18,19}\). The definition of outcome variables and postnatal ascertainment in different studies are shown in appendix S3.

Quality

The results of the Newcastle-Ottawa Scale quality assessment of case-control and cohort studies are summarized in appendix S4. All included cohort studies met the following NOS quality criteria: selection of the non-affected cohort drawn from the same community as the affected cohort, selection of apparently isolated SUA only (exclusion of prenatally diagnosed anomalies), comparability of cohorts and assessment of outcome through record linkage. 2/3 studies also met the items for representativeness of the exposed cohort, i.e. that study population is similar to the
general population, and adequate assessment of outcome. Studies scored poorly on adequacy of follow up.

All four case-control studies met the following NOS criteria: adequate case definition, representative case series, controls with no history of disease (SUA), comparability of cases and controls, same method of postnatal ascertainment for cases and controls and a same rate of complete outcome (response) in cases and controls. Ascertainment of SUA post partum (exposure) and selection of controls were met in 2/4 studies and 1/4 study respectively.

All studies reporting on birth weight and SGA adequately described how pregnancy dating was performed and how SGA was defined. Postnatal confirmation of SUA was described in four of seven studies. In the remaining three studies, postnatal SUA confirmation was not described. Reasons for fetal or neonatal karyotyping were described in 67% of studies.

**Small for gestational age**

When we pooled four case control studies we found an association between an iSUA and SGA at birth (figure 2) that was not statistically significant (odds ratio for SGA in fetuses with an iSUA was 1.6 (95%CI 0.97-2.6, p-value 0.06)). The reported odds ratios in the four individual studies ranged from 1.1 to 3.3.

**Figure 2.** Small for gestational age (<p10) in infants with an apparently isolated SUA compared to three vessel cord infants. M-H, Mantel-Hanzel

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SUA Events</th>
<th>TVC Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bombyx (2008)</td>
<td>35</td>
<td>255</td>
<td>1.05 [0.64, 1.72]</td>
<td></td>
</tr>
<tr>
<td>Cornall (2003)</td>
<td>18</td>
<td>82</td>
<td>2.03 [1.05, 3.95]</td>
<td></td>
</tr>
<tr>
<td>Horton (2010)</td>
<td>12</td>
<td>68</td>
<td>3.32 [1.01, 10.89]</td>
<td></td>
</tr>
<tr>
<td>Predanic (2005)</td>
<td>6</td>
<td>84</td>
<td>1.54 [0.42, 5.66]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>489</strong></td>
<td><strong>653</strong></td>
<td><strong>1.59 [0.97, 2.60]</strong></td>
<td></td>
</tr>
</tbody>
</table>

SUA, single umbilical artery; TVC, three-vessel cord; SGA, small for gestational age (<p10)

Three case-control studies reported mean birth weight of fetuses with apparently iSUA. Figure 3 shows that fetuses with iSUA did not have significantly lower mean birth weights than TVC fetuses (mean weight 3105 versus 3158 grams; mean difference 49 grams, 95% CI -154.7 to 52.6, p-value 0.33).

**Figure 3.** Birth weight in infants with an apparently isolated SUA compared to three vessel cord infants.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SUA Mean SD</th>
<th>TVC Mean SD</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bombyx (2008)</td>
<td>3,085 621</td>
<td>3,078 673</td>
<td>1,00 41.7%</td>
<td>7.00 [-105.40, 119.40]</td>
</tr>
<tr>
<td>Horton (2010)</td>
<td>3,275 404</td>
<td>3,423 374</td>
<td>1,148.00 -17.15%</td>
<td></td>
</tr>
<tr>
<td>Predanic (2005)</td>
<td>3,285 595</td>
<td>3,274 627</td>
<td>1,00 22.7%</td>
<td>-6.00 [-190.85, 178.85]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>407</strong></td>
<td><strong>407</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>51.04 [-154.71, 52.63]</strong></td>
</tr>
</tbody>
</table>

SUA, single umbilical artery; TVC, three-vessel cord; IV, Inverse Variance

34
Perinatal mortality
One cohort study and three case-control studies reported incidences of perinatal mortality (figure 4). Although there seems to be an association between an iSU A and increased perinatal mortality, the meta-analysis did not indicate statistical significance (OR 2.0, 95% CI 0.95-4.2, p-value 0.07).

Figure 4. Perinatal mortality in infants with an apparently isolated SUA compared to three vessel cord infants.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SUA Events</th>
<th>TVC Events</th>
<th>Total Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bombyx (2008)</td>
<td>6</td>
<td>255</td>
<td>4</td>
<td>285</td>
</tr>
<tr>
<td>Cornali (2003)</td>
<td>2</td>
<td>82</td>
<td>2</td>
<td>214</td>
</tr>
<tr>
<td>Horton (2010)</td>
<td>0</td>
<td>68</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td>Hua (2010)</td>
<td>4</td>
<td>281</td>
<td>441</td>
<td>63655</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>686</td>
<td>64222</td>
<td>100.0%</td>
<td>1.98 [0.94, 4.17]</td>
</tr>
</tbody>
</table>

SUA, single umbilical artery; TVC, three-vessel cord;

Aneuploidy
Three studies reported prevalence of aneuploidy in the apparently isolated SUA group. The study by Predanic et al.9 had no cases of aneuploidy among cases and controls. As a result, results of this study could not be weighed in the meta-analysis. The other two studies7,8 showed contradictory results. Lubusky et al. had no cases aneuploidy among 77 fetuses with a SUA, while the aneuploidy rate in the controls was 5.3%. The aneuploidy rate in the other study by Granese et al. was 2.5% among 39 SUA cases and 0.14% among the controls.

In view of these contradictory results, we could not pool the results (see figure 5). Due to the lack of population-based studies, we summarized the results of case series on Aneuploidy in iSU A fetuses (table 1). Among 695 iSU A cases reported in sixteen studies25,6,18-30, there were four cases of aneuploidy (0.58%). The average maternal age in these studies was 30.1 years. The incidence of aneuploidy could not be compared to that in the general population31 for reasons described in the discussion.

Figure 5. Aneuploidy in fetuses with an apparently isolated SUA. M-H, Mantel-Hanzel

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SUA Events</th>
<th>TVC Events</th>
<th>Total Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predanic (2005)</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>84</td>
</tr>
<tr>
<td>Lubusky (2007)</td>
<td>0</td>
<td>77</td>
<td>109</td>
<td>2045</td>
</tr>
<tr>
<td>Granese (2007)</td>
<td>1</td>
<td>39</td>
<td>18</td>
<td>12557</td>
</tr>
</tbody>
</table>

SUA, single umbilical artery; TVC, three-vessel cord;

Discussion
Our meta-analysis of published data indicates that iSU A is associated with a non-significant trend for increased risk of SGA and perinatal mortality. However, well-designed and properly powered studies are lacking.
The quality of the studies so far has several weaknesses. First, study populations differed with regard to a priori risk of anomalies. One study only comprised pregnancies with an increased risk of aneuploidy based on serum screening results, maternal age or findings at prior ultrasound examination\textsuperscript{18}, the risk profile of included patients was not described in other studies\textsuperscript{16,19}. As a result, the reported association between iSUA and aneuploidy may be affected by selection bias.

\begin{table}[h]
\centering
\caption{Aneuploidy in fetuses with an apparently isolated SUA}
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
Author & Publication year & Study design & Study group / risk for aneuploidy & Maternal age in years mean +/- SD (range) & Karyotyped SUA & SUA abnormal karyotype & SUA total # cases \\
\hline
Nyberg & 1991 & Case series & High risk only & Not reported & Not reported & 0 & 15 \\
Abuhamad & 1995 & Case series & High risk only & 30.3 +/- 6.13 & 0 & 0 & 50 \\
Catanzarite & 1995 & Case series & High risk only & Not reported & Not reported & 0 & 45 \\
Parilla & 1995 & Case series & Mixed & 31.0 +/- 5.1 & 17 & 0 & 50 \\
Wu & 1997 & Case series & Unknown & 30.9 +/- 3.2 & 8 & 0 & 19 \\
Chow & 1998 & Case series & Unknown & Not reported & Not reported & 1 & 81 \\
Lee & 1998 & Case series & Mixed & Not reported & 22 & 1 & 23 \\
Geipel & 2000 & Case series & Mixed & Not reported & 0 & 0 & 59 \\
Budurick & 2001 & Case series & High risk only & Not reported & 14 & 0 & 21 \\
Pierce & 2001 & Case series & Unknown & 25 & Not reported & 0 & 48 \\
Cristina & 2005 & Case-control* & Unselected & 30.8 +/- 5.4 & Not reported & 0 & 36 \\
Predanic & 2005 & Case-control & Unknown & 31.2 +/- 5.2 & Not reported & 0 & 84 \\
Volpe & 2005 & Case series & Mixed & 30.0 +/- 5.0 & 25 & 1 & 25 \\
Granese & 2007 & Cohort & Unselected & 27.2 (15-42) & Not reported & 1 & 39 \\
Lubusky & 2007 & Cohort & High risk only & Not reported & 77 & 0 & 77 \\
Dane & 2009 & Case series & Unknown & Not reported & Not reported & 0 & 23 \\
\hline
\textbf{Total (weighted average)} & & & & (30.1) & 163 & 4 & 695 \\
\hline
\end{tabular}
\end{table}

US, ultrasound; SUA, single umbilical artery; GA, gestational age; SD, standard deviation; * No incidence of aneuploidy reported in control group

Postnatal confirmation of SUA was described for only 57\% (4/7) of studies. Therefore there is no certainty about the true number of iSUAs. As the reported specificity of prenatal ultrasound in detecting SUA is high (average 98.9\%, range 93.4\% to 100.0\%) it is unlikely that TVC fetuses in the SUA group positively biased the outcome findings.

\textbf{Birth weight and SGA}

This meta-analysis did not show a statistically significant difference in birth weight and incidence of SGA between iSUA fetuses and TVC fetuses, although the results were on the verge of statistical significance. It has been hypothesised that the relative low birth weight in the iSUA group may be secondary to a relative high prevalence of preterm birth.\textsuperscript{32} The odds ratio for preterm birth in fetuses with an iSUA compared to TVC fetuses was 2.1 (95\%CI 1.4-3.2) for delivery before 37 weeks and 3.3 (95\%CI 1.4- 7.7) for delivery before 34 weeks\textsuperscript{33}. Especially late preterm birth (<37weeks) might partially be iatrogenic.

The association of iSUA with relative low birth weight and increased incidence of SGA is inversely correlated with the sample size of studies. Large studies show no difference in SGA and birth weight, whereas smaller studies report a significant association. This might be the result of publication bias and is reflected in the considerable heterogeneity between studies (SGA $I^2 = 33\%$ and Birth weight $I^2 = 40\%$), which declines greatly if the smallest study is not considered in the meta-analysis (SGA $I^2 = 20\%$ and Birth weight $I^2 = 0\%$). This indicates that the actual incidence of SGA and low birth weight in fetuses with an iSUA is not clinically relevant.
Perinatal mortality
The meta-analysis did not reveal a statistical significant difference in perinatal mortality between fetuses with an iSUA and TVC, but the OR was 2.0 and the lower bound of the confidence interval close to 1. The non-significant result might be due to the limited sample size. On the other hand, studies that show a trend towards increased perinatal mortality in iSUA fetuses may be more easily submitted for publication. If anything, the association of iSUA with perinatal loss is weak. Moreover, attention should be drawn to the observation that the prevalence of perinatal mortality in the control groups of eligible studies was almost two-fold the average in the general population (7 per 1000 births), which indicates that studies involve high-risk populations.34

Aneuploidy
Based on this systematic review no firm conclusions can be drawn on the association between iSUA and aneuploidy. The only two eligible studies had conflicting results ($I^2 = 93\%$). The low incidence of the outcome of interest combined with the relatively small sample size might have been the most important contributor: one or two cases of aneuploidy in iSUA group or TVC group can completely alter the study results. All included studies were too small to either show or refute a difference in occurrence of aneuploidy.

Due to the lack of population-based studies, we summarized the results of case series. Table 1 shows study characteristics of these case series. Aneuploidy incidence in these studies could not be compared to the incidence in the general population for several reasons. First, the low incidence of aneuploidy combined with the relatively small population under investigation. Second, there is a high risk of publication bias in case series. Third, the influence of maternal age on aneuploidy risk plays a role, but is hard to compare between studies. Eligible studies described different populations with different a priori risks of aneuploidy and different maternal age. It is not reliable to use the age related risk of the weighed average age of the study population to calculate the true population risk of aneuploidy. Calculating the true aneuploidy risk is only possible if the actual age of all participants is used, but these data were not available. Average maternal age was only available in 8/16 studies.

A final limitation is that karyotyping was only performed if anomalies or sono-markers were diagnosed prenatally or aneuploidy was suspected after birth. In the absence of sonographically demonstrated concurrent anomalies, iSUA is not an indication for invasive karyotyping because most cases of iSUA likely result from secondary atrophy of an artery.30 Consequently, although it seems unlikely, it is possible that diagnoses of aneuploidy have been missed, both in iSUA fetuses and in TVC fetuses.

In conclusion, we found no statistical significant evidence that fetuses with an iSUA have an increased risk of aneuploidy.

Conclusion
Fetuses with an apparently isolated SUA potentially have an increased risk of impaired fetal growth and perinatal mortality. However, even in meta-analysis results were not statistically significant and large studies showed smaller differences than small studies, suggesting publication bias. Furthermore, the three population-based studies on the risk of aneuploidy show strong heterogeneity, indicating unclarity in this matter. More large-scale, prospective cohort-studies are needed to further clarify this association and identify appropriate management protocols for iSUA fetuses.
References


## Appendix 5.1. Excluded studies after screening full text articles for eligibility

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication Year</th>
<th>Title</th>
<th>Journal</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itoh et al.</td>
<td>1976</td>
<td>Single umbilical artery—a review of 37 cases—.</td>
<td>Aeta Obstet Gynaecol Jpn.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Björk et al.</td>
<td>1983</td>
<td>Vascular anomalies of the umbilical cord: I. Obstetric implications.</td>
<td>Early Hum Dev.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Grall et al.</td>
<td>1983</td>
<td>The single umbilical artery. Apropos of 194 observations</td>
<td>Zhonghua Yi Xue Za Zhi.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Zhu et al.</td>
<td>1984</td>
<td>A single umbilical artery—analysis of 14 cases</td>
<td>Prenat Diagn.</td>
<td>case series</td>
</tr>
<tr>
<td>Hermann et al</td>
<td>1988</td>
<td>Single umbilical artery: prenatal findings</td>
<td>J Gynecol Obstet Biol Reprod.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Jaurua et al.</td>
<td>1989</td>
<td>Ultrasonic study of the single umbilical artery syndrome. A series of 80 cases</td>
<td>Am J Dis Child</td>
<td>only postnatal diagnosis / no prenatal diagnosis</td>
</tr>
<tr>
<td>Segovia et al.</td>
<td>1990</td>
<td>Single umbilical artery: review of 32 cases</td>
<td>Paediatr Perinat Epidemiol.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Lilja et al.</td>
<td>1991</td>
<td>Infants with single umbilical artery studied in a national registry. General epidemiological characteristics.</td>
<td>Zentralbl Gynaekol.</td>
<td>case series</td>
</tr>
<tr>
<td>Lilja et al.</td>
<td>1992</td>
<td>Infants with single umbilical artery studied in a national registry. 2: Survival and malformations in infants with single umbilical artery.</td>
<td>Arch Dis Child</td>
<td>case series</td>
</tr>
<tr>
<td>Bourke et al.</td>
<td>1993</td>
<td>Isolated single umbilical artery—the case for routine renal screening.</td>
<td>Ultrasound Obstet Gynecol.</td>
<td>only postnatal diagnosis / no prenatal diagnosis</td>
</tr>
<tr>
<td>Cardona et al.</td>
<td>1993</td>
<td>Significance of a single umbilical artery at birth</td>
<td>Obstet Gynecol.</td>
<td>case series</td>
</tr>
<tr>
<td>Abuhamad et al.</td>
<td>1995</td>
<td>Single umbilical artery: does it matter which artery is missing?</td>
<td>Prenat Diagn.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Biache et al.</td>
<td>1995</td>
<td>Prognostic value of a single umbilical artery, 87 cases</td>
<td>J Gynecol Obstet Biol Reprod.</td>
<td>only postnatal diagnosis / no prenatal diagnosis</td>
</tr>
<tr>
<td>Parilla et al.</td>
<td>1995</td>
<td>The clinical significance of a single umbilical artery as an isolated finding on prenatal ultrasound.</td>
<td>Obstet Gynecol.</td>
<td>case series</td>
</tr>
<tr>
<td>Blazer et al.</td>
<td>1997</td>
<td>Single umbilical artery—right or left? does it matter?</td>
<td>Int J Gynecol Obstet.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Ulm et al.</td>
<td>1997</td>
<td>Umbilical artery Doppler velocimetry in fetuses with a single umbilical artery.</td>
<td>J Clin Ultrasound.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
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<tr>
<td>Chow et al.</td>
<td>1998</td>
<td>Frequency and nature of structural anomalies in fetuses with single umbilical arteries.</td>
<td>Int J Gynaecol Obstet.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
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<tr>
<td>Lee et al.</td>
<td>1998</td>
<td>Perinatal Management and Outcome of Fetuses with Single Umbilical Artery Diagnosed Prenatally.</td>
<td>J Matern Fetal Invest.</td>
<td>case series</td>
</tr>
<tr>
<td>Goldkrautel et al</td>
<td>1999</td>
<td>Doppler velocimetry in the fetus with a single umbilical artery.</td>
<td>J Reprod Med.</td>
<td>no distinction between isolated &amp; non-isolated SUA</td>
</tr>
<tr>
<td>Geipel et al.</td>
<td>2000</td>
<td>Prenatal diagnosis of single umbilical artery; determination of the absent side, associated anomalies, Doppler findings and perinatal outcome.</td>
<td>Ultrasound Obstet Gynecol.</td>
<td>case series</td>
</tr>
<tr>
<td>Budrick et al.</td>
<td>2001</td>
<td>The single umbilical artery in a high-risk patient population: what should be offered?</td>
<td>J Ultrasound Med.</td>
<td>case series</td>
</tr>
<tr>
<td>Pierce et al.</td>
<td>2001</td>
<td>Perinatal outcome following fetal single umbilical artery diagnosis.</td>
<td>J Matern Fetal Med.</td>
<td>case series</td>
</tr>
</tbody>
</table>
Raio et al 2003 Ductus venous blood flow velocity characteristics of fetuses with single umbilical artery.


Friedberg et al 2004 Changing indications for fetal echocardiography in a University Center population.


Cristina et al 2005 Perinatal results following the prenatal ultrasound diagnosis of single umbilical artery.


Agata et al 2007 Single umbilical artery: what does it mean for the fetus?

Dornfried et al 2007 Screening infants with an isolated single umbilical artery for renal anomalies: nonsense?


Mu et al 2008 The perinatal outcomes of a symptomatic isolated single umbilical artery in full-term neonates.


Dane et al 2009 Fetuses with single umbilical artery: Analysis of 45 cases.

Deshpande 2009 Do babies with isolated single umbilical artery need routine postnatal renal ultrasonography?

Suess et al 2009 Arterial-adaptive dilatation and Doppler velocimetry in normal fetuses with a single umbilical artery.

Boon de et al 2010 Is screening for renal anomalies warranted in neonates with isolated single umbilical artery?

Bagli et al 2010 Ultrasound predictors of birth weight in euploid fetuses with isolated single umbilical artery.

Daglits et al 2010 Isolated single umbilical artery and fetal karyotype.

Defigueiredo et al 2010 Isolated single umbilical artery: need for specialist fetal echocardiography?

Murphy-Kasperek et al 2010 Single umbilical artery risk factors and pregnancy outcomes.

Prufumo et al 2010 Single umbilical artery and congenital heart disease in selected and unselected populations.

Burshtein et al 2011 Is single umbilical artery an independent risk factor for perinatal mortality?

Santillan et al 2012 Single Umbilical Artery: Does Side Matter?

Ultrasound Obstet. Gynecol. case series

Ultrasound Obstet. Gynecol. no distinction between isolated & non-isolated SUA

Prenat. Diagn. no distinction between isolated & non-isolated SUA

Genet. Med. no distinction between isolated & non-isolated SUA

Acta Obstet. Gynecol. Scand. Article on aneuploidy in a high risk population based on serum Screening or suspicion of congenital anomalies case series

Minerva Ginecol. only postnatal diagnosis / no prenatal diagnosis case series

An. Pediatr. (Lisb.) only postnatal diagnosis / no prenatal diagnosis case series

Ginekol. Pol. only postnatal diagnosis / no prenatal diagnosis case series

Early Hum. Dev. only postnatal diagnosis / no prenatal diagnosis case series

Indian Journal of Radiol. Imag. only postnatal diagnosis / no prenatal diagnosis case series

J. Ultrasound Med. only postnatal diagnosis / no prenatal diagnosis case series

Pediatr. Neonatol. other: no quantitative data on outcome of SUA fetuses only postnatal diagnosis / no prenatal diagnosis case series

Am. J. Perinatol. case series

Clinical and Experimental Obs. and Gyn. Other: no data on outcome of interest case series


Neonatology only postnatal diagnosis / no prenatal diagnosis case series


Ultrasound Obstet. Gynecol. case series

Obstet. Gynecol. only postnatal diagnosis / no prenatal diagnosis case series

Ultrasound Obstet. Gynecol. case series

Arch. Gynecol. Obstet. only postnatal diagnosis / no prenatal diagnosis case series

Fetal Diagn. Ther. no distinction between isolated & non-isolated SUA
Appendix S2. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Title</th>
<th>Journal</th>
<th>Country of study</th>
<th>Baseline study dates</th>
<th>No. of isolated SUA</th>
<th>Type of Study</th>
<th>Study group</th>
<th>SUA diagnosis</th>
<th>GA ultrasound in weeks</th>
<th>Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenall et al</td>
<td>2003</td>
<td>Antenatal detection of a single umbilical artery: does it matter?</td>
<td>Prenatal Diagnosis</td>
<td>UK</td>
<td>1995-2005</td>
<td>82</td>
<td>Care control</td>
<td>Mixed</td>
<td>US with confirmation at birth</td>
<td>20 weeks scan+</td>
<td>70-95% (95-95)</td>
</tr>
<tr>
<td>Predanic et al</td>
<td>2005</td>
<td>Fetal growth assessment and neonatal birth weight in fetuses with an isolated single umbilical artery</td>
<td>Obstet. Gynecol</td>
<td>USA</td>
<td>1999-2004</td>
<td>84</td>
<td>Care control</td>
<td>Unknown</td>
<td>US with confirmation at birth</td>
<td>18-23</td>
<td>95% (95-95)</td>
</tr>
<tr>
<td>Granese et al</td>
<td>2007</td>
<td>The value of single umbilical artery in the prediction of fetal aneuploidy: findings in 12,672 pregnant women</td>
<td>Ultrasound Quarterly</td>
<td>USA</td>
<td>1998-2002</td>
<td>39</td>
<td>Cohort retrospective</td>
<td>Unselected</td>
<td>US, confirmation at birth not described</td>
<td>(16-23)</td>
<td>95% (95-95)</td>
</tr>
<tr>
<td>Lubsky et al</td>
<td>2007</td>
<td>Single umbilical artery and its sitting in the second trimester of pregnancy: Relation to chromosomal defects.</td>
<td>Prenatal Diagnosis</td>
<td>Czech Rep.</td>
<td>Not reported</td>
<td>77</td>
<td>Cohort retrospective</td>
<td>High risk only</td>
<td>US, confirmation at birth not described</td>
<td>18-36 (22)</td>
<td>95% (95-95)</td>
</tr>
<tr>
<td>Bombrys et al</td>
<td>2008</td>
<td>Pregnancy outcome in isolated single umbilical artery</td>
<td>Am. J. Perinatol</td>
<td>USA</td>
<td>2000-2004</td>
<td>297</td>
<td>Case control</td>
<td>Unselected</td>
<td>US with confirmation at birth</td>
<td>24.3 ± 7.2</td>
<td>95% (95-95)</td>
</tr>
<tr>
<td>Horton et al</td>
<td>2010</td>
<td>Perinatal outcomes in isolated single umbilical artery</td>
<td>Obstet. Gynecol</td>
<td>USA</td>
<td>2010-2007</td>
<td>281</td>
<td>Cohort retrospective</td>
<td>Mixed</td>
<td>US, confirmation at birth not described</td>
<td>19.0 ± 1.6</td>
<td>95% (95-95)</td>
</tr>
<tr>
<td>Hu et al</td>
<td>2010</td>
<td>Single umbilical artery and its associated findings.</td>
<td>Obstet. Gynecol</td>
<td>USA</td>
<td>2010-2007</td>
<td>281</td>
<td>Cohort retrospective</td>
<td>Mixed</td>
<td>US, confirmation at birth not described</td>
<td>19.0 ± 1.6</td>
<td>95% (95-95)</td>
</tr>
</tbody>
</table>

Appendix S3. Definition of outcome variables and ascertainment of outcome after birth

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Type of Study</th>
<th>Determination of GA</th>
<th>Definition SGA</th>
<th>Pregnancy-dating and SGA definition adequately described</th>
<th>Ascertainment of karyotype</th>
<th>Karyotyping described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenall et al</td>
<td>2003</td>
<td>Case control</td>
<td>Unknown</td>
<td>Weight &lt; 10th percentile</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Predanic et al</td>
<td>2005</td>
<td>Case control</td>
<td>LM confirmed by US</td>
<td>Weight &lt; 10th percentile (trend line)</td>
<td>Yes</td>
<td>Other: only if dysmorphic features</td>
<td>Yes</td>
</tr>
<tr>
<td>Granese et al</td>
<td>2007</td>
<td>Cohort retrospective</td>
<td>Unknown</td>
<td>Weight &lt; 10th percentile (trend line)</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Lubsky et al</td>
<td>2007</td>
<td>Cohort prospective</td>
<td>Unknown</td>
<td>Weight &lt; 10th percentile (trend line)</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Bombrys et al</td>
<td>2008</td>
<td>Case control</td>
<td>US only</td>
<td>Weight &lt; 10th percentile</td>
<td>Yes</td>
<td>All SUA &amp; all TFC chromosome analysis</td>
<td>Yes</td>
</tr>
<tr>
<td>Horton et al</td>
<td>2010</td>
<td>Case control</td>
<td>LM confirmed by US</td>
<td>Weight &lt; 10th percentile</td>
<td>Yes</td>
<td>All SUA &amp; all TFC chromosome analysis</td>
<td>Yes</td>
</tr>
<tr>
<td>Hu et al</td>
<td>2010</td>
<td>Cohort retrospective</td>
<td>Unknown</td>
<td>Weight &lt; 10th percentile</td>
<td>Yes</td>
<td>All SUA &amp; all TFC chromosome analysis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Percentage of adequate definition within studies: 100%

67%

Appendix S4. Newcastle-Ottawa quality assessment of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Title</th>
<th>Type of Study</th>
<th>Selection</th>
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<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>Comparability</th>
<th>C1</th>
<th>Outcome</th>
<th>Q5</th>
<th>O2</th>
<th>O3</th>
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<tbody>
<tr>
<td>Greenall et al</td>
<td>2003</td>
<td>Antenatal detection of a single umbilical artery: does it matter?</td>
<td>Case control</td>
<td>XXX</td>
<td>x</td>
<td>x</td>
<td>X</td>
<td>X</td>
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<td>xxx</td>
<td>x x x</td>
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<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Predanic et al</td>
<td>2005</td>
<td>Fetal growth assessment and neonatal birth weight in fetuses with an isolated single umbilical artery</td>
<td>Case control</td>
<td>XXX</td>
<td>x</td>
<td>x</td>
<td>X</td>
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<tr>
<td>Granese et al</td>
<td>2007</td>
<td>The value of single umbilical artery in the prediction of fetal aneuploidy: findings in 12,672 pregnant women</td>
<td>Cohort retrospective</td>
<td>XXX</td>
<td>x</td>
<td>x</td>
<td>X</td>
<td>X</td>
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<td>xxx</td>
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<tr>
<td>Lubsky et al</td>
<td>2007</td>
<td>Single umbilical artery and its sitting in the second trimester of pregnancy: Relation to chromosomal defects.</td>
<td>Cohort prospective</td>
<td>XX</td>
<td>x</td>
<td>x</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Bombrys et al</td>
<td>2008</td>
<td>Pregnancy outcome in isolated single umbilical artery</td>
<td>Case control</td>
<td>XX</td>
<td>x</td>
<td>x</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Horton et al</td>
<td>2010</td>
<td>Perinatal outcomes in isolated single umbilical artery</td>
<td>Case control</td>
<td>XXXX</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Hu et al</td>
<td>2010</td>
<td>Single umbilical artery and its associated findings.</td>
<td>Cohort retrospective</td>
<td>XXX</td>
<td>x</td>
<td>x</td>
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</tbody>
</table>

S1, adequate case definition / representativeness of the exposed cohort; S2, representativeness of the cases / selection of the non-exposed cohort drawn from the same community as the exposed cohort; S3, selection of controls from community / adequate ascertainment of exposure; S4, definition of controls / selection of apparently isolated SUA only (exclusion of prenatally diagnosed anomalies); C1, comparability of cases and controls / cohorts on the basis of the design or analysis; Q1, adequate assessment of outcome; Q2, same method of ascertainment for cases and controls / follow-up long enough for outcome to occur; Q3, adequacy of follow-up (all subjects accounted for / subjects lost to follow-up unlikely to cause bias)
Chapter 4

Association between fetal sex and adverse perinatal outcome, a nationwide cohort study

Bart Jan Voskamp, Myrthe JCS Peelen Anita CJ Ravelli, Robin van der Lee, Ben Willem J Mol, Eva Pajkrt, Wessel Ganzvoort, Brenda M Kazemier

In preparation
Chapter 4

Abstract

Objective: To assess whether fetal gender is independently associated with fetal death, neonatal death and neonatal morbidity.

Study design: We performed a cohort study using the Netherlands Perinatal Registry. The study population comprised all Caucasian women with a singleton delivery between 25\textsuperscript{0} and 42\textsuperscript{6} weeks gestational age (1999 to 2007). Fetuses with structural or chromosomal abnormalities were excluded. The Dutch reference birth weight curves stratified for sex and parity were used. Outcomes were fetal death, neonatal death (from the onset of labor until 28 days after birth), perinatal death (fetal death + neonatal death) and a composite of neonatal morbidity, including IRDS, sepsis, NEC, meconium aspiration, and intra-ventricular hemorrhage. Outcomes were expressed stratified by birth weight percentile (<p10, p10-90, >p90), and gestational age at delivery (25\textsuperscript{0}-31\textsuperscript{6}, 32\textsuperscript{0}-36\textsuperscript{6}, 37\textsuperscript{0}-42\textsuperscript{6} weeks). Multivariable logistic regression analyses were performed to assess the association between fetal sex and outcome.

Results: We studied 1,299,244 pregnancies. Fetal and neonatal death rates did not differ between males and females in most groups. Males suffered less fetal death between 25\textsuperscript{0} and 31\textsuperscript{6} weeks if <p10 (OR 0.67, 95%CI 0.53-0.84) or p10-90 (OR 0.74, 95%CI 0.65-0.85) and between 32\textsuperscript{0} and 36\textsuperscript{6} if p10-90 (OR 0.86, 95%CI 0.75-0.98). Males (<p90) suffered more neonatal death if born between 25\textsuperscript{0} and 31\textsuperscript{6} weeks GA if <p10 (OR 1.51, 95%CI 1.04-2.19) or p10-90 (OR 1.22, 95%CI 1.02-1.47). Males were significantly more likely than females to suffer neonatal morbidity (at term p10-90: OR 1.36, 95%CI 1.28-1.44).

Conclusion: Fetal sex was not independently associated with fetal death and neonatal death. Males were at increased risk of neonatal morbidity. Active management in extremely preterm males may have resulted in decreased perinatal mortality at the expense of neonatal morbidity.
Introduction

Fetal sex is associated with a number of aspects of pregnancy like intra-uterine growth, preterm birth, and perinatal outcome. Some associations are well established and are used to determine the optimal policy of pregnancy care, while others are still debated. Previous studies have suggested a male predominance in spontaneous abortions, fetal death, perinatal death, fetal distress, respiratory distress syndrome, and low Apgar Scores. The problem is that in these studies outcomes were either adjusted for absolute birth weight and gestational age at delivery, or that male/female ratios for adverse outcomes were calculated. Adjustment for absolute weight potentially leads to comparison of small for gestational age males with appropriately grown females because males are on average heavier than females. Using male/female ratios for adverse outcome causes bias because there are more males than females. This might have caused structural overestimation of adverse outcome among male infants in previous studies. Birth weight percentiles can be used to circumvent this bias. Birth weight percentiles are used to express growth instead of absolute weight, and are suitable to assess associations between abnormal growth and pregnancy outcome.

The objective of this study was to re-evaluate the association between fetal sex and adverse pregnancy outcome (fetal death, neonatal death and neonatal morbidity). Moreover, we wanted to assess if differences between males and females depend on the presence of abnormal fetal growth and gestational age at delivery.

Methods

Dataset
This study was performed in a nationwide cohort with the use of The Netherlands Perinatal Registry (PRN). The PRN consists of population-based data that contain information on pregnancies, deliveries, and re-admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of newborn neonates. Records are entered in the PRN registry at the child’s level. The coverage of the PRN registry is approximately 96% of all deliveries in The Netherlands. It contains pregnancies of ≥22 weeks gestational age and a birth weight of ≥500 g and is used primarily for an annual assessment of the quality indicators of obstetric care.

Ethical approval
The data in the perinatal registry are anonymous; therefore ethical approval was not needed. The Dutch Perinatal Registry gave their approval for the use of their data for this study (approval number 13.73).

Inclusion and exclusion criteria
We included all Caucasian women who delivered a singleton between 25th and 42nd weeks gestational age in The Netherlands between January 1, 1999, and December 31, 2007. We excluded all cases with congenital anomalies.
**Outcome measures**

Our primary outcome measures were fetal death, neonatal death, perinatal death, and a composite of neonatal morbidity. Fetal death was defined as death diagnosed between 25th weeks gestational age and the onset of labor. Neonatal death was defined as death between the onset of labor and 28 days after birth. Perinatal death was defined as the sum of fetal and neonatal death. The composite measure of neonatal morbidity consisted of: respiratory distress syndrome (RDS), neonatal sepsis, necrotizing enterocolitis (NEC), meconium aspiration, and intraventricular hemorrhage (IVH) within the first month. If an infant suffered from neonatal morbidity and died within 28 days after birth, it was considered to have suffered neonatal death and not morbidity.

The Dutch reference curves for birth weight by gestational age stratified for parity, sex and ethnic background were used. Pregnancy dating was performed by last menstrual period (LMP), or ultrasound measurements before 20 weeks of gestation (crown-rump-length (CRL) or head-circumference (HC) measurement. If the gestational age by ultrasound measurement differed more than 6 days from the last menstrual period, the pregnancy was dated on ultrasound measurement. Small for gestation (SGA) was defined as a birth weight below the 10th percentile for gestation (<p10), appropriately grown for gestation (AGA) was defined as a birth weight between the 10th and 90th percentile (p10-90) for gestation, and large for gestation (LGA) was defined as birth weight above the 90th percentile (>p90) for gestation.

**Population characteristic and clinical characteristics**

We registered demographic and obstetric characteristics including maternal age, parity and socioeconomic status (SES). Parity was categorized into 0 (first birth), 1 (second birth) and 2+ (third or higher birth). The SES score is based on mean income level, the percentage of households with a low income, the percentage of inhabitants without a paid job and the percentage of households with on average a low education in a postal code area. The continuous SES score was categorized into a high, middle and low group, based on percentile ranges (25th percentile, median, 75th percentile).

**Statistical analysis**

Demographic and obstetric baseline characteristics were compared between males and females using the Student t test and Chi Square test as appropriate.

We tested for interaction between sex and GA at delivery and between sex and birth weight percentile. These tests were performed separately for our four outcome measures. If statistically significant (p<0.001), analyses were performed stratified for gestational age at delivery and birth weight percentile.

Logistic regression analyses were performed to determine the association between fetal sex and pregnancy outcome, expressed as odds ratios (OR) with 95% confidence intervals (CI) both unadjusted and adjusted for birth weight percentile and gestational age at delivery.

The data were analyzed with the SAS statistical software package (version 9.2; SAS Institute Inc., Cary, NC).

All statistical tests were 2-sided; a probability value of 0.05 was chosen as the threshold for statistical significance.
Results

From January 1, 1999 until December 31, 2007 a total of 1,636,565 pregnancies were identified in the PRN database. After exclusion of non-Caucasian pregnancies (n=258,908 (15.82%)), multiple pregnancies (n=63,857 (3.90%)), infants with congenital anomalies (n=22,043 (1.35%)), and infants born before 25\textsuperscript{th} weeks or after 42\textsuperscript{nd} weeks GA (n=6,967 (0.43%)), our study population consisted of 1,299,244 pregnancies.

Baseline characteristics of this cohort are presented in Table 1. There were more males (n=665,983; 51.2%) than females (n=633,261; 49.8%). There were no statistical significant differences in maternal baseline characteristics between the two groups. Women with a male fetus were more likely (all p<.001) than women with a female fetus to undergo induction of labor (35.6% vs. 35.1%), caesarean section (14.3% vs. 13.3%) or vaginal instrumental delivery (12.4% vs. 10.1%). The rate of preterm delivery (<37 weeks GA) was significantly higher among males than among females (6.29% vs. 5.30%, OR 1.2, 95% confidence interval (CI) 1.18-1.22; p<0.001).

Finally, average birth weight in males was 124 grams (95% CI 122.2-126.2) higher than in females (3526 grams vs. 3401 grams; p<0.001).

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
 & Male infants & Female infants & P-value for differences \\
 & (n=665,983) & (n=633,261) & \\
\hline
**Maternal characteristics** & & & \\
Maternal age, mean, (SD) & 30.7 & 30.7 & 0.59 \\
Nulliparous, % & 47.5 & 47.4 & 0.14 \\
Low socio-economic status, % & 18.9 & 18.9 & 0.38 \\
\hline
**Pregnancy and delivery** & & & \\
Induction of labor, % & 35.6 & 35.1 & <0.001 \\
Caesarean section & 14.3 & 13.3 & <0.001 \\
Elective caesarean section % & 6.0 & 6.4 & <0.001 \\
Emergency caesarean section % & 8.3 & 6.9 & <0.001 \\
Vaginal instrumental delivery & 12.4 & 10.1 & <0.001 \\
\hline
**Neonatal characteristics** & & & \\
Gestational age at delivery (weeks), median (IQR) & 39.2 (1.92) & 39.3 (1.83) & <0.001 \\
Delivery <32 weeks GA, % & 0.85 & 0.72 & <0.001 \\
Delivery <37 weeks GA, % & 6.3 & 5.3 & <0.001 \\
Birth weight (gram), mean (SD) & 3,526 (595) & 3,401 (561) & <0.001 \\
Birth weight percentile, mean (SD) & 51.2 (29.0) & 51.0 (29.2) & 0.001 \\
\hline
\end{tabular}
\caption{Characteristics of the 1,299,244 singleton pregnancies in the Netherlands, 1999-2007}
\end{table}

SD, standard deviation

Interaction

Interaction between sex and gestational age at delivery was significant for fetal death (p<.001), neonatal death (p<.001), perinatal death (p<.001) and neonatal morbidity (p<.001). Interaction between sex and birth weight percentile was also significant for all outcome measures (all p<.001). Therefore, outcomes are presented stratified for gestational age at delivery (three strata of gestational age: 25\textsuperscript{th}-31\textsuperscript{st}, 32\textsuperscript{nd}-36\textsuperscript{rd}, and 36\textsuperscript{rd}-42\textsuperscript{nd} weeks) and fetal growth (three strata of birth weight percentile: <p10, p10-90, >p90).
Fetal death
Table 2 shows the odds ratios for fetal death separate for three strata of gestational age at delivery (25<sup>th</sup>-31<sup>st</sup>, 32<sup>nd</sup>-36<sup>th</sup>, and 36<sup>th</sup>-42<sup>nd</sup>) and three strata of birth weight percentile (SGA, AGA, and LGA). In the very preterm period (25<sup>th</sup>-31<sup>st</sup>) fetal death - and subsequent delivery - occurred less often in SGA and AGA males than in females (adjusted Odds Ratio (aOR) 0.67, 95% confidence interval (CI) 0.53-0.83 and aOR 0.74, 95% CI 0.65-0.85 respectively). In the late preterm period (32<sup>nd</sup>-36<sup>th</sup> weeks) fetal death - and subsequent delivery - also occurred slightly less often in AGA males than in females (adjusted aOR 0.86, 95% CI 0.75-0.98 respectively). At term, there was no statistically significant difference between males and females (aOR 0.93, 95% CI 0.84-1.02).

The incidence of fetal death in males and females stratified by GA at delivery and birth weight percentiles, are shown in figure 1a.

**Figure 1.** Adverse pregnancy outcome by birth weight percentile, separate for fetal sex and for three strata of gestational age.

Incidences (%) on a logarithmic scale. 1A fetal death (diagnosed between 25<sup>th</sup>-31<sup>st</sup> weeks gestational age and the onset of labor); 1B, neonatal death (between the onset of labor and 28 days after birth); 1C, perinatal death (sum of fetal and neonatal death); 1D, composite morbidity (respiratory distress syndrome (RDS), neonatal sepsis, necrotizing enterocolitis (NEC), meconium aspiration, and intraventricular hemorrhage (IVH) within the first month) in males (continuous lines) and females (interrupted lines) stratified by GA at delivery (represented by different line colors) and birth weight percentiles (x-axis).
Neonatal death
The rates of neonatal death are shown in table 3. In most groups, there were no differences between males and females. However, both SGA and AGA males that are born extremely preterm (25⁺⁰⁻31⁺⁶ weeks GA) have an increased risk of neonatal death compared to females (aOR 1.51, 95% CI 1.04-2.19 and aOR 1.22, 95% CI 1.02-1.47).

Perinatal death
Perinatal death rates do not differ significantly between males and females in most groups (Table 4 and figure 1c). However, males delivered extremely preterm (25⁻⁰ to 31⁻⁶ weeks) have lower risks of perinatal death compared to females if they are SGA (aOR 0.75, 95% CI 0.59-0.96) or AGA (aOR 0.87, 95% CI 0.77-0.98).

Composite morbidity
The composite morbidity of males and females is shown in table 5 and figure 1d. The odds for composite morbidity are significantly increased in males compared to females in almost all strata, with odds ratios ranging from 1.23 to 1.45.

Compared to females, composite morbidity is not increased in LGA males born extremely preterm (25⁻⁰ to 31⁻⁶ weeks) (aOR 1.13, 95% CI 0.86-1.49), SGA infants born late preterm (32⁻⁰ to 36⁻⁶ weeks) (aOR 1.13, 95% CI 0.93-1.38) and SGA infants born at term (37-42 weeks)[aOR 1.11, 95% CI 0.97-1.27].

Discussion
In our study we analyzed 1,299,244 singleton deliveries and assessed differences in pregnancy outcomes between males and females. Birth weight percentiles were used to adjust for differences in fetal growth. Fetal death and neonatal death were comparable for males and females in most groups. However, fetal death was higher among very preterm (25⁻⁰ to 31⁻⁶ weeks) SGA and AGA females, and neonatal death was higher among very preterm (25⁻⁰ to 31⁻⁶ weeks) SGA and AGA males. Perinatal death rate was lower among very preterm (25⁻⁰ to 31⁻⁶ weeks) SGA and AGA males compared to females. Neonatal morbidity occurred more often among males, regardless of GA and growth.

Limitations
There are some limitations of this study. First, neonatal mortality data were only available until 28 days after birth. We found no difference in perinatal morbidity between males and females, and higher neonatal morbidity among males. It remains unsure whether the difference in neonatal morbidity results in a difference in neonatal death in the first year after birth.

Second, in case of fetal death - especially in the preterm period- the gestational age of delivery is not the same as the moment of fetal demise. Although this might cause a structural underestimation of birth weight percentile, it is unlikely that there is a gender-based bias. Also, the overestimation of SGA is likely small at term because - according to the Dutch protocol - all pregnant women undergo weekly checkups including Doppler auscultation of the fetal heart rate.
### Table 2. Fetal death rate in males and females

<table>
<thead>
<tr>
<th></th>
<th>Male infants (n=665,983)</th>
<th>Female infants (n=633,261)</th>
<th>unadjusted</th>
<th>adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>OR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Birth weight &lt;p10 (SGA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-31 weeks GA</td>
<td>526/1,023 51.4</td>
<td>464/734 63.2</td>
<td>0.67 (0.56 - 0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>284/3,626 7.8</td>
<td>188/2,939 6.4</td>
<td>1.25 (1.03 - 1.51)</td>
<td>0.03</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>393/55,918 0.7</td>
<td>334/54,695 0.6</td>
<td>1.11 (1.00 - 1.33)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Birthweight p10-p90 (AGA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-31 weeks GA</td>
<td>494/4,201 11.8</td>
<td>532/3,385 15.7</td>
<td>0.71 (0.63 - 0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>466/30,735 1.5</td>
<td>418/24,190 1.7</td>
<td>0.91 (0.77 - 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>730/500,068 0.2</td>
<td>749/478,140 0.2</td>
<td>0.91 (0.84 - 1.03)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Birth weight ≥p90 (LGA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-31 weeks GA</td>
<td>48/425 11.3</td>
<td>55/416 13.2</td>
<td>0.83 (0.55 - 1.26)</td>
<td>0.39</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>27/1,858 1.5</td>
<td>17/1,896 0.9</td>
<td>1.67 (0.89 - 3.00)</td>
<td>0.12</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>106/68,129 0.2</td>
<td>94/66,865 0.1</td>
<td>1.11 (0.84 - 1.46)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: birth weight percentile, GA at delivery

SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; CI, confidence interval

### Table 3. Neonatal death rate in males and females

<table>
<thead>
<tr>
<th></th>
<th>Male infants (n=665,983)</th>
<th>Female infants (n=633,261)</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>OR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Birth weight &lt;p10 (SGA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-31 weeks GA</td>
<td>89/1,023 8.7</td>
<td>47/734 6.4</td>
<td>1.25 (0.97 - 1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>53/3,626 1.5</td>
<td>52/2,939 1.8</td>
<td>0.83 (0.56 - 1.21)</td>
<td>0.32</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>135/55,918 0.2</td>
<td>119/54,695 0.2</td>
<td>1.11 (0.87 - 1.42)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Birthweight p10-p90 (AGA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-31 weeks GA</td>
<td>341/4,201 8.1</td>
<td>239/3,385 7.1</td>
<td>1.11 (0.98 - 1.38)</td>
<td>0.09</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>160/30,735 0.5</td>
<td>122/24,190 0.5</td>
<td>1.00 (0.81 - 1.31)</td>
<td>0.79</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>358/500,068 0.1</td>
<td>294/478,140 0.1</td>
<td>1.11 (1.00 - 1.36)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Birth weight ≥p90 (LGA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-31 weeks GA</td>
<td>34/425 8.0</td>
<td>32/416 7.7</td>
<td>1.00 (0.63 - 1.72)</td>
<td>0.87</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>11/1,858 0.6</td>
<td>13/1,896 0.7</td>
<td>0.83 (0.39 - 1.93)</td>
<td>0.72</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>38/68,129 0.1</td>
<td>35/66,865 0.1</td>
<td>1.11 (0.67 - 1.69)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: birth weight percentile, GA at delivery

SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; CI, confidence interval
Table 4. Perinatal death in males and females

<table>
<thead>
<tr>
<th>Birth weight &lt;p10 (SGA)</th>
<th>Male infants</th>
<th>Female infants</th>
<th>unadjusted</th>
<th>adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-32 weeks GA</td>
<td>615/1,023 60.2</td>
<td>493/734 67.2</td>
<td>0.74 (0.60 - 0.90) 0.003</td>
<td>0.75 (0.59 - 0.96) 0.02</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>337/3,626 9.3</td>
<td>240/2,939 8.2</td>
<td>1.15 (0.97 - 1.37) 0.11</td>
<td>1.06 (0.89 - 1.27) 0.53</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>528/55,918 0.9</td>
<td>453/54,695 0.8</td>
<td>1.14 (1.01 - 1.30) 0.04</td>
<td>1.12 (0.98 - 1.27) 0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birthweight p10-p90 (AGA)</th>
<th>Male infants</th>
<th>Female infants</th>
<th>unadjusted</th>
<th>adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-32 weeks GA</td>
<td>835/4,201 19.9</td>
<td>771/3,385 22.8</td>
<td>0.84 (0.75 - 0.94) 0.002</td>
<td>0.87 (0.77 - 0.98) 0.02</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>626/30,735 2.0</td>
<td>540/24,190 2.2</td>
<td>0.91 (0.81 - 1.02) 0.11</td>
<td>0.89 (0.79 - 1.00) 0.052</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>1,088/500,068 0.2</td>
<td>1043/478,140 0.2</td>
<td>1.00 (0.92 - 1.09) 0.95</td>
<td>0.99 (0.91 - 1.08) 0.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth weight ≥p90 (LGA)</th>
<th>Male infants</th>
<th>Female infants</th>
<th>unadjusted</th>
<th>adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-32 weeks GA</td>
<td>82/425 19.3</td>
<td>87/416 20.9</td>
<td>0.90 (0.65 - 1.27) 0.56</td>
<td>0.94 (0.66 - 1.34) 0.74</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>38/1,858 2.1</td>
<td>32/1,896 1.6</td>
<td>1.30 (0.80 - 2.11) 0.29</td>
<td>1.22 (0.75 - 2.00) 0.42</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>144/68,129 0.2</td>
<td>129/66,865 0.2</td>
<td>1.10 (0.86 - 1.39) 0.45</td>
<td>1.08 (0.85 - 1.38) 0.50</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: birth weight percentile, GA at delivery
SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; CI, confidence interval

Table 5. Neonatal morbidity* in males and females

<table>
<thead>
<tr>
<th>Birth weight &lt;p10 (SGA)</th>
<th>Male infants</th>
<th>Female infants</th>
<th>unadjusted</th>
<th>adjusted**</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-31 weeks GA</td>
<td>340/1,023 33.2</td>
<td>190/734 25.9</td>
<td>1.43 (1.15 - 1.76) &lt;0.001</td>
<td>1.44 (1.15 - 1.81) 0.002</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>284/3,626 7.8</td>
<td>188/2,939 6.4</td>
<td>1.25 (1.03 - 1.51) 0.03</td>
<td>1.13 (0.93 - 1.38) 0.22</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>434/55,918 0.8</td>
<td>382/54,695 0.7</td>
<td>1.11 (0.97 - 1.28) 0.13</td>
<td>1.11 (0.97 - 1.27) 0.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birthweight p10-p90 (AGA)</th>
<th>Male infants</th>
<th>Female infants</th>
<th>unadjusted</th>
<th>adjusted**</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-31 weeks GA</td>
<td>2,412/4,201 57.4</td>
<td>1,747/3,385 51.6</td>
<td>1.25 (1.15 - 1.39) &lt;0.001</td>
<td>1.26 (1.15 - 1.38) &lt;0.001</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>2,125/30,735 6.9</td>
<td>1,355/24,190 5.6</td>
<td>1.25 (1.17 - 1.34) &lt;0.001</td>
<td>1.23 (1.15 - 1.33) &lt;0.001</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>2,619/500,068 0.5</td>
<td>1,847/478,140 0.4</td>
<td>1.43 (1.28 - 1.44) &lt;0.001</td>
<td>1.36 (1.28 - 1.44) &lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth weight ≥p90 (LGA)</th>
<th>Male infants</th>
<th>Female infants</th>
<th>unadjusted</th>
<th>adjusted**</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-31 weeks GA</td>
<td>228/425 19.3</td>
<td>211/416 20.9</td>
<td>1.11 (0.86 - 1.47) 0.40</td>
<td>1.13 (0.86 - 1.49) 0.39</td>
</tr>
<tr>
<td>32-36 weeks GA</td>
<td>155/1,858 2.1</td>
<td>111/1,896 1.6</td>
<td>1.43 (1.14 - 1.89) &lt;0.001</td>
<td>1.45 (1.11 - 1.89) 0.007</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>358/68,129 0.2</td>
<td>294/66,865 0.2</td>
<td>1.25 (1.10 - 1.43) &lt;0.001</td>
<td>1.25 (1.10 - 1.43) &lt;0.001</td>
</tr>
</tbody>
</table>

* Neonatal morbidity consists of: Sepsis, infant respiratory distress syndrome, meconium aspiration, intra-ventricular hemorrhage
**Odds ratios are adjusted for: birth weight percentile, GA at delivery
SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; CI, confidence interval
Also, we used population based birth weight percentiles. Individual growth potential and placental characteristics might have enabled more accurate prediction of growth restriction and adverse outcome.\textsuperscript{19,20} We were not able to correct for this because maternal length and weight, and placental weight and pathology are not registered in the Dutch Perinatal Registry. Therefore the Dutch reference curves for birth weight by gestational age separate for parity, sex and ethnic background were used.\textsuperscript{17} To avoid bias through ethnic difference and anomalous fetuses, only Caucasian women with a singleton pregnancy were included and all infants with congenital anomalies were excluded. We do not expect a systematical sex based bias.

Finally, the PRN database does not contain data on how pregnancy dating is performed. Until 2011, no uniform pregnancy dating was performed in the Netherlands. Historically, it was common practice to date pregnancies based on LMP. Since the 1980s the use of ultrasound was gradually introduced in obstetric care. During our study period CRL and HC measurements had already increasingly replaced LMP for dating, but no quantitative data are available on how pregnancy was dated in individual cases. However, it is unlikely that a systematic bias was caused by sex differences in pregnancy dating.

\textbf{Strengths}

The main strength of this study is the size (1,299,244 pregnancies) and composition of the cohort (only Caucasians with a singleton without congenital anomalies). Cohorts of all previous studies were smaller (549\textsuperscript{10} up to 469,152\textsuperscript{20} pregnancies) and often included anomalous fetuses and/or twins. The proportion of male infants, the incidence of fetal deaths, neonatal deaths, perinatal deaths and composite morbidity that we found in this study, are in accordance with previous research.\textsuperscript{6,13,21-25} Data are derived from a large, well-maintained population-based national perinatal registry (1999-2007). The vast majority of the caregivers contribute to the PRN registry; therefore, it comprises approximately 96\% of all pregnancy and birth characteristics in The Netherlands. The 4\% missing birth data are due to 1-2\% non-reporting general practitioners and 2-3\% non-reporting midwives.

Another strength is the fact that - in contrast to previous studies - outcomes were adjusted for birth weight percentile and gestational age at delivery. Combined with the use of population-based growth curves for Caucasians, separate for sex and parity, we were able to compare infants with the same birth weight percentiles and gestational ages. As a result, the outcomes solely represent the influence of sex on the outcomes of interest.

Finally, this is to our knowledge the first study that tested for interaction and consequently performed analyses stratified for gestational age at delivery and birth weight percentile.

\textbf{Interpretation of the results}

Previous studies showed increased fetal death, neonatal death and neonatal morbidity in males compared to females.\textsuperscript{9-13} These higher adverse outcome rates might be caused by the increased risk of preterm delivery in males,\textsuperscript{2,8} adjustment for absolute birth weight instead of birth weight percentile, and calculation of male/female-ratios of adverse outcome that were not adjusted for differences in total number of male and female infants born. After adjustment for confounding factors, we found - in most groups - no difference in fetal death, neonatal death and perinatal death between males and females. This study confirms an increased risk of neonatal morbidity in males.\textsuperscript{13}

The differences between subgroups help us identify and exclude possible mechanisms that underlie differences between males and females. Higher prenatal death among females and lower
neonatal death among males in extremely preterm infants (25<sup>th</sup> to 31<sup>st</sup> weeks) might result from management decisions based on ultrasound fetal weight estimation. Guidelines advice taking gestational age and estimated fetal weight into account when deciding upon optimal perinatal management. During the study period, it was common practice to base decisions of intervening in pregnancy and the decision for active neonatal resuscitation was based on a minimum (estimated) fetal weight of 500 grams. Since males are on average heavier than females, this management could have led to active management - cesarean sections and neonatal support - in males more often than in females. This might have reduced fetal and neonatal death in these males at the expense of higher neonatal morbidity. Simultaneously, the fact that more often non-active management was chosen in female pregnancies might have led to increased fetal death due to placental insufficiency - because no caesarean section was performed in case of fetal distress and EFW <500 grams - and to lower neonatal death and neonatal morbidity because severe SGA females die in utero more often than males.

The excess composite morbidity among AGA (p10-90) males at all gestational ages does not result in increased death before 28 days after birth. However, it remains unsure what effect this has on the - one-year - neonatal death and long-term health outcomes in males. Moreover, the causes of the higher risk of adverse outcome in males after the onset of delivery compared to females remains unsure and further research is needed to elucidate this.

We did not include mode of delivery into the multivariable regression model because induced and instrumental deliveries are often a result of suspected compromised fetal condition rather than a confounder of adverse outcome. Including mode of delivery in the regression model would possibly introduce a systematic bias at the expense of females, who had in this study lower rates of induced deliveries, caesarean sections, and instrumental vaginal deliveries. The increased instrumental delivery rates among males (26.7%) compared to females (23.4%) might have prevented even higher rates of neonatal deaths and adverse outcome among males. However, we cannot exclude that the instrumental deliveries caused rather than prevented neonatal morbidity.

**Implications**

The results of this study matter because they contradict results from previous studies, which may have led to the erroneous idea that males are doing worse than females in terms of fetal and neonatal death. The main implication of this study is that in prenatal counseling, males and females with a certain birth weight percentile for gestation have comparable risks of fetal and neonatal death. We think that using birth weight percentiles enables easier and more uniform risk assessment to decide upon management, also in extremely preterm infants.

**Unanswered questions; proposals for future research**

Future research should aim at unraveling mechanisms that might play a role in the increased neonatal morbidity in males, in order to find out if measures can be taken to decrease neonatal morbidity in males.
References


(14) Meray N, Reitsma JB, Ravelli ACJ, Bonsel GJ. Probabilistic record linkage is a valid and transparent tool to combine databases without a patient identification number. Journal of Clinical Epidemiology 2007; 60(9):883-891.


Chapter 5

Birth weight ratio as an alternative to birth weight percentile to express infant weight in research and clinical practice: a nationwide cohort study

Bart Jan Voskamp, Brenda M Kazemier, Ewoud Schuit, Ben Willem J Mol, Eva Pajkrt, Wessel Ganzvoort

Submitted
Abstract

Objective: To compare birth-weight-ratio and birth-weight-percentile to express infant weight when assessing pregnancy outcome.

Study design: We performed a cohort study using the Netherlands Perinatal Registry. The study population comprised all Caucasian women who delivered a singleton between 25\textsuperscript{th} and 42\textsuperscript{nd} weeks gestation (1999 to 2007). Fetuses with structural or chromosomal abnormalities were excluded. The Dutch reference curves stratified by sex and parity were used to determine birth weight percentiles. Birth weight ratio was calculated as the observed birth weight divided by the median birth weight for gestational age. The discriminative ability of birth weight ratio and birth weight percentile to identify infants at risk of perinatal death (fetal death and neonatal death) or adverse pregnancy outcome (composite measure of: perinatal death and severe neonatal morbidity) were compared using the area under the curve. Outcomes were expressed stratified by gestational age at delivery separate for birth weight ratio and birth weight percentile.

Results: We studied 1,299,244 pregnant women, with an overall perinatal death rate of 0.62%. Birth weight ratio and birth weight percentile have equivalent overall discriminative performance for perinatal death and adverse perinatal outcome. In late preterm infants (33\textsuperscript{rd}-36\textsuperscript{th} weeks), birth weight ratio has better discriminative ability than birth weight percentile for perinatal death (0.68 vs. 0.63, p<0.01) or adverse pregnancy outcome (0.67 vs. 0.60, p<0.001).

Conclusion: Birth-weight-ratio is a potentially valuable instrument to identify infants at risk of perinatal death and adverse pregnancy outcome and provides several advantages for use in research and clinical practice. Moreover, it allows comparison of groups with different average birth weights.
Introduction

Gestational age at delivery and birth weight are considered important predictors of adverse pregnancy outcome.\textsuperscript{1,2} Accurate assessment of fetal growth in relation to gestational age is therefore an important tool for risk assessment in antenatal care.

Fetal and growth is usually expressed in percentiles. Birth weight percentile curves are calculated from cross-sectional data of newborns.\textsuperscript{3} Thus, birth weight percentiles (BWpercentiles) indicate the value (e.g. 10%) below which a certain percentage of the observations in a group of newborns (10%) can be found. BWpercentiles are often dichotomized, and small for gestational age (SGA) is commonly defined as birth weight below the 10\textsuperscript{th}, 5\textsuperscript{th} or 2.3\textsuperscript{rd} percentile for gestational age in a population-specific reference growth curve.\textsuperscript{4,5} The BWpercentile tells us if an infant belongs to a certain part of the percentile distribution, but does not contain any information about the absolute deviation of infant weight from the median birth weight for gestation. As a result, percentiles do not allow comparison of growth between groups with different growth characteristics (for example: different sexes or ethnicities). Moreover, at the tails of the normal distribution (e.g. at the 2\textsuperscript{nd} percentile), a percentile contains a much wider range of absolute birth weights than close to the median (e.g. at the 50\textsuperscript{th} percentile). Consequently, the use of percentiles and their dichotomization may lead to loss of information that may be useful for patient care and parental counseling.

Birth weight ratio (BW\textit{ratio}) is an alternative method to express growth of an individual with respect to the median. It is defined as the ratio of observed birth weight divided by the median birth weight of the population-specific reference growth curve. Values above 1 indicate ‘larger for gestational age than the median’ and values below 1 indicate ‘smaller for gestational age than the median’. It may offer a solution to the limitations associated with BWpercentiles.

Our objective was to compare BW\textit{ratio} and BWpercentile to express infant growth when assessing pregnancy outcome.

Methods

\textbf{Dataset}

This study was performed using a nationwide cohort using data from The Netherlands Perinatal Registry (PRN). The PRN consists of population-based data on pregnancies, deliveries, neonatal characteristics, and re-admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of newborn neonates.\textsuperscript{6,7} Records are entered in the PRN registry at the child’s level. The coverage of the PRN registry is approximately 96\% of all deliveries in The Netherlands. It contains pregnancies of ≥ 22 weeks’ gestation and a birth weight of ≥500 g and is used primarily for an annual assessment of the quality indicators of obstetric care.

\textbf{Ethical approval}

The data in the perinatal registry are anonymous; therefore ethical approval was not needed. The Dutch Perinatal Registry gave their approval to use their data for this study (approval number 13.72).
Inclusion and exclusion criteria
We included all Caucasian women who delivered a singleton between 25\(^{\text{rd}}\) and 42\(^{\text{nd}}\) weeks gestation in the Netherlands between January 1, 1999, and December 31, 2007. All cases with congenital anomalies were excluded.\(^8\)

Outcome measures
Outcome measures were perinatal death and a composite of perinatal death and neonatal morbidity. Perinatal death was defined as the sum of intra-uterine fetal death (diagnosed after 25\(^{\text{rd}}\) weeks GA) and neonatal death (until 28 days after birth). The composite of adverse pregnancy outcome consisted of: perinatal death, respiratory distress syndrome (RDS), sepsis, necrotizing enterocolitis (NEC), meconium aspiration, and intraventricular hemorrhage (IVH) within the first month of birth. If an infant suffered from neonatal morbidity and died within 28 days after birth, it was only considered as perinatal death in the analyses.

The Dutch reference curves for birth weight by gestational age stratified for parity, sex and ethnic background were used.\(^9\) Pregnancy dating was performed using last menstrual period (LMP), or by ultrasound measurements before 20 weeks of gestation (crown-rump-length (CRL) or head-circumference (HC) measurement).

We defined SGA as birth weight below the 10\(^{\text{th}}\) or 5\(^{\text{th}}\) percentile for gestation. To obtain the best possible comparability with SGA, low BWRatio cut-off values of 0.85 and 0.80 were chosen such that (after rounding them to the closest 0.05 value) they resulted in equally large groups of low-BWRatio-infants in the whole population as with the 10\(^{\text{th}}\) and 5\(^{\text{th}}\) birth weight percentiles.

We defined LGA as birth weight above the 90\(^{\text{th}}\) or 95\(^{\text{th}}\) percentile for gestation. To obtain the best possible comparability with LGA, high BWRatio cut-off values 1.25 and 1.30 were chosen such that (after rounding them to the closest 0.05 value) they resulted in groups of high-BWRatio-infants in the whole population that correspond best with the 90\(^{\text{th}}\) and 95\(^{\text{th}}\) birth weight percentiles.

Population characteristic and clinical characteristics
We registered demographic and obstetric characteristics including maternal age, parity and socio-economic status (SES).\(^10\) Parity was categorized into 0 (first birth), 1 (second birth) and 2+ (third or higher birth).

Statistics
Baseline characteristics were described and presented as means with standard deviations (SD), median with range or as percentages as appropriate.

We tested for interaction between BWRatio and GA at delivery as well as BWpercentile and GA at delivery. These tests were performed separately for the two outcome measures. If statistically significant (p<0.05), analyses were performed stratified for gestational age at delivery in four categories according to the WHO criteria; extremely preterm (24\(^{\text{rd}}\)-27\(^{\text{nd}}\) weeks’ gestation), very preterm (28\(^{\text{nd}}\)-32\(^{\text{nd}}\) weeks’ gestation), moderate to late preterm (33\(^{\text{rd}}\)-36\(^{\text{rd}}\) weeks’ gestation) and term delivery (37\(^{\text{rd}}\)-42\(^{\text{nd}}\) weeks’ gestation).\(^11\)

We plotted distributions of perinatal death and adverse pregnancy outcome for BWRatio and BWpercentile. In addition distributions of perinatal death and adverse pregnancy outcome stratified for gestational age at delivery for BWRatio and BWpercentile were plotted.

We also calculated – separate for BWRatio and BWpercentile and four strata of gestational age at birth – the population-attributable risk (PAR) of abnormal fetal growth for perinatal death and adverse pregnancy outcome. PAR was based on the prevalence (P) of abnormal growth and the
relative risk (RR) of perinatal death and adverse pregnancy outcome in abnormally grown (low BWratio, SGA) and normally grown infants: PAR % = [P*(RR-1)/(P*(RR-1)+1)]*100.12

Finally, receiver operator characteristics (ROC) curves were constructed for the whole cohort and for abnormally grown infants only, to compare discriminative ability of birth weight ratio and birth weight percentile for our outcome measures (perinatal death and adverse pregnancy outcome) in the four gestational categories. All statistical tests were 2-sided; a probability value of 0.05 was chosen as the threshold for statistical significance.

The data were analyzed with the SAS statistical software package (version 9.2; SAS Institute Inc., Cary, NC).

Results

From January 1, 1999 until December 31, 2007 a total of 1,636,565 pregnancies were registered in the PRN database. We excluded cases that were non-Caucasian (n=258,908 (15.82%)), Multiple pregnancies (n=63,857 (3.90%)), infants with congenital anomalies (n=22,043 (1.35%)), and infants born before 25\textsuperscript{*} weeks or after 42\textsuperscript{*} weeks GA (n=6,967 (0.43%)). After application of the inclusion and exclusion criteria the study population consisted of 1,299,244 pregnancies. Baseline characteristics of the population are shown in table 1.

**Table 1.** Characteristics of the 1,299,244 pregnancies in the Netherlands, 1999-2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=1,299,244)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Maternal age, mean (SD)</td>
<td>30.7 (4.58)</td>
</tr>
<tr>
<td>Nulliparous, %</td>
<td>47.5</td>
</tr>
<tr>
<td>Low socio-economic status, %</td>
<td>18.9</td>
</tr>
<tr>
<td>Boys</td>
<td>51.3</td>
</tr>
<tr>
<td><strong>Pregnancy and delivery</strong></td>
<td></td>
</tr>
<tr>
<td>Induction of labor, %</td>
<td>35.3</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>14.3</td>
</tr>
<tr>
<td>Elective cesarean section %</td>
<td>6.2</td>
</tr>
<tr>
<td>Emergency cesarean section %</td>
<td>11.3</td>
</tr>
<tr>
<td>Vaginal instrumental delivery</td>
<td>12.4</td>
</tr>
<tr>
<td><strong>Neonatal characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery (weeks), median (IQR)</td>
<td>39.2 (1.86)</td>
</tr>
<tr>
<td>Extremely premature (GA &lt;29\textsuperscript{*0} weeks), n (%)</td>
<td>4,048 (0.3)</td>
</tr>
<tr>
<td>Very premature (GA &lt;33\textsuperscript{*0} weeks), n (%)</td>
<td>13,885 (1.1)</td>
</tr>
<tr>
<td>Mild premature (GA &lt;37\textsuperscript{*0} weeks), n (%)</td>
<td>75,429 (5.81)</td>
</tr>
</tbody>
</table>

SD, standard deviation

Distribution of cases

The distribution of birth weight ratios and birth weight percentiles for four strata of gestational age at birth are shown in figure 1a and 1b. Figure 1a shows that most infants are born with a BWratio around one, and that both higher and lower BWratios are less common. Moreover, 80% of cases had
a BW ratio between 0.85 and 1.25. These infants occupy approximately one third of the width of the graph, while the low BW ratio and high BW ratio infants occupy the remaining two thirds. Hence, the spread in BW ratio is much larger in the extremes of the birth weight ratio distribution than when using birth weight percentiles. These characteristics of BW ratio distributions make it possible to better distinguish between different degrees of low BW ratios and high BW ratios.

Figure 1b contains the distribution of birth weight percentiles and shows that the population is cut into 100 (approximately) equal parts. As a result, any given percentile always contains about 1% of the population. Consequently, the central 80% of the graph represents 80% of the population, while this only corresponds to approximately one third of the BW ratio distribution. Whereas SGA and LGA infants (20% of the population), logically cover 20% of the percentile distribution, while this group represents the remaining two thirds of the BW ratio distribution.

Figure 1a also shows that the BW ratio of late premature (33\textsuperscript{0}-36\textsuperscript{6} weeks gestation) and term (37\textsuperscript{0}-42\textsuperscript{6} weeks) infants is normally distributed. Distribution of the birth weight ratio of extremely premature (25\textsuperscript{0}-28\textsuperscript{6} weeks gestation) or very premature (29\textsuperscript{0}-32\textsuperscript{6} weeks gestation) is negatively skewed.

**Figure 1.** The incidence of birth weight ratios and birth weight percentiles for four strata of gestational age at birth separate for birth weight ratio (A) and birth weight percentiles (B).

Incidence (%)

![Graph showing birth weight ratios and percentiles for different gestational ages](image)

**Incidence of abnormal growth**

The lines in figure 1a suggest higher rates of low BW ratios and high BW ratios among infants that are born preterm. At term (37-42 weeks GA), 9.67% [118,331/1,223,815] of infants are born with a BW ratio <0.85. In the preterm period the incidences are significantly higher (p<0.001) than in the term group: 17.04% [10,487/61,544] (33-36 weeks), 25.73% [2,531/9,837] (29-32 weeks) and 37.8% [1,530/4,084] (25-28 weeks) respectively.

At term (37-42 weeks GA), 6.64% [81,312/1,223,815] of infants are born with a high BW ratio (>1.25). In the preterm period, the incidences are significantly higher (p<0.001) than in the term group: 8.43% [5,188/61,544] (33-36 weeks), 18.39% [1,809/9,837] (29-32 weeks) and 16.48% [667/4,084] (25-28 weeks), respectively.

These findings confirm the presence of an association between prematurity and the incidence of abnormal growth (BW ratio <0.85 as well as BW ratio >1.25).\textsuperscript{13-15}
Perinatal death and composite morbidity

Incidences of perinatal death and adverse pregnancy outcome are shown in figure 2 and 3. Incidences are shown separate for four strata of gestational age at birth, by birth weight ratios (fig.2a and 3a) and birth weight percentiles (fig.2b and 3b).

Comparison of mortality rates in figure 2a and 2b shows that especially in the late preterm period (33-36 weeks) and at term (37-42 weeks), birth weight ratio allows more accurate differentiation between different SGA grades than birth weight percentiles. This is illustrated by figure 2. Although it seems in figure 2b that perinatal death between 33 and 36 weeks gestation does not rise above 10% in infants with a birth weight at the 15% percentile, figure 2a shows that perinatal death rate rises until over 40%, depending on the severity of growth restriction.

On the other side of the growth spectrum, birth weight ratio also allows more precise differentiation between different severities of LGA.

Both birth weight ratio and birth weight percentile show a gestation related death rate in the normal range (BWRatio 0.85-1.25 and p10-p90, respectively) with higher death rates towards both ends of the growth spectrum. The same effects at the ends of the growth spectrum were found for adverse pregnancy outcome (Figure 3a and 3b).

Population-attributive risk of abnormal growth for death and adverse pregnancy outcome

The percentage of perinatal death and adverse pregnancy outcome that can be attributed to abnormal growth depends on gestational age at delivery, on whether abnormal growth is defined by BWRatio (low-/high-BWRatio) or BWpercentile (SGA/LGA), and on the cut-off value that is used. PAR of abnormal fetal growth for perinatal death at different gestational ages are shown in table 2. Depending on gestation and on the definition of abnormal growth, 14–35% of perinatal death and 2–13% of adverse pregnancy outcome can be attributed to abnormal growth.

<table>
<thead>
<tr>
<th>Table 2. Population-attributive risk of abnormal fetal growth, for four definitions of abnormal growth by birth weight ratio and birth weight percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Population-attributive risk percentage (PAR%)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Birth weight ratio</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>&lt;0.80</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>25th-26th weeks</td>
</tr>
<tr>
<td>Perinatal Death</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
</tr>
<tr>
<td>29th-32nd weeks</td>
</tr>
<tr>
<td>Perinatal Death</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
</tr>
<tr>
<td>33rd-36th weeks</td>
</tr>
<tr>
<td>Perinatal Death</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
</tr>
<tr>
<td>37th-42nd weeks</td>
</tr>
<tr>
<td>Perinatal Death</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
</tr>
</tbody>
</table>

The population-attributive risk of abnormal growth is higher for death than for adverse pregnancy outcome, which means that a larger percentage of perinatal deaths than adverse pregnancy
outcome can be attributed to abnormal growth. PAR of suboptimal growth for perinatal death is small in extremely premature infants, increases with advancing gestational age with a peak in late preterm infants (33-36 weeks) and decrease at term.

Also, PAR of abnormal growth - for example for perinatal death at term - is higher if less stringent cut-off values to define abnormal growth are chosen (e.g. the 10th percentile instead of the 5th percentile, 22% vs. 17%).

**Discriminative ability of birth weight ratio and birth weight percentile**

The areas under the receiver operator characteristics curves are shown in Table 3. When assessing the complete growth spectrum, there were no differences in areas under the curve (AUC) between birth weight ratio and birth weight percentile to distinguish between those with and without perinatal death in extremely preterm, very preterm, late preterm and term infants. Accordingly, the discriminative ability of birth weight ratio and birth weight percentile for our composite adverse pregnancy outcome did not differ at any gestational age either. The discriminative ability of both methods for death was poor to fair (range 0.64-0.73), and the discriminative ability for adverse pregnancy outcome was bad to poor (range 0.55-0.65).16

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Birth weight ratio</th>
<th>Birth weight percentile</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>25th-28th weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal Death</td>
<td>0.73</td>
<td>0.73</td>
<td>0.78</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
<td>0.65</td>
<td>0.65</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>29th-32th weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal Death</td>
<td>0.65</td>
<td>0.65</td>
<td>0.88</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
<td>0.56</td>
<td>0.56</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>33rd-36th weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal Death</td>
<td>0.70</td>
<td>0.69</td>
<td>0.69</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
<td>0.56</td>
<td>0.56</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>37th-42th weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal Death</td>
<td>0.64</td>
<td>0.64</td>
<td>0.77</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
<td>0.55</td>
<td>0.55</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 4 shows that if only SGA cases (birth weight below the 10th percentile) were assessed, the discriminative ability of BWratio was better than that of BWpercentile for death in the late preterm period (33rd-36th weeks) (0.68 vs. 0.63, p<0.01) and at term (0.69 vs. 0.67, p<0.05). The discriminative ability of BWratio was also better than that of BWpercentile for adverse pregnancy outcome in the late preterm period (33rd-36th weeks) (0.67 vs. 0.60, p<0.001).
Table 4. Discriminative ability of birth weight ratio and birth weight percentile in case of birth weight below the 10th percentile for gestational age

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>25th-28th weeks</th>
<th>29th-32nd weeks</th>
<th>33rd-36th weeks</th>
<th>37th-42nd weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birth weight ratio</td>
<td>Birth weight percentile</td>
<td>P-value</td>
<td>Birth weight ratio</td>
</tr>
<tr>
<td>Perinatal Death</td>
<td>0.70</td>
<td>0.76</td>
<td>0.09</td>
<td>0.69</td>
</tr>
<tr>
<td>Composite adverse outcome</td>
<td>0.61</td>
<td>0.63</td>
<td>0.75</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Discussion

Discriminative ability of BWRatio for perinatal death or adverse pregnancy outcome is comparable to that of birth weight percentile. Birth weight ratio is - for smaller and larger than average infants - a more discriminative instrument for perinatal death and adverse pregnancy outcome than birth weight percentile.

Our findings confirm an association between abnormal fetal growth and premature delivery, and our data show that approximately one out of five perinatal deaths can be attributed to being SGA.

Limitations

Some limitations need to be addressed. First, a possible limitation is related to the use population based birth weight percentiles. Although there exists no unanimity about the question whether references should be based on population birth weight characteristics, or on individual growth potential, the latter might have better discriminative ability for adverse outcome, both with BWratios and BWpercentiles. We were not able to use customized growth curves because maternal length and weight, and placental weight and pathology are not registered in the Dutch Perinatal Registry. Therefore the Dutch reference curves for birth weight by gestational age separate for parity, sex and ethnic background were used. We think however that not being able to use customized growth curves was only a minor limitation, because the concepts put forward in this paper can also be applied if growth is expressed using customized charts.
Figure 2. Incidences of perinatal death stratified by gestational age at delivery separate for birth weight ratio (A) and birth weight percentiles (B).

- **Perinatal death**
  - **Incidence (%)**
  - **A**
    - low-BWratio
    - high-BWratio
  - **B**
    - SGA
    - 25-28 wks
    - 29-32 wks
    - 33-36 wks
    - 37-42 wks
    - LGA
Figure 3. Incidences of adverse perinatal outcome stratified by gestational age at delivery separate for birth weight ratio (A) and birth weight percentiles (B).
Second, the PRN database does not contain data on how pregnancy dating is performed. Until 2011, no uniform pregnancy dating was performed in the Netherlands. Historically, it was common practice to date pregnancies based on LMP. Since the 1980’s the use of ultrasound was gradually introduced in obstetric care. During our study period Crown Rump Length and Head Circumference measurements had already increasingly replaced LMP for dating, but no quantitative data are available on how pregnancy was dated in individual cases. However, it is unlikely that a systematic bias was caused by gender differences in pregnancy dating.

Strengths
The main strength of this study is the size (1,299,244 pregnancies) and composition (only Caucasians with a singleton without congenital anomalies) of the cohort. The incidence of fetal deaths, neonatal deaths, perinatal deaths and composite morbidity that we found in this study, are in accordance with previous research.24-29 There is no reason to suspect a systematical gender or parity based bias. The concepts discussed in this paper can be used to assess distribution of growth and risk of abnormal growth and its relation to pregnancy outcome in other populations.

Data are derived from a large, well-maintained population-based national perinatal registry (1999-2007). The vast majority of the caregivers contribute to the PRN registry; therefore, it comprises approximately 96% of all pregnancy and birth characteristics in The Netherlands. The 4% missing birth data are due to 1-2% non-reporting general practitioners and 2-3% non-reporting midwives. The use of population-based growth curves for Caucasians, separate for gender and parity, minimizes risk of systematic bias caused by one of these factors.

Finally, this is to our knowledge the first study that compared birth weight ratio and birth weight percentiles using ROC curves. This allowed us to statistically substantiate our findings.

Interpretation of the results
As shown in figure 1b, only a distribution based on BWRatio tells us how growth is distributed within a population. It shows that most infants are born with a birth weight ratio of around one, and incidences of BWRatios decrease towards both ends of the distribution.

This study confirms that preterm delivery is associated with increased SGA and LGA rates as compared to term delivery,14,15 and that the relation between fetal growth and the risk of adverse pregnancy outcome also depends on gestational age at delivery. This means that the relative risk of adverse outcome for an infant with a certain BWRatio or BWpercentile at 30 weeks gestation is not the same as that at 40 weeks gestation.

The results also show that birth weight ratios are not normally distributed in infants that are delivered extremely- or very preterm (25-32 weeks) (figure 1a). Percentiles are only suitable for use in a normally distributed population and are therefore less suitable to express growth in premature and extremely premature infants.

Finally, birth weight ratio allows comparison of groups with different average weights and weight distributions, for example male infants and female infants or infants of different ethnic origins. Percentiles and ratios both allow comparison of groups, but - as explained before - information on distance from the mean and the incidence of different ratios within a population is lost when percentiles are used.

The different representation of growth with BWRatio and BWpercentile that is explained above has two effects that result in better interpretability of infant growth when BWRatio is used.
First, the use of BWpercentile causes a loss of discriminative power, especially among SGA and LGA infants. For example, all infants with birthweight <1st percentile (1% of the population and BWpercentile distribution), cover about 10% of the BWratio distribution, thus allowing better differentiation within this group of small infants with BWratio.

Second, birth weight percentiles suggest that an infant (born at term) with a birth weight at the 25th percentile is much lighter than an infant at the 75th percentile. However, this is not the case. The birth weight ratios in this example are 0.9 (25th percentile) and 1.1 (75th percentile) and are both very close to 1.0. The seemingly large difference if growth is expressed in percentiles is caused by the fact that a population is by definition divided into 100 equally large groups instead of groups based on birth weight in relation to the median and that most infants have a birth weight close to the median.

There are two reasons for the fact that neither BWpercentile nor BWratio has high sensitivity and specificity for death and adverse outcome, and that only a limited proportion of death and adverse outcome can be attributed to fetal growth below the 10th percentile.

First, unlike other tests, increased risk of death (or adverse outcome) is not associated with a one-directional change in the risk factor (birth weight ratio or percentile). Both low and high birth weight ratios (or percentiles) are associated with increased risk of death (or adverse outcome).

Second, both death and adverse outcome occur at all gestational ages, and across the whole growth spectrum. There seems to be a gestational age related basic risk (horizontal part of the line) with increased death and adverse outcome rates at both ends of the growth spectrum.

Implications
In view of the results we think that BWratio could complement BWpercentiles in clinical practice and can play a role in scientific research. It allows differentiation of SGA infants that is not possible with BWpercentile, it is easy to understand and therefore useful for patient counseling. It also enables comparison of populations with different baseline characteristics.

Finally, this study shows the need to redefine cut-off values that define abnormal fetal growth. Historically, these cut-off values have been set at the 2.5th, 5th and 10th percentile. However, this study shows that the relation between fetal growth and the risk of adverse pregnancy outcome differs depending on gestational age at delivery. Therefore, future research should focus on defining cut-off values to identify infants at risk of clinically relevant poor growth. To do this, consequences of abnormal growth should be weighed against potential treatment benefit of early detection and intervention, also taking into account costs of follow-up and potential adverse effects of interventions. Given the potentially better associations with adverse pregnancy outcome, such research should be performed using customized weight percentiles.
References


(12) Miettinen O.S. Proportion of disease caused or prevented by a given exposure, trait or intervention. American Journal of Epidemiology 1974; 85(12):737-744.


Chapter 6

Association between fetal sex and fetal growth, a nationwide cohort study

Bart Jan Voskamp, Brenda M Kazemier, Myrthe JCS Peelen, Ben Willem J Mol,
Eva Pajkrt, Wessel Ganzevoort

Submitted
Abstract

**Objective:** Male sex seems to be associated with adverse pregnancy outcome. The aim of this study was to evaluate if fetal sex is associated with abnormal fetal growth, and whether this relation is influenced by gestational age at delivery.

**Study design:** We performed a cohort study using The Netherlands Perinatal Registry. The study population comprised all Caucasian women who delivered a singleton baby between 25^{10} and 42^{6} weeks gestation (1999 to 2007). Fetuses with structural or chromosomal abnormalities were excluded. We expressed growth using the birth-weight-ratio, which is calculated as the observed birth weight divided by the median birth weight for gestational age, stratified by sex and parity. Our main outcome was abnormal fetal growth, defined as a low birth-weight-ratio (<0.85). Incidences of birth-weight-ratios were compared between males and females separate for four strata of GA at delivery. Logistic regression analyses were performed to compare fetal growth between males and females at different gestational ages.

**Results:** We studied 1,299,244 pregnancies. The overall incidence of birth-weight-ratios <0.85 was 10.21% among males and 10.25% among females. Males were as likely as females to have a birth-weight-ratio <0.85 when born before 33^{10} weeks (25^{10}-28^{6} weeks: Odds Ratio (OR) 0.91, 95% confidence interval (CI) 0.80-1.03, and 29^{10}-32^{6} weeks: OR 0.95, 95%CI 0.87-1.05), and slightly but significantly less likely than females to have a birth-weight-ratio <0.85 if born after 33^{10} weeks GA (33^{10}-36^{6} weeks: OR 0.96 95% CI 0.92-1.00 and 37^{10}-42^{6} weeks: OR 0.98, 95% CI 0.97-1.00).

**Conclusion:** Male fetuses are not at increased risk of having abnormal fetal growth as compared to female fetuses.
Introduction

There is an association between fetal sex and fetal growth\(^1\) with males being on average heavier than females. Associations between male sex and poor pregnancy outcome such as preterm birth,\(^2\) perinatal death and morbidity have been described in literature.\(^9\)–\(^12\) This may be explained by higher rates of spontaneous preterm delivery of males,\(^7\) and by the association between male sex and placental insufficiency and pre-eclampsia, although studies on this latter subject show conflicting results\(^13\)–\(^18\).

Another possible explanation of the described association of male sex with increased adverse pregnancy outcome is that a male at a given gestational age and with a certain birth weight is relatively more growth restricted than a female at the same gestational age with the same birth weight. Thus, the consequences for a small for gestational age (SGA) male may be larger than for a female with the same birth weight. In the search for possible explanations for higher adverse outcome rates in males, it has not yet been evaluated whether fetal sex is associated with abnormal fetal growth.

The aim of this study was to evaluate if fetal sex is associated with abnormal fetal growth, and whether this relation is influenced by gestational age at delivery.

Methods

**Dataset**

We performed a cohort study using data from the Netherlands Perinatal Registry (PRN). The PRN is a nationwide prospective registry with population-based data that contains information on pregnancies, deliveries, and re-admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of newborn neonates.\(^19\)–\(^20\) Records are entered in database at the level of the child at the moment of birth. The coverage of the PRN is approximately 96% of all deliveries in The Netherlands. It contains pregnancies of \(\geq 22\) weeks' gestation and a birth weight of \(\geq 500\) g and is used primarily for annual assessment of quality indicators in obstetric care.

**Ethical approval**

The data in the PRN are anonymous; therefore ethical approval was not needed for this study. The Dutch Perinatal Registry gave their approval for the use of their data for this study (approval number 13.71).

**Inclusion and exclusion criteria**

We included all Caucasian women who delivered a singleton baby between 25\(^{\circ}\) and 42\(^{\circ}\) weeks gestational age in The Netherlands between January 1, 1999, and December 31, 2007. In order to assess differences in a homogeneous population and to minimize the risk of biased results due to other factors than those associated with fetal sex, we excluded multiple pregnancies, non-Caucasian women and all cases with congenital anomalies\(^21\).

**Outcome measures**

Birth weight is usually expressed in percentiles. However, percentiles are not suitable to assess growth differences between males and females adequately because belonging to a certain percentile
only provides information about how many cases are smaller or larger than the median but provides no information about the absolute deviation from the median. Birth-weight-ratio, defined as the observed birth weight divided by the median birth weight for gestational age, is an alternative method to express growth of an individual with respect to the distribution in the population. It allows comparison of growth between sexes and quantitative assessment of how weight is distributed. Therefore, outcomes were presented by birth-weight-ratio. Values above 1 indicate ‘larger for gestational age than the median’ and values below 1 indicate ‘smaller for gestational age than the median’. The Dutch reference curves for birth weight by gestational age stratified for parity, sex and ethnic background were used.\textsuperscript{22} Pregnancy dating was performed by last menstrual period (LMP), or ultrasound measurements before 20 weeks of gestation (crown-rump-length (CRL) or head-circumference (HC) measurement).

Low birth-weight-ratio was defined as <0.85 and <0.80 and high birth-weight-ratio as >1.25 or >1.30. These birth-weight-ratio cut-off values were chosen because they are closest to the percentile cut-off values at term for SGA (<10\textsuperscript{th} and <5\textsuperscript{th} percentile) and large for gestational age (LGA) (>90\textsuperscript{th} and >95\textsuperscript{th} percentile), which are often used to identify pregnancies at risk of adverse pregnancy outcome.\textsuperscript{23,24} Our main outcome was a birth-weight-ratio <0.85. We also assessed if there were gender related differences in birth-weight-ratio <0.80 and -birth-weight-ratio >1.25 or >1.30.

**Population characteristic and clinical characteristics**

We obtained demographic and obstetric characteristics including maternal age, parity and socio-economic status (SES). Parity was categorized into 0 (first birth), 1 (second birth) and 2+ (third or higher birth). The SES score was based on mean income level, the percentage of households with a low income, the percentage of inhabitants without a paid job and the percentage of households with on average low education in a postal code area.\textsuperscript{30} The continuous SES score was categorized into a high, middle and low group based on percentile ranges (25th percentile, median, 75th percentile).

**Statistics**

We compared demographic and obstetric baseline characteristics between males and females using the Student t test and Chi-Square test as appropriate.

We then assessed the relationship between gestational age at delivery and birth-weight-ratio incidence for males and females using cumulative percentages of males and females born with a birth-weight-ratio <0.85, <0.80, >1.25 or >1.30.

We tested for interaction between sex and GA at delivery. If statistically significant (p<0.05), analyses were performed stratified in four groups based on GA at delivery (25\textsuperscript{th}-28\textsuperscript{th}, 29\textsuperscript{th}-32\textsuperscript{th}, 33\textsuperscript{rd}-36\textsuperscript{th} and 37\textsuperscript{rd}-42\textsuperscript{nd}).

Logistic regression analysis was performed to determine the association between fetal sex and fetal growth (birth-weight-ratio <0.85, <0.80, >1.25 or >1.30), expressed as odds ratios (OR) with 95% confidence intervals (CI) both unadjusted and adjusted for gestational age at delivery.

The data were analyzed with the SAS statistical software package (version 9.2; SAS Institute Inc., Cary, NC). All statistical tests were 2-sided; a probability value of 0.05 was chosen as the threshold for statistical significance.
Results

From January 1, 1999 until December 31, 2007 a total of 1,636,565 pregnancies were identified in the PRN database. We excluded women that were non-Caucasian (n=258,908 (15.82%)), women with multiple pregnancies (n=63,857 (3.90%)), women whose infant had a congenital anomaly (n=22,043 (1.35%)), and infants born before 25th weeks or after 42th weeks GA (n=6,967 (0.43%)). After application of the inclusion and exclusion criteria our study population consisted of 1,299,244 pregnancies.

Baseline characteristics of this cohort are presented in Table 1. There were more males (n=665,983; 51.2%) than females (n=633,261; 49.8%). There were no statistical significant differences in maternal baseline characteristics between the two groups. The average birth weight in males was approximately 100 grams higher than in females. Induction of labor, caesarean section and vaginal instrumental delivery were more prevalent among males. The rate of preterm delivery (<37th weeks GA) was significantly higher among males than among females (6.29% vs. 5.30%, p<0.001).

| Table 1. Characteristics of the 1,299,244 singleton pregnancies in the Netherlands, 1999-2007 |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Maternal characteristics                      | Male infants (n=665,983) | Female infants (n=633,261) | P-value for differences |
| Maternal age, mean, (SD)                      | 30.7             | 30.7             | 0.59             |
| Nulliparous, %                                | 47.5             | 47.4             | 0.14             |
| Low socio-economic status, %                  | 18.9             | 18.9             | 0.38             |
| Pregnancy and delivery                        |                  |                  |                  |
| Induction of labor, %                         | 35.6             | 35.1             | <0.001           |
| Caesarean section                             | 14.3             | 13.3             | <0.001           |
| Elective caesarean section %                  | 6.0              | 6.4              | <0.001           |
| Emergency caesarean section %                 | 8.3              | 6.9              | <0.001           |
| Vaginal instrumental delivery                 | 12.4             | 10.1             | <0.001           |
| Neonatal characteristics                      |                  |                  |                  |
| Gestational age at delivery (weeks), median (IQR) | 39.2 (1.92)     | 39.3 (1.83)     | <0.001           |
| Delivery <32 weeks GA, %                      | 0.85             | 0.72             | <0.001           |
| Delivery <37 weeks GA, %                      | 6.3              | 5.3              | <0.001           |
| Birth weight (gram), mean (SD)                | 3,526 (595)      | 3,401 (561)      | <0.001           |
| Birth weight percentile, mean (SD)            | 51.2 (29.0)      | 51.0 (29.2)      | 0.001            |

SD, standard deviation

Interaction
Interaction between sex and gestational age at delivery was significant for birth-weight-ratio <0.85 (p<0.001), <0.80 (p<0.001), >1.25 (p<.001), but not >1.30 (p0.13). Therefore, outcomes are presented stratified for gestational age at delivery.

Small for gestational age
The overall incidence of a birth-weight-ratio <0.85 was 10.21% among males and 10.25% among females. Odds ratios of having a low birth-weight-ratio at delivery are shown in table 2 separate for four strata of gestational age.
### Table 2. Low birth-weight-ratio rate in males and females

<table>
<thead>
<tr>
<th>Birth-weight-ratio &lt; 0.80</th>
<th>Male infants (n=665,983) %</th>
<th>Female infants (n=633,261) %</th>
<th>unadjusted</th>
<th>adjusted*</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-28 weeks GA</td>
<td>691/2192 31.5</td>
<td>637/1856 34.3</td>
<td>0.88 (0.77 - 1.01)</td>
<td>0.06</td>
<td>0.89 (0.78 - 1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>29-32 weeks GA</td>
<td>1148/5609 20.5</td>
<td>868/4228 20.5</td>
<td>1.00 (0.90 - 1.10)</td>
<td>0.94</td>
<td>1.00 (0.91 - 1.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>3799/34067 11.2</td>
<td>3294/2747 12.0</td>
<td>0.92 (0.88 - 0.97)</td>
<td>0.001</td>
<td>0.92 (0.87 - 0.96)</td>
<td>0.001</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>27781/624115 4.5</td>
<td>26793/599700 4.5</td>
<td>1.00 (0.98 - 1.01)</td>
<td>0.66</td>
<td>0.99 (0.97 - 1.00)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: GA at delivery

### Table 3. High birth-weight-ratio rate in males and females

<table>
<thead>
<tr>
<th>Birth-weight-ratio &gt; 1.25</th>
<th>Male infants (n=665,983) %</th>
<th>Female infants (n=633,261) %</th>
<th>unadjusted</th>
<th>adjusted*</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>OR (95%CI)</td>
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</tr>
<tr>
<td>25-28 weeks GA</td>
<td>339/2192 15.5</td>
<td>328/1856 17.7</td>
<td>0.85 (0.72 - 1.01)</td>
<td>0.06</td>
<td>0.84 (0.71 - 1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>29-32 weeks GA</td>
<td>926/5609 16.5</td>
<td>881/4228 20.8</td>
<td>0.75 (0.68 - 0.83)</td>
<td>&lt;0.001</td>
<td>0.76 (0.68 - 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>2530/34067 7.4</td>
<td>2658/2747 9.7</td>
<td>0.75 (0.71 - 0.79)</td>
<td>&lt;0.001</td>
<td>0.74 (0.70 - 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>41139/624115 6.6</td>
<td>40173/599700 6.7</td>
<td>0.98 (0.97 - 1.00)</td>
<td>0.02</td>
<td>0.98 (0.96 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: GA at delivery

<table>
<thead>
<tr>
<th>Birth-weight-ratio &gt; 1.30</th>
<th>Male infants (n=665,983) %</th>
<th>Female infants (n=633,261) %</th>
<th>unadjusted</th>
<th>adjusted*</th>
<th>p-value</th>
<th>p-value</th>
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<tr>
<td></td>
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<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
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<tr>
<td>25-28 weeks GA</td>
<td>220/2192 10.0</td>
<td>239/1856 12.9</td>
<td>0.76 (0.62 - 0.92)</td>
<td>&lt;0.001</td>
<td>0.74 (0.61 - 0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>29-32 weeks GA</td>
<td>591/5609 10.5</td>
<td>625/4228 14.9</td>
<td>0.68 (0.60 - 0.77)</td>
<td>&lt;0.001</td>
<td>0.68 (0.60 - 0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>1154/34067 3.4</td>
<td>1467/2747 5.3</td>
<td>0.62 (0.58 - 0.67)</td>
<td>&lt;0.001</td>
<td>0.62 (0.57 - 0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>19893/624115 3.2</td>
<td>20107/599700 3.4</td>
<td>0.95 (0.93 - 0.97)</td>
<td>&lt;0.001</td>
<td>0.94 (0.92 - 0.96)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: GA at delivery
Late preterm (33^w^0^d^0 - 36^w^6^d^6 weeks) and term (37^w^0^d^0 - 42^w^6^d^6 weeks) males were less likely to have a birth-weight-ratio <0.85 than females (16.8% vs. 17.4%; aOR 0.96, 95% CI 0.92-1.00 and 9.6% vs. 9.7%; aOR 0.98, 95% CI 0.97-1.00 in late preterm and term pregnancies, respectively).

The overall incidence of birth-weight-ratio <0.80 did not differ between males and females (5.02% vs. 4.99%; p=0.45). Odds ratios for having a birth-weight-ratio <0.80, separate for four strata of gestational age at delivery are shown in table 2. Late preterm (33^w^0^d^0 - 36^w^6^d^6 weeks) males were less likely to have a birth-weight-ratio <0.80 than females (11.2% vs. 12.0%; aOR 0.92, 95% CI 0.87-0.96).

Large for gestational age
The overall incidence of a birth-weight-ratio >1.25 was lower in males than females (12.59% vs. 13.52%; p<0.001). The odds ratios for having a birth-weight-ratio >1.25 and >1.30, separate for four strata of gestational age at delivery are shown in table 3. At term, males were slightly less likely to have a birth-weight-ratio >1.25 (aOR 0.98, 95%CI 0.96-0.99) and also to have a birth-weight-ratio >1.30, (aOR 0.94, 95%CI 0.92-0.96). In the preterm period, the decreased risk for males to have a birth-weight-ratio >1.25 and >1.30 became more pronounced (33^w^0 - 36^w^6 weeks: aOR 0.74, 95%CI 0.70-0.79 and aOR 0.62, 95%CI 0.57-0.67 for birth-weight-ratio >1.25 an >1.30 respectively).

Discussion
Our data from 1,299,244 singleton deliveries show that the male predominance in adverse perinatal outcome 9-12 is not caused by a higher incidence of low birth-weight-ratios among males. After correction for observed physiological differences in birth weights between males and females, a male infant born at a given gestational age is not more likely to have a low birth-weight-ratio than a female born at the same gestational age. However, the high birth-weight-ratio rate is higher among females than males, especially in the preterm period.

Limitations
This study has some limitations. First, males are on average heavier than females, therefore it is not possible to compare absolute birth weights if one wants to assess differences in fetal growth or differences in perinatal outcome. As a consequence, a substitute has to be used to compare these groups with different weights. Birth weight percentiles or birth-weight-ratio can be used as substitutes for fetal growth and they both allow comparison of fetal growth between males and females. Hereby, males with a certain birth weight percentile or birth-weight-ratio and gestational age at delivery are compared to females with the same characteristics. Birth-weight-ratio was chosen because it also allows assessment and comparison of birth weight distribution. Understandably, this cannot be done with birth weight percentile, as every percentile always contains 1% of the population and one could never assess if the e.g. smallest 1% of males (1^st percentile) are smaller than the smallest 1% of females. Although perfect comparability cannot be assured, we think that the birth-weight-ratio is an appropriate measure to compare fetal growth between populations with different distribution of influential characteristics.

Second, we used population-based medians, stratified for fetal sex and parity. Individual growth potential and placental characteristics might have enabled more accurate identification of growth
We were not able to correct for this, because maternal length and weight, and placental weight and pathology are not registered in the PRN. Therefore the Dutch reference curves for birth weight by gestational age separate for parity, sex and ethnic background were used. To avoid bias through ethnic difference and anomalous fetuses, only Caucasian women with a singleton pregnancy were included and all infants with congenital anomalies were excluded. However, we do not expect a systematic sex based bias.

Finally, the PRN database does not contain data on how pregnancy dating is performed. Until 2011, no uniform pregnancy dating was performed in the Netherlands. Historically, it was common practice to date pregnancies based on LMP. Since the 1980s the use of ultrasound was gradually introduced in obstetric care. During our study period CRL and HC measurements had already increasingly replaced LMP for dating, but no quantitative data are available on how pregnancy was dated in individual cases. However, it is unlikely that a systematic bias was caused by sex differences in pregnancy dating.

Strengths
The main strength of this study is the size (1,299,244 pregnancies) and composition (only Caucasians with a singleton without congenital anomalies) of the cohort. Data were derived from a large, well-maintained population-based national perinatal registry (1999-2007). The vast majority of the caregivers contribute to the PRN registry; therefore, it comprises approximately 96% of all pregnancy and birth characteristics in The Netherlands. The 4% missing birth data are due to 1-2% non-reporting general practitioners and 2-3% non-reporting midwives. The proportion of males, prematurity and average birth weight are in accordance with previous research.

Another strength is that in contrast to previous studies- outcomes were adjusted for birth-weight-ratio and gestational age at delivery. Combined with the use of population-based growth curves for Caucasians, stratified for sex and parity, this results in comparison of infants with the same birth weight percentiles and gestational ages. As a result, the outcomes solely represent the influence of sex on the outcomes of interest. The increased risk of perinatal death in males that was found in previous studies, might be at least partially explained by incorrect adjustment for confounding. Because adjustment was performed for birth weight instead of birth weight percentile, SGA males were partly compared to normally grown females (with the same birth weight and gestational age), leading to a systematic bias to the detriment of males.

Finally, this is to our knowledge the first study that tested for interaction and consequently performed analyses that were stratified for gestational age at delivery. This provides a more accurate representation of the results than in previous studies.

Considerations about the results
As discussed earlier, we used birth-weight-ratio to compare growth of male and female fetuses and found that male fetuses are generally heavier than female fetuses, median birth-weight-ratio at each gestational age is similar for males and females, and that the distribution around the median for average grown infants (birth-weight-ratio 0.85-1.20) is comparable for both sexes. This supports the hypothesis that growth is influenced by genetic factors as also suggested by crown rump length differences between males and females already present between the 8th and 12th week of gestation. From our results we cannot conclude to what extent hormonal and placental factors play a role in growth differences between males and females. However, males are not at increased risk of having a low birth-weight-ratio compared to females, suggesting no increased incidence of placental dysfunction in pregnancies with a male fetus.
We found higher incidences of birth-weight-ratios >1.25 and >1.30 among females compared to males. This difference is present at all gestational ages, but most pronounced in extremely (25–28 weeks) and very preterm (29–32 weeks) infants. Increased placental reserves in females compared to males can be an explanation. A male with a certain high birth-weight-ratio is heavier than a female with the same birth-weight-ratio, imposing a greater burden on placental capacity. Placental capacity will therefore sooner constitute a limiting factor for fetal growth in high birth-weight-ratio males than in high birth-weight-ratio females, resulting in higher rates of high birth-weight-ratios among females.

We think our results are reliable and generalizable because they come from a large population based cohort. The results show no increased low birth-weight-ratio risk in males, suggesting that increased risk of adverse perinatal outcome in males is not caused by differences in fetal growth.

Implications
The main implication of this study is that, based on these data, there is no reason to treat or counsel differently based on infant sex and expected low- or high birth-weight-ratio. However, absolute birth weight should be weighed differently in males than in females, and the (expected) birth-weight-ratio or percentile should be taken into account when considering intervening in a pregnancy. Both in males and females, especially when born preterm, practitioners should be aware of potential risks of neonatal morbidity and act accordingly.

Unanswered questions; proposals for future research
Future research should focus on the unraveling of mechanisms that might play a role in the increased neonatal morbidity in males, in order to find out if measures can be taken to decrease neonatal morbidity in males. Future research should also be done to develop and evaluate models that contain birth-weight-ratio to predict neonatal outcome in preterm infants. Birth-weight-ratio could possibly improve models that are based on estimated absolute weight, gestational age and fetal sex.
References


Chapter 7

Detecting pregnancies at risk of term SGA using 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester ultrasound growth parameters

Bart Jan Voskamp, Karline vd Kamp, Wessel Ganzevoort, Ewoud Schuit, Ben Willem J Mol,
Rosalinde JM Snijders, Eva Pajkrt

In preparation
Abstract

Objective: To assess if relative growth between the 2nd and 3rd trimester improves identification of infants at risk of being born small for gestation, and to assess if changing cut-off values for follow-up after 3rd trimester ultrasound scan affects SGA detection of term infants.

Methods: Between 2001 and 2013 we performed a retrospective cohort study in a tertiary referral hospital in the Netherlands. All singleton neonates born between 36th and 42nd weeks of gestation were included. We assessed if using the difference between the 2nd trimester estimated to median-fetal-weight-ratio (EFW ratio) and the 3rd trimester EFWratio improved identification of infants at risk of being born SGA (birth weight <10th percentile for gestation).

Results: We included 5180 infants, of whom 16.7% [867/5180] were born SGA. Receiver operator characteristics show that ultrasound fetal weight estimation in the 3rd trimester (area under the curve (AUC) 0.84, 95%Confidence interval (CI) 0.83-0.86) has better discriminative ability than in the 2nd trimester (AUC 0.69, 95%CI 0.67-0.72). Adding the standardized difference between 2nd trimester EFWratio and 3rd trimester EFWratio does not improve the discriminative ability of the model to predict SGA (AUC 0.84, 95%CI 0.83-0.86). Using 3rd trimester EFWratio cut-off 0.90 instead of 0.85 as threshold to perform follow-up of fetal growth, potentially increases sensitivity for SGA at birth from 39.0% to 60.8%, still being 86.3% specific.

Conclusion: Adding the difference between 2nd trimester BWratio and 3rd trimester BWratio did not improve identification of infants at risk of being born SGA. Changing cut-off values for follow-up after 3rd trimester ultrasound potentially increases SGA detection with acceptable false-positive rates.
Introduction

Small for gestational age (SGA) neonates are defined as neonates born with a weight below a certain percentile (2.5\textsuperscript{th}, 5\textsuperscript{th} or 10\textsuperscript{th} percentile) of the growth curve for a given gestational age. SGA is associated with an increased risk of adverse pregnancy outcome and adverse events in the postpartum phase.\textsuperscript{1-4} SGA severity is associated with (perinatal) death risk.\textsuperscript{5} It is assumed that prenatal detection of SGA could improve fetal outcome by close fetal monitoring and induction of labor or emergency instrumental delivery when the fetal condition seems compromised.\textsuperscript{6}

Characteristics of pregnant women, such as ethnicity and anthropometric parameters, and prenatal ultrasound growth measurements are used to identify pregnancies at increased risk of SGA. In developed countries, growth measurements are generally performed during the mid-trimester anomaly scan. Third trimester ultrasound is increasingly used to identify cases at risk of SGA. Despite these tests that aim to increase SGA detection, the majority of SGA cases remain undiagnosed until birth.\textsuperscript{7-10}

Poor antenatal SGA detection might have several causes: inaccuracy of ultrasound biometry, onset of growth impairment after the third trimester growth ultrasound, or reassurance of fetal growth in poorly growing infants that are not yet SGA at 30-weeks but that already have declining fetal growth following the mid-trimester scan.

The aim of this study was to assess if fetal growth between the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester ultrasound scan significantly improves SGA detection based on 3rd trimester ultrasound parameters. We also wanted to assess the influence of using higher cut-off values for follow-up of fetal growth after the 3\textsuperscript{rd} trimester ultrasound scan (ie. also performing follow-up on infants that seem less growth restricted) on SGA detection of term infants.

Methods

Study design
We conducted a retrospective cohort study of all singleton neonates born in our tertiary referral center between 36\textsuperscript{th} and 42\textsuperscript{nd} weeks of gestation, between January 1\textsuperscript{st} 2001 and December 31\textsuperscript{st} 2013. We assessed if relative difference in the estimated to median-fetal-weight-ratio between the second and the third trimester would have improved identification of SGA pregnancies.

Inclusion and exclusion criteria
We included women with a singleton pregnancy who had at least one ultrasound growth assessment during the second trimester (between 18\textsuperscript{nd} and 23\textsuperscript{rd} weeks GA) and at least one ultrasound growth assessment during the third trimester (between 28\textsuperscript{nd} and 33\textsuperscript{rd} weeks GA) with complete data on bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and who delivered at a gestational age between 36\textsuperscript{th} and 42\textsuperscript{nd} weeks.

In order to minimize the risk of biased results due to other factors that are associated with impaired fetal growth, we excluded all infants with structural or chromosomal anomalies.

Data collection
We searched the electronic ultrasound database of the Academic Medical Center - a tertiary referral hospital that provides care for women with high and low risk pregnancies -, to identify pregnancies in which ultrasound growth assessment had been performed both in the 2\textsuperscript{nd} trimester (between 18\textsuperscript{nd}
and 23\textsuperscript{rd} weeks gestation), and in the 3\textsuperscript{rd} trimester (between 28\textsuperscript{nd} and 33\textsuperscript{rd} weeks gestation). If more than one ultrasound was performed in either trimester, the latest measurement was used for the analysis. All scans were performed by - Fetal Medicine Foundation certified - sonographers using a standard protocol.

Information from the ultrasound database was complemented using the hospital birth database. We collected information on maternal characteristics (age, parity, and body mass index (BMI)), prenatal growth assessment (gestational age and BPD, HC, AC, FL at 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester ultrasound), gestational age at delivery, and neonatal characteristics (sex and birth weight).

**Outcome measures**
Gestational age was predominantly based on first trimester ultrasound crown rump length (CRL) measurement. Data on pregnancy dating in individual cases was not available.

We used two measures - EFW and median weight for gestation- to express fetal weight during pregnancy, and one - birth weight percentile - to express neonatal weight at birth.

Estimated fetal weight of all infants at 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester ultrasound was calculated with the Hadlock formula \( \text{Log}_{10} \text{EFW} = 1.3596 + 0.0064(\text{HC}) + 0.0424(\text{AC}) + 0.174(\text{FL}) + 0.00061(\text{BPD})(\text{AC} - 0.00386(\text{AC})(\text{FL})) \).\textsuperscript{11} Also, gestation specific median fetal weight of all infants at 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester ultrasound was calculated with the Hadlock in utero fetal weight standard- that contains median fetal weight by gestational age.\textsuperscript{12} With the outcomes of the EFW and gestation specific median fetal weight, we calculated the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester EFW ratio for every fetus, which was defined as the EFW at the time of ultrasound divided by the gestation specific median fetal weight.\textsuperscript{12} We used three EFW ratio cut-off values to define small for gestation during pregnancy: 0.85, 0.90, and 0.95.

Birth weight percentiles of all neonates were calculated with the Dutch reference curves\textsuperscript{13}, using birth weight, parity, sex and gestational age. SGA at birth was defined as birth weight below the 10\textsuperscript{th} or 5\textsuperscript{th} percentile for gestation.

Finally we calculated for all infants the standardized 2\textsuperscript{nd} to 3\textsuperscript{rd} trimester EFW ratio difference ((3\textsuperscript{rd} trimester BW ratio - 2\textsuperscript{nd} trimester BW ratio)/ (days between 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester biometry)).

**Analysis**
Baseline characteristics were described and presented as means with standard deviations (SD), median with range, or as percentages as appropriate.

We performed univariable analysis using measures of central tendency and dispersion, as well as simple linear and multiple regression analyses. 2\textsuperscript{nd} Trimester EFW ratio, 3\textsuperscript{rd} trimester EFW ratio and 2\textsuperscript{nd} to 3\textsuperscript{rd} trimester EFW ratio difference, maternal age, BMI, and parity in relation to SGA at birth were analyzed in multiple regression models.

Multivariable logistic regression analysis was used to identify variables that provided a significant independent contribution in explaining the rate of SGA at birth and thus to assess if combining 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester EFW ratio information improves prenatal identification of SGA at birth.

Receiver–operating characteristics (ROC) curves were generated for each diagnostic test (2nd trimester EFW ratio, 3rd trimester EFW ratio and 2nd to 3rd trimester EFW ratio difference) to evaluate their diagnostic ability to predict SGA (<10\textsuperscript{th} percentile) at birth. The areas under the ROC curves (AUCs) and the 95% CIs of these areas were calculated.

We calculated test characteristics (sensitivity (Sens), specificity (Spec), positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (LR+)) of different 2\textsuperscript{nd} and 3\textsuperscript{rd}
trimester EFW ratio cut-off values (0.85, 0.90, and 0.95) to predict SGA (<10th percentile and <5th percentile).
Statistical analyses were conducted with SPSS version 19.0 for Windows. All statistical tests were 2-sided; a probability value of 0.05 was chosen as the threshold for statistical significance.

Results

In the study period, 7,120 pregnancies with complete data on 2nd trimester ultrasound, 3rd trimester ultrasound and pregnancy outcome were identified in our prenatal database. We excluded multiple pregnancies (n=319 (4.5%)), infants with congenital anomalies (n=107 (1.4%)), and infants born before 36th weeks or after 42nd weeks GA (n=609 (8.6%)). After application of our inclusion and exclusion criteria our study population consisted of 5,180 pregnancies. Baseline characteristics of our population are shown in table 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort (n=5,180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (± SD)</td>
<td>32.3 (5.8)</td>
</tr>
<tr>
<td>BMI*, median (range)</td>
<td>24.5 (16.1-57.0)</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
<td>1,937 (37.4)</td>
</tr>
<tr>
<td>Fetal male sex, n (%)</td>
<td>2,616 (50.5)</td>
</tr>
<tr>
<td>GA at 2nd trimester US, median days (range)</td>
<td>143 (126-167)</td>
</tr>
<tr>
<td>GA at 3rd trimester ultrasound, median days (range)</td>
<td>224 (196-237)</td>
</tr>
<tr>
<td>GA at delivery, mean days (SD)</td>
<td>273.4 (9.7)</td>
</tr>
<tr>
<td>Birthweight, median grams (range)</td>
<td>3,225 (890-5,500)</td>
</tr>
<tr>
<td>SGA &lt;p10, n (%)</td>
<td>865 (16.7)</td>
</tr>
</tbody>
</table>

SD, standard deviation; BMI, body mass index; GA, gestational age; SGA, small for gestational age

Univariable logistic regression analyses showed that women who delivered an SGA infant were younger (31.3 vs. 32.1 years, p<0.001), and had a lower BMI (23.7 vs. 24.6, p<0.001) than women who delivered a non-SGA infant (table 2).

Table 2. Factors associated with SGA (<p10) at birth

<table>
<thead>
<tr>
<th>Factor</th>
<th>SGA (&lt;10th percentile) (n=867)</th>
<th>not-SGA (n=4,313)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years, mean (± SD)</td>
<td>31.3 (6.3)</td>
<td>32.2 (5.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI*, median (IQR)</td>
<td>23.7 (6.5)</td>
<td>24.6 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
<td>308 (35.5)</td>
<td>1,635 (37.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>426 (49.1)</td>
<td>2,191 (50.8)</td>
<td>0.38</td>
</tr>
<tr>
<td>2nd trim EFW ratio, mean (SD)</td>
<td>0.93 (0.10)</td>
<td>1.00 (0.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3rd trim EFW ratio, mean (SD)</td>
<td>0.88 (0.11)</td>
<td>1.02 (0.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2nd - 3rd trim EFW ratio difference, mean (SD)</td>
<td>- 0.07 (0.13)</td>
<td>0.04 (0.15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Also the 2nd trimester EFW ratio and the 3rd trimester EFW ratio were lower in the SGA group than in the non-SGA group (0.93 vs. 1.00 and 0.88 vs. 1.02 (both p<0.001) respectively), and that the 2nd to 3rd trimester EFW ratio difference was lower in the SGA group than in the non-SGA group (-0.07 vs. -0.04, p<0.001) indicating less growth between the 2nd and 3rd trimester ultrasound in the SGA group.

| Table 3. Multivariable models to predict SGA (<10th percentile and <5th percentile) at birth |
|-----------------------------------------------|-----------------|
| SGA (<10th percentile) at birth               | AUC 95%CI        |
| Age, BMI, Primiparity, Sex, 2nd trimester EFW ratio | 0.69 (0.67-0.72) |
| Age, BMI, Primiparity, Sex, 3rd trimester EFW ratio | 0.84 (0.83-0.86) |
| Age, BMI, Primiparity, Sex, 3rd trimester EFW ratio, 2nd3rd EFW ratio diff | 0.84 (0.83-0.86) |
| Age, BMI, Primiparity, Sex, 3rd trimester AC ratio | 0.82 (0.80-0.84) |
| SGA (<5th percentile) at birth                |                 |
| Age, BMI, Primiparity, Sex, 2nd trimester EFW ratio | 0.71 (0.70-0.76) |
| Age, BMI, Primiparity, Sex, 3rd trimester EFW ratio | 0.87 (0.85-0.89) |
| Age, BMI, Primiparity, Sex, 3rd trimester EFW ratio, 2nd3rd EFW ratio diff | 0.87 (0.85-0.89) |
| Age, BMI, Primiparity, Sex, 3rd trimester AC ratio | 0.85 (0.83-0.87) |

SGA, small for gestation; BMI, body mass index; EFW, estimated fetal weight; AC, abdominal circumference.

Multivariable logistic regression models (table 3) to predict SGA (<10th percentile) at birth showed that a model containing the 3rd trimester EFW ratio has better discriminative ability than a model containing 2nd trimester EFW ratio (AUC 0.84, 95%CI 0.83-0.86 vs. AUC 0.69, 95%CI 0.67-0.72). A model containing the 3rd trimester EFW ratio is not significantly better than a model containing the 3rd trimester AC ratio (AUC 0.84, 95%CI 0.83-0.86 vs. 0.82, 95%CI 0.80-0.84). Adding the 2nd to 3rd trimester EFW ratio difference to a model containing the 3rd trimester EFW ratio does not add discriminative ability (both AUC 0.84, 95%CI 0.83-0.86). This is illustrated by the ROC curves in figure 1. We also assessed the discriminative ability of different models to predict SGA (<5th percentile) at birth. Table 3 shows that the results are in accordance with those for the prediction of SGA (<10th percentile). Complete data on univariable analysis and on the multivariable prediction models is shown in appendix 1.

Test characteristics of different cut-off values to detect SGA (weight <10th percentile) at birth (table 4) show that if in the 2nd trimester an EFW ratio of 0.85 (7.4% of the population) is used, 17.8% of SGA infants are detected with a specificity of 94.6%, and that if in the 3rd trimester an EFW ratio of 0.85 (10.4% of the population) is used, 39.0% of SGA infants are detected with a specificity of 95.3%. Using higher cut-off values in the third trimester (e.g. 0.90) to detect SGA increases sensitivity and decreases specificity. A 3rd trimester EFW ratio cut-off of 0.90 (21.5% of our population) has a sensitivity of 60.8% and specificity of 86.3%. An EFW ratio cut-off 0.95 (36.7% of our population) has a sensitivity of 79.0% and specificity of 71.8%. Compared to detection of SGA <10th percentile, detection of SGA <5th percentile has higher sensitivity (49.5% (EFW ratio <0.85) to 84.6% (EFW ratio <0.95)) and lower specificity (93.6% (EFW ratio <0.85) to 68.2% (EFW ratio <0.95)).
Discussion

In this study we found that 2nd Trimester EFW ratio and 3rd trimester EFW ratio are both predictors of SGA at birth, with significantly better discriminative ability in the 3rd trimester. Adding information on relative growth between 2nd and 3rd trimester ultrasound does not enhance the ability of 3rd trimester ultrasound to detect infants at risk of SGA at birth.

Furthermore, we found that a model that contains EFW ratio does not significantly improve SGA detection compared to a model that contains 3rd trimester AC ratio. This study confirms the low sensitivity of prenatal ultrasound to detect SGA at birth, even in a population that contains many high-risk patients. We quantified the test characteristics of different EFW cut-off values during 2nd and 3rd trimester ultrasound to detect SGA (<10th and <5th percentile) at birth, and showed that adjusting 3nd trimester cut-offs for follow-up can increase SGA detection from 39.0% to 60.8% and still being 86.3% specific.

Limitations
Our study has some limitations. First, we assessed the influence of fetal and maternal characteristics on birth weight instead of adverse outcome. Given the low incidence of adverse pregnancy outcome, our sample size did not allow us to look at adverse pregnancy outcome, therefore we assessed birth weight as a risk factor for adverse outcome.15

Second, we used population-based charts to express birth weight and SGA. Previous studies showed a better association between individualized growth charts and adverse outcome.21415 We were not able to use these because we did not have information on maternal characteristics needed for individualized curves. We believe however, that the validity of the principles in this paper do not depend on the use of population based / individualized growth charts. The same applies to the fact that we used a population from a tertiary referral center. The exact numbers might not be generalizable to an unselected/low-risk population, the principles described in this paper will.

Strengths
A strength of this study is the size of the cohort with information on 2nd and 3rd trimester ultrasound and on pregnancy outcome, allowing us to answer the question if growth between the 2nd and 3rd trimester ultrasound scan improves identification of SGA infants. This is to our knowledge the first study to assess this question.

Second, we used parity and sex specific charts to assess pregnancy outcome allowing better differentiation between constitutional smallness and intra-uterine growth restriction than with unstratified charts.

Finally, we used 2nd and 3rd trimester EFW ratios as variables to identify pregnancies at risk of SGA and expressed SGA at birth. It was not possible to use percentiles prenatally because there are no prenatal reference curves with standard deviation - needed to calculate percentiles - (for HC, BPD, AC, and FL) that are validated for the Dutch population. An advantage of EFW ratios is that they contain information on the absolute deviation from the median, whereas percentiles only contain information about the proportion of a population that is larger / smaller. Also - in contrast to percentiles - ratios are not influenced by outliers in the population and are therefore less susceptible to population related bias.
Figure 1. Receiver operating characteristics of different SGA prediction models.
<table>
<thead>
<tr>
<th></th>
<th>2nd trimester EFW ratio</th>
<th>3rd trimester EFW ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of population (%)</td>
<td>&lt;0.85 (7.4%)</td>
<td>&lt;0.90 (19.1%)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.85 (10.4%)</td>
<td>&lt;0.90 (21.5%)</td>
</tr>
<tr>
<td><strong>SGA (&lt;10th percentile) at birth</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>17.76</td>
<td>39.91</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>94.64</td>
<td>85.05</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>40.00</td>
<td>34.91</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>85.13</td>
<td>87.56</td>
</tr>
<tr>
<td>LR+</td>
<td>3.32</td>
<td>2.67</td>
</tr>
<tr>
<td><strong>SGA (&lt;5th percentile) at birth</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>23.38</td>
<td>47.60</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>94.19</td>
<td>83.77</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>29.09</td>
<td>23.01</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>92.35</td>
<td>94.01</td>
</tr>
<tr>
<td>LR+</td>
<td>4.03</td>
<td>2.93</td>
</tr>
</tbody>
</table>

SGA, small for gestation; EFW, estimated fetal weight; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio
Considerations about results
This study shows that adding 2nd to 3rd trimester growth does not add discriminative ability to a model based on 3rd trimester ultrasound to detect pregnancies at risk of SGA and provides an answer to the clinical question what to do if normal 3rd trimester biometry is observed but EFW ratio/percentile has declined between the 2nd and the 3rd trimester scan.

This study also quantifies, and gives insight to the low antenatal detection rates of SGA, \(^7\)\(^8\)\(^16\) and shows that if third trimester ultrasound is used with cut-off values for referral/follow up at the 10th percentile for gestation (EFW ratio 0.85), the majority of SGA cases will remain undiagnosed until birth. It also shows that an opportunity for SGA detection lies in changing 3rd trimester cut-off values for follow-up, as earlier suggested by de Reu and colleagues. \(^17\) In our population using a 3rd trimester EFW ratio cut-off 0.90 instead of 0.85 would have led to follow-up of an extra 11.1% of pregnancies and 21.8% increase in SGA detection. For each SGA-infant (<10th percentile), two women without fetal growth deviation are unnecessary intensively investigated and probably worried. Given the potential risks of unidentified SGA in late pregnancy \(^7\)\(^9\) and the relatively low burden (non-invasive, no hospital admission) of follow-up, we find these false positive rates acceptable. Subsequent investigations may reveal the presence or absence of growth deviations on a pathological basis.

Previous research showed decreased diagnostic accuracy of ultrasound after 36 weeks gestation. \(^10\) Specifically, abdominal circumference measurements are harder to perform late in gestation. It has therefore become uncommon to perform ultrasound biometry after 36 weeks gestation. It has not been assessed however, if measurements are also inaccurate in (suspected) SGA pregnancies, or that ultrasound increases SGA detection late in gestation. This is especially interesting because we do not know whether SGA remains undetected due to inaccuracy of ultrasound measurements, or that most undetected SGA develops late in pregnancy (after 36 weeks). Future research should therefore focus on evaluating potential benefit of ultrasound biometry late in gestation to detect SGA (in pregnancies deemed high-risk based on 3rd trimester ultrasound).

We think that the concepts put forward in this paper can be used in clinical practice and contribute to finding ways to increase antenatal SGA detection and to decrease adverse pregnancy outcome.

Implications
This study shows that adding 2nd to 3rd trimester growth does not add discriminative ability to a model based on 3rd trimester ultrasound to detect pregnancies at risk of SGA. This parameter should thus not be used to make policy about biometric follow-up in pregnancy.

Clinicians should consider performing follow-up of fetal growth if 3rd trimester (28\(^{10}\) - 33\(^{16}\) weeks) EFW ratio is <0.90 to differentiate between constitutional smallness and growth restriction. Future prospective research should be performed to assess influence of using different cut-off values on pregnancy outcome and costs. Based on our findings, there is no indication to change cut-off values of 2nd trimester ultrasound for follow-up.
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Chapter 8

Optimal timing of delivery in small for gestational age fetuses near term, a national cohort study

Brenda M Kazemier, Bart Jan Voskamp, Anita CJ Ravelli, Eva Pajkrt, Christianne JM de Groot, Ben Willem J Mol

Submitted
Abstract

Objective: Small for gestational age (SGA) fetuses are at increased risk of antepartum and postpartum death, but it is unknown what the optimal gestational age is to deliver these high-risk fetuses. Postponement of delivery may lead to an increased risk of antepartum death, whereas early delivery may lead to complications related to neonatal prematurity. Our aim was to study the competing risks of antepartum death versus intrapartum/neonatal death in isolated SGA fetuses to obtain their optimal timing of delivery.

Methods: National cohort study of all singleton births delivered between 36<sup>0</sup> and 42<sup>6</sup> weeks obtained from the Netherlands Perinatal Registry (1999-2007). Women with hypertension, pre-eclampsia, diabetes or carrying a pregnancy with congenital anomalies or in non-cephalic presentation were excluded. The remaining cohort was divided into 3 groups; birthweight by gestational age below the 5<sup>th</sup> percentile (SGA<P5 group, N=61,021), between 5<sup>th</sup> and 10<sup>th</sup> percentile (SGA P5-10 group, N= 58,902) and above the 10<sup>th</sup> percentile (non-SGA group, N= 1,168,523).

Numbers of antepartum, intrapartum/neonatal death and neonatal morbidity were analysed using the fetus/neonate-at-risk approach. We also compared the risk of delivery (intrapartum/neonatal death at week x) with the risk of expectant management (risk of antepartum death at week x plus risk intrapartum/neonatal death at the subsequent week) between the groups.

Results: In the non-SGA group is delivery associated with significantly less mortality than expectant management for one week from 39 weeks onward (0.84 vs 1.06 per 1000, RR1.26 95%CI 1.05-1.50). For the SGA P5-10 and SGA<P5 delivery is associated with less mortality from 38 weeks onward although this only reaches statistical significance from 40 weeks onwards (2.91vs 1.54 per 1000 RR1.89 95% CI 1.15-3.11, and 9.48 vs 3.85 per 1000 RR2.46 95%CI 1.80-3.36 respectively).

Conclusion: Delivery of SGA fetuses in the 38<sup>th</sup> and 39<sup>th</sup> week is associated with the best perinatal outcome whereas for non-SGA fetuses this is the 39<sup>th</sup>-40<sup>th</sup> week. Delivering a SGA fetus before these optimal weeks is associated with a steep increase of neonatal death, delivering a SGA fetus after these optimal weeks is associated with a steep increase of antepartum death.
Introduction

Small-for-gestational age (SGA) is most commonly defined as birthweight below the 10th percentile for a particular gestational age and thus contains by definition 10% of the population. The group of SGA fetuses consists of a mixture of growth restricted and constitutionally small fetuses. Up to 72% of unexplained antepartum deaths are associated with SGA\(^1\). The more pronounced the SGA, the higher the risk of antepartum death\(^2\). Moreover, neonates that are born SGA are at increased risk of adverse events in the postpartum phase\(^3-5\).

The time frame of term delivery between 37 and 42 weeks is considered physiologic for all women. However, it is not known whether this time frame is also optimal for delivery of an SGA fetus, since the increased risk of antepartum death is not incorporated in this concept of normalcy.

Up to date there is little evidence to guide clinicians in their decision regarding the optimal timing of delivery in these high-risk pregnancies. Postponement may lead to an increased risk of antepartum death, whereas early delivery may lead to prematurity and its related complications. Although the DIGITAT trial was designed to answer this question, the study was not powered to examine the risk of antepartum death\(^6\). A recent study defined optimal timing of delivery for these fetuses based on the risk of stillbirth\(^2\). However, the risk of neonatal death with delivery was not incorporated in this theory.

Our objective was to study, in isolated SGA fetuses, the competing risks of antepartum death with on-going pregnancy versus neonatal death with delivery. In addition, we studied the probability of neonatal morbidity to place any conclusions about optimal timing of delivery in context with the probability of neonatal morbidity.

Methods

Database

Data were obtained from the Netherlands Perinatal Registry (PRN) between 1999 and 2007.\(^7\)

The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns.\(^8,9\) The PRN contains population-based data on pregnancies, provided care, i.e. interventions, referrals, deliveries and (re)admission of newborns of 96% of all deliveries in the Netherlands. Details on entry, linkage, aggregation, validation and verification of the data are published elsewhere\(^8,9\). This study used anonymous registry data so no ethical approval was needed. The Dutch perinatal registry gave permission for the use of their data (approval number 12.21).

Inclusion and exclusion criteria

The study population comprised all singleton deliveries between 36\(^{10}\) and 42\(^{16}\) weeks of gestation. Gestational age was based on ultrasound or last menstrual period. We excluded congenital anomalies, chronic or pregnancy induced hypertension, pre-eclampsia and diabetes, because timing of delivery could have been influenced by such co-morbidity. In addition we excluded non-cephalic presentation since breech position is associated with an increased risk of neonatal mortality and morbidity.
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Determinant: SGA groups
We assumed that the proportion of growth-restricted fetuses is probably higher among fetuses with severe SGA (birthweight by gestational age below the 5th percentile, P5) than among fetuses with moderate SGA (birthweight by gestational age between the 5th and 10th percentile, P5-10), as the latter group likely contains more constitutionally small fetuses. We therefore stratified our analysis into birthweight below the 5th percentile (SGA<P5 group), birthweight between the 5th and 10th percentile (SGA P5-10 group) and a group with birthweight above the 10th percentile (non-SGA group) according to Dutch reference curves for birthweight by gestational age (corrected for parity, fetal sex and ethnic background) 10.

Outcome measures
We looked at three outcome measures: antepartum death, intrapartum/neonatal death and neonatal morbidity. Antepartum deaths were all deaths occurring before the start of the delivery. Intrapartum/neonatal deaths were those occurring during labour or in the first 28 days of life. We grouped intrapartum and neonatal death since most intrapartum deaths are caused by events during labour and delivery 11,12. Neonatal morbidity was a composite outcome measure, containing any of the following; meconium aspiration, necrotizing enterocolitis, respiratory distress syndrome, birth trauma, intraventricular haemorrhage or neonatal intensive care admission for at least 24 hours.

Statistical Analysis
We compared baseline characteristics among the three SGA groups with Anova tests and chi-square tests when appropriate. Gestational age-specific risks of antepartum deaths, intrapartum/neonatal deaths and neonatal morbidity were estimated using the fetus/neonate-at-risk approach 13-15. A moving average (death at a specific day + deaths of day before and day after divided by 3) was applied to correct for daily fluctuations in figure 2.

Antepartum death
For a fetus to be at risk of antepartum death (AD) at 36+0 it is obviously necessary to be alive at 36+0. Consequently, the risk of antepartum death was calculated as a proportion of the ongoing pregnancies (OP) at a particular gestation.

Risk of antepartum death at day n = AD_n / OP_n * 1000

Cumulative risk of antepartum death
The cumulative risk of antepartum death at day N was calculated by summing the risks of antepartum death of the previous days. Inevitably, the cumulative risk of antepartum death will increase with increasing gestation. The cumulative risk represents the risk of antepartum death in case of expectant management from 36+0 weeks (n0) onward.

Cumulative risk of antepartum death at day n = (AD_n0 / OP_n0 * 1000) + (AD_n1 / OP_n1 * 1000) ... (AD_n / OP_n * 1000)

Intrapartum/neonatal death
In concurrence, the risk of intrapartum/neonatal death (IND) at any gestational age is obtained by dividing the number of intrapartum and neonatal deaths at that gestation by the number of
neonates at risk of intrapartum/neonatal death at that gestation. The neonates at risk of intrapartum/neonatal death at a certain gestational age include all delivered neonates (DN) that did not die antepartum.

Risk of intrapartum/neonatal death at day \( n \) = \( \frac{IND_n}{DN_n} \times 1000 \)

**Neonatal morbidity**
The denominator used for the risk of neonatal morbidity (NM) are all alive fetuses (AF) born at that gestation, since only alive fetuses can suffer morbidity.

Risk of neonatal morbidity at day \( n \) = \( \frac{NM_n}{AF_n} \times 1000 \)

**Nadir**
We consider the intersection of the line representing the risk of intrapartum/neonatal death with the line representing the cumulative risk of antepartum death, as the period associated with the lowest risk of death. This point is referred to as the nadir.

**Comparison probability of death with delivery versus expectant management**
To statistically back up our findings via the graph method, we also compared the probability of death in case of delivery versus expectant management. Once delivery has started, either spontaneously or by induction of labour, the probability of death is based on intrapartum/neonatal death. With expectant management the probability of death is based on the composite of intrapartum/neonatal death and the probability of antepartum death. The probability of death between delivery and expectant management per one week gestation was compared as previously proposed by Rosenstein et al.\(^{16}\). For example, delivery in the 36\(^{th}\) week was compared to an expectant management in the 36\(^{th}\) week and subsequent delivery in the 37\(^{th}\) week. The probability of death with delivery is defined as the risk of intrapartum/neonatal deaths in that week divided by neonates born during that week.

**Probability of death with delivery at week \( x \) = \( \frac{IND_x}{DN_x} \times 1000 \)**

The probability of death with one week expectant management was defined as the risk of antepartum death during that week plus the risk of intrapartum/neonatal death with delivery in the subsequent week. The confidence interval of this composite outcome was calculated using the sum of the variances plus twice the covariance of the estimates of antepartum death and intrapartum/neonatal death.

**Probability of death with one week expectant management at week \( x \) = ( \( AD_x + \frac{IN_{x+1}}{DN_{x+1}} \) ) \(*1000.\)**

We compared for each week separately the probability of death in case of delivery versus expectant management for one week.

A number needed to deliver to prevent one death was calculated by taking the reciprocal of the absolute risk difference between delivery and expectant management for one week. Data analyses were conducted with SAS (SAS institute Inc, Cary, NC, USA version 9.2).
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Results

From January 1, 1999 until December 31, 2007 a total of 1,491,534 singleton deliveries from 36<sup>th</sup> week onwards without congenital anomalies were identified in the PRN database. We excluded hypertensive complications or maternal diabetes (125,865) and non-cephalic presentation (77,223). After application of our inclusion and exclusion criteria 1,288,446 deliveries made up our study population: 61,021 deliveries in the SGA<P5 group (4.7%), 58,902 in the SGA P5-10 group (4.6%) and 1,168,523 in the non-SGA group (90.7%).

Maternal and neonatal baseline characteristics of the cohort are shown in Table 1, separate for the three birthweight categories. Women with SGA are more often non-Caucasian than women without SGA (23.6%, 23.1%, and 15.9% respectively; P<0.001). The same was true for low socioeconomic status (33.0%, 31.0% and 24.4% respectively P<0.001). Induced delivery was more common in the SGA<P5 group than in the SGA P5-10 and non-SGA group (35.5%, 29.2% and 29.9%; P<0.001). Mean gestational age at delivery was the same in the SGA<P5 and non-SGA group (40+0 weeks) but was a slightly longer in the SGA P5-10 group (40+2 weeks) (P-value <0.001).

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Non-SGA (N=1,168,523)</th>
<th>SGA P5-10 (N=58,902)</th>
<th>SGA&lt;P5 (N=61,021)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, (mean. SD)</td>
<td>30.4 (4.8)</td>
<td>29.9 (5.2)</td>
<td>29.9 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low SES, %</td>
<td>24.4</td>
<td>31.0</td>
<td>33.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Caucasian, %</td>
<td>15.9</td>
<td>23.1</td>
<td>23.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nulliparous, %</td>
<td>43.5</td>
<td>43.0</td>
<td>44.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at delivery, weeks, median</td>
<td>40+0</td>
<td>40+2</td>
<td>40+0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction of labour, %</td>
<td>29.9</td>
<td>27.1</td>
<td>32.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caesarean section, %</td>
<td>9.2</td>
<td>7.7</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elective Caesarean section, %</td>
<td>3.0</td>
<td>2.2</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency Caesarean section (fetal distress, non progression)</td>
<td>6.2</td>
<td>5.5</td>
<td>8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td>51.3</td>
<td>51.6</td>
<td>50.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Birth weight, (gram), mean</td>
<td>3600</td>
<td>2915</td>
<td>2637</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Antepartum death occurred more often in the SGA<P5 group (8.0%) and in the SGA P5-10 group (2.6%), compared to the non-SGA group (1.2%) (both p<0.001). In addition, intrapartum/neonatal death was more prevalent in the SGA<P5 group (5.9%) and the SGA P5-10 group (2.1%) than in the non-SGA group (0.6%) (both p<0.001). Finally, neonatal morbidity was more common in the SGA<P5 group (11.1%) and the SGA P5-10 group (5.8%) than in the non-SGA group (4.3%) (both p<0.001) (Table 2).

Table 2 presents the gestational age specific risks of antepartum death, intrapartum/neonatal death and neonatal morbidity per 1000 births for the three different SGA groups. For readability reasons we displayed the risks per week (risks per day are available upon request).
The absolute number of women as well as the percentiles and cumulative percentiles of total births are shown in table 2. Remarkably, although the number of induced deliveries was higher in the SGA<P5 group (table 1), the number of early deliveries before 38 weeks was higher in the non-SGA group (Table 2: 6.7% versus. 7.2% p<0.001, respectively).

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>36°-36°</th>
<th>37°-37°</th>
<th>38°-38°</th>
<th>39°-39°</th>
<th>40°-40°</th>
<th>41°-41°</th>
<th>42°-42°</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total births, N</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-SGA</td>
<td>24,452</td>
<td>59,305</td>
<td>153,450</td>
<td>280,392</td>
<td>352,140</td>
<td>232,183</td>
<td>66,601</td>
<td>1,168,523</td>
</tr>
<tr>
<td>SGA P5-10</td>
<td>829</td>
<td>2,445</td>
<td>7,136</td>
<td>14,382</td>
<td>18,239</td>
<td>12,231</td>
<td>3,640</td>
<td>58,902</td>
</tr>
<tr>
<td>SGA&lt;P5</td>
<td>1,019</td>
<td>3,082</td>
<td>7,744</td>
<td>14,701</td>
<td>18,254</td>
<td>12,481</td>
<td>3,740</td>
<td>61,021</td>
</tr>
<tr>
<td><strong>Total births, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-SGA</td>
<td>2.09</td>
<td>5.08</td>
<td>13.13</td>
<td>24.00</td>
<td>30.14</td>
<td>19.87</td>
<td>5.70</td>
<td>100</td>
</tr>
<tr>
<td>SGA P5-10</td>
<td>1.41</td>
<td>4.15</td>
<td>12.12</td>
<td>24.42</td>
<td>30.96</td>
<td>20.76</td>
<td>6.18</td>
<td>100</td>
</tr>
<tr>
<td>SGA&lt;P5</td>
<td>1.67</td>
<td>5.56</td>
<td>17.67</td>
<td>42.09</td>
<td>73.06</td>
<td>93.82</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td><strong>Total births, cumulative %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-SGA</td>
<td>2.09</td>
<td>7.17</td>
<td>20.30</td>
<td>44.30</td>
<td>74.43</td>
<td>94.30</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>SGA P5-10</td>
<td>1.41</td>
<td>5.56</td>
<td>17.67</td>
<td>42.09</td>
<td>73.06</td>
<td>93.82</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>SGA&lt;P5</td>
<td>1.67</td>
<td>6.72</td>
<td>19.41</td>
<td>43.50</td>
<td>73.42</td>
<td>93.87</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Gestational age specific risks of antepartum death, intrapartum/neonatal death and neonatal morbidity for different SGA groups
The risks of antepartum death, intrapartum/neonatal death and neonatal morbidity per 1000 births are plotted in figure 1 for each week of gestation. All risks are highest for the SGA<P5 group, followed by the SGA P5-10 group. The risk differences between the groups are most pronounced at the beginning and the end of the term period (i.e. 36-37 weeks for the risks of intrapartum/neonatal death and neonatal morbidity and 41-42 weeks for the risk of antepartum death).

**Figure 1.** Risks of death and morbidity in the different SGA groups.
Figure 2 displays the antepartum, intrapartum/neonatal death, and neonatal morbidity per day for the three SGA groups. For the non-SGA group, the lines representing the risk of intrapartum/neonatal death overlap the line representing the cumulative risk of antepartum death between 39+0 and 39+6. For the SGA P5-10 group, the lines representing the risk of intrapartum/neonatal death overlap the line representing the cumulative risk of antepartum death at 38+3 until 40+0 weeks. The intersection in the SGA<5 group is at 39+3.

The probability of death with delivery in a certain week versus the probability of death with one week expectant management are represented in table 3.

**Table 3. Probability of death per 1000 with delivery or expectant management for one week**

<table>
<thead>
<tr>
<th></th>
<th>Probability of death per 1000 (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 36 (36^w^-36^w^)</td>
</tr>
<tr>
<td><strong>Non-SGA</strong> delivery in week</td>
<td>3.34 (3.28-3.40)</td>
</tr>
<tr>
<td>one week expectant</td>
<td>1.95 (1.22-2.69)</td>
</tr>
<tr>
<td><strong>SGA P5-10;</strong> delivery in week</td>
<td>9.8 (9.68-9.88)</td>
</tr>
<tr>
<td>one week expectant</td>
<td>4.77 (2.03-1.6)</td>
</tr>
<tr>
<td><strong>SGA&lt;5;</strong> delivery in week</td>
<td>22.8 (20.3-25.6)</td>
</tr>
<tr>
<td>one week expectant</td>
<td>14.5 (5.00-24.0)</td>
</tr>
</tbody>
</table>

SGA, small for gestational age; Bold numbers are statistically significant better strategies, either delivery in a week or expectant management for one week.

Table 4 provides the relative risks and the absolute risk differences including a number needed to deliver at that gestational age to prevent a single excess death. The probabilities of death of both delivery and expectant management are relatively low in the non-SGA group compared to the SGA groups. At the 36^th^ week, expectant management is associated with significantly less mortality than delivery (1.95 vs 3.34 per 1000, RR 0.58 95%CI 0.45-0.75). Also at the 37^th^ week expectant management is associated with less mortality than delivery (1.44 vs 1.78 per 1000, RR 0.81 95%CI 0.64-1.02) At the 38^th^ week, expectant management is associated with less mortality although the confidence intervals of the probability of death overlap (1.09 95%CI 0.89-1.28 vs. 1.26 95%CI 1.24-1.28 per 1000). From the 39^th^ week onwards, delivery is associated with significantly less mortality than expectant management for one week (0.84 vs. 1.06 per 1000, RR1.26 95%CI 1.05-1.50). The numbers needed to deliver to prevent one death vary from 4,627 at 39 weeks to 1,303 at 41 weeks (table 4).
<table>
<thead>
<tr>
<th>Relative risk</th>
<th>95%CI</th>
<th>Absolute risk difference</th>
<th>Number needed to deliver</th>
<th>Relative risk</th>
<th>95%CI</th>
<th>Absolute risk difference</th>
<th>Number needed to deliver</th>
<th>Relative risk</th>
<th>95%CI</th>
<th>Absolute risk difference</th>
<th>Number needed to deliver</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>0.58</td>
<td>-1.41</td>
<td>x</td>
<td>0.49</td>
<td>(0.20-1.17)</td>
<td>-5.03</td>
<td>x</td>
<td>0.64</td>
<td>(0.39-1.04)</td>
<td>-8.28</td>
<td>x</td>
</tr>
<tr>
<td>37</td>
<td>0.81</td>
<td>-0.34</td>
<td>x</td>
<td>0.51</td>
<td>(0.25-1.02)</td>
<td>-2.24</td>
<td>x</td>
<td>0.54</td>
<td>(0.37-0.79)</td>
<td>-6.25</td>
<td>x</td>
</tr>
<tr>
<td>38</td>
<td>0.86</td>
<td>-0.17</td>
<td>x</td>
<td>1.35</td>
<td>(0.70-2.60)</td>
<td>0.64</td>
<td>1,558</td>
<td>1.13</td>
<td>(0.89-1.59)</td>
<td>0.79</td>
<td>1,262</td>
</tr>
<tr>
<td>39</td>
<td>1.26</td>
<td>0.22</td>
<td>4,627</td>
<td>1.02</td>
<td>(0.58-1.78)</td>
<td>0.04</td>
<td>23,840</td>
<td>1.12</td>
<td>(0.83-1.52)</td>
<td>0.61</td>
<td>1,637</td>
</tr>
<tr>
<td>40</td>
<td>1.97</td>
<td>0.75</td>
<td>1,335</td>
<td>1.89</td>
<td>(1.15-3.11)</td>
<td>1.37</td>
<td>729</td>
<td>2.46</td>
<td>(1.80-3.36)</td>
<td>5.63</td>
<td>178</td>
</tr>
<tr>
<td>41</td>
<td>1.68</td>
<td>0.77</td>
<td>1,303</td>
<td>2.42</td>
<td>(1.33-4.41)</td>
<td>2.67</td>
<td>373</td>
<td>1.16</td>
<td>(0.83-1.63)</td>
<td>1.11</td>
<td>898</td>
</tr>
</tbody>
</table>
Figure 2. Balance between antepartum death, intrapartum/neonatal death and neonatal morbidity in the different SGA groups.

No SGA

SGA P5-P10

SGA <P5
For the SGA P5-10 group, there is a trend towards less mortality in the 36th and 37th week with expectant management but the confidence intervals overlap (4.77 vs. 9.80 per 1000 at 36 weeks and 2.31 vs 4.55 per 1000 at 37 weeks). From 38 weeks onwards, delivery is associated with less mortality than expectant management but the confidence intervals overlap. From the 40th week onwards, the differences are statistically significant (2.91 vs. 1.54 per 1000, RR 1.89 95% CI 1.15-3.11). The numbers needed to deliver to prevent one death are 1,558 at 38 weeks and 373 at 41 weeks.

For the SGA<P5 group, expectant management is only favourable in the 36th (22.8 vs. 14.5 per 1000, RR0.64 95% CI 0.39-1.04) and 37th week (13.6 vs. 7.38 per 1000, RR 0.54 95% CI 0.37-0.79). The mortality risks of delivery are lower from 38 weeks onwards although the confidence intervals overlap at 38 and 39 weeks. From 40 weeks onwards delivery is statistically better (3.85 vs. 9.48 per 1000, RR 2.46 95% CI 1.80-3.36). The numbers needed to deliver to prevent one death are 1,262 at 38 weeks and 898 at 41 weeks.

**Discussion**

Our data show that the optimal timing of delivery according to mortality risk in SGA<P5 as well as the SGA P5-10 group is at 38 to 39 weeks, whereas for non-SGA pregnancies this is at 39 to 40 weeks. Delivering a small for gestational age fetus outside this optimal window is associated with a steep increased probability of antepartum death, neonatal death and morbidity compared to non-SGA fetuses. Even fetuses with a birth weight between the 5th and 10th percentile are at increased risk of these adverse outcomes compared to non-SGA fetuses.

Our findings are robust, since both via the intersection of the lines of antepartum death and intrapartum/neonatal death, and via the comparison between the probability of death with delivery and with expectant management, we find the same results.

The strength of this study is the size of the cohort (1,294,547), including patients over a long and recent period (1999-2007), with data derived from a reliable and validated linked population-based database.8,9 The registry includes almost all deliveries in the country (96%) and is therefore a good reflection of our population. In addition, we were able to exclude congenital anomalies and comorbidities, creating a cohort with isolated SGA.

Moreover, this study incorporates the risk of antepartum death with ongoing pregnancy as well as the risk of intrapartum/neonatal death with delivery. Most other studies investigating the timing of delivery in SGA only take the risk of stillbirth into account.2,17

Ideally, this study should be done in a population without any medical interference to study the natural course of pregnancy. We chose to include both women in whom labour was induced as well as those who had a spontaneous onset of labour. In the Netherlands, most antepartum deaths are induced. Analysing only spontaneous deliveries would therefore introduce selection bias because doing so would exclude the majority of antepartum deaths. The fact that we included induced deliveries, implicated that we introduced a medical decision factor that could have influenced our outcomes. In view of the fact that induction was clinically applied and probably based on factors indicating a poor outcome, we hypothesize that the effects would even have been stronger when the natural course would have been followed. Indeed, more women in the SGA group < P5 had labour induced.
One of our study limitations was the use of birth weight instead of estimated fetal weight. We base our decisions to intervene in a pregnancy on estimated fetal weight. Due to the use of registry data instead of original patient records, we do not know which fetuses were suspected to be SGA or growth restricted. As a result, we could not extrapolate which pregnancies had interventions because of the suspected growth restriction. Based on clinical practice, we assumed that pregnancies with abnormal Dopplers or fetal distress were more likely to be delivered earlier than other pregnancies (worst first). However, also SGA fetuses at term with normal umbilical artery Dopplers have lower neurodevelopmental scores \(^{18}\) suggesting also a risk for the fetuses without Doppler abnormalities.

Difficulty with studying antepartum death is that the exact time of the death is mostly not known. The antepartum death could have occurred days before the diagnosis. As a result, the risks at earlier gestational age are probably higher than currently displayed. This would shift the line representing the risk of antepartum death to the left, possibly leading to an earlier optimal timing of delivery. In addition, intrauterine fetal weight gain or loss after antepartum death could have led to misclassification of birth weight percentile in individual cases.

A further point of discussion is the gestational age estimation. Our database does not contain information about pregnancy dating. Although in our study period ultrasound increasingly replaced last menstrual period for dating, no data are available on how pregnancy was dated in individual cases.

Our findings are supported by a secondary analysis of the DIGITAT trial. In the DIGITAT trial, women with suspected growth restriction between 36\(^{10}\) and 41\(^{10}\) were randomized for induction of labour or expectant management \(^{6}\). The goal of the secondary analysis was to assess the neonatal morbidity of both groups in more detail. That analysis showed that the incidence of neonatal morbidity in IUGR at term is comparable and relatively mild either after induction or after expectant management. However, neonatal admissions are lower after 38 weeks of pregnancy. They concluded that if induction to prevent possible stillbirth is considered, it is reasonable to delay until 38 weeks, provided watchful monitoring \(^{39}\). Another study looked at the risk of stillbirth in the SGA group near term and reported that the risk of stillbirth becomes steeper from 39 weeks onwards \(^2\). This is in concurrence with our finding that optimal timing of delivery in SGA fetuses lasts until 39 weeks.

Our conclusion differs from a recent study which advocates a policy of delivery at 37-38 weeks of SGA fetuses based on the 5-fold increased risk of stillbirth \(^{17}\). Notably, the risk of neonatal death was not taken into account. Although our study underlines the fivefold increased risk of stillbirth/antepartum death at and over 37 weeks, our conclusion about the optimal timing of delivery is different because we incorporated both antepartum as well as intrapartum/neonatal risk of death.

Notably, our results also indicate that for women without SGA delivery at 39 weeks is associated with the lowest risk of death. Currently a randomized trial is running in the United States randomizing nulliparous women for induction of labour at 39 weeks of gestation versus expectant management and induction at 42 weeks (NCT01076062)\(^{29}\), which is powered (N=200) on caesarean delivery as primary endpoint. In the future, we need larger studies to address the impact of induction of labour on perinatal mortality and long term neonatal development.

Our results are important since many clinicians induce suspected SGA fetuses at 36 or 37 weeks of gestation without other indications for delivery to prevent antepartum death in these fetuses. Although the Hippocrates oath taught us doctors “first do no harm”, our results indicate that by inducing SGA infants in the early term period in the absence of other indications for delivery, infants might (unintentionally) be harmed.
We think that with the current knowledge it is reasonable to delay delivery of isolated SGA infants until 38 weeks without other indications for delivery and watchful monitoring. It is important to realize that the earlier mentioned DIGITAT study indicated that, based on randomized data, there was no harm observed from induction of labour in terms of an increased Caesarean section rate or poor neonatal outcome rate, and that financial costs were comparable. 

Obviously, maternal preferences and maternal and fetal condition should be taken into account in the ultimate decision, but our data shown that in pregnancies with suspected SGA, induction of labour should be the advised policy from 38 weeks onwards.
References


(20) www.clinicaltrials.gov Clinical Trials. 2013.
## Appendix 1. Univariable analysis of factors associated with SGA at birth and multivariable models to predict SGA (<10<sup>th</sup> percentile and <5<sup>th</sup> percentile) at birth

### Birthweight <10<sup>th</sup> percentile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>p-value</td>
<td>OR (95%CI)</td>
<td>p-value</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.98 (0.97 to 0.99)</td>
<td>0.001</td>
<td>0.98 (0.97 to 1.00)</td>
<td>0.03</td>
<td>1.01 (0.99 to 1.03)</td>
</tr>
<tr>
<td>BMI (per point)</td>
<td>0.96 (0.94 to 0.97)</td>
<td>&lt;0.001</td>
<td>0.96 (0.94 to 0.98)</td>
<td>&lt;0.001</td>
<td>0.97 (0.95 to 0.99)</td>
</tr>
<tr>
<td>Primiparity</td>
<td>1.12 (0.96 to 1.30)</td>
<td>0.15</td>
<td>1.24 (1.00 to 1.53)</td>
<td>0.05</td>
<td>1.20 (1.20 to 1.93)</td>
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<tr>
<td>Male sex</td>
<td>0.94 (0.81 to 1.09)</td>
<td>0.38</td>
<td>1.26 (1.04 to 1.54)</td>
<td>0.02</td>
<td>1.14 (1.23 to 1.91)</td>
</tr>
<tr>
<td>2nd trimester EFW ratio</td>
<td>6.13E-4 (2.7E-4 to 14.0E-4)</td>
<td>&lt;0.001</td>
<td>0.001 (0.00 to 0.003)</td>
<td>&lt;0.001</td>
<td>6.9E-7 (1.9E-7 to 26.0E-7)</td>
</tr>
<tr>
<td>3rd trimester EFW ratio</td>
<td>0.01 (3.6E-7 to 27.0E-7)</td>
<td>&lt;0.001</td>
<td>0.001 (0.006 to 0.017)</td>
<td>&lt;0.001</td>
<td>0.01 (0.36 to 2.54)</td>
</tr>
<tr>
<td>2nd trimester AC ratio</td>
<td>5.5E-12 (0.8E-12 to 39.2E-12)</td>
<td>&lt;0.001</td>
<td>0.001 (0.006 to 0.017)</td>
<td>&lt;0.001</td>
<td>0.01 (0.36 to 2.54)</td>
</tr>
<tr>
<td></td>
<td>AUC (95%CI)</td>
<td></td>
<td>AUC (95%CI)</td>
<td></td>
<td>AUC (95%CI)</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.67 to 0.72)</td>
<td></td>
<td>0.69 (0.67 to 0.72)</td>
<td></td>
<td>0.69 (0.67 to 0.72)</td>
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</table>

### Birthweight <5<sup>th</sup> percentile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>p-value</td>
<td>OR (95%CI)</td>
<td>p-value</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.99 (0.97 to 1.00)</td>
<td>0.09</td>
<td>0.98 (0.96 to 1.00)</td>
<td>0.07</td>
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</tr>
<tr>
<td>BMI (per point)</td>
<td>0.95 (0.93 to 0.97)</td>
<td>&lt;0.001</td>
<td>0.96 (0.93 to 0.98)</td>
<td>&lt;0.001</td>
<td>0.97 (0.95 to 1.00)</td>
</tr>
<tr>
<td>Primiparity</td>
<td>1.25 (1.03 to 1.52)</td>
<td>0.03</td>
<td>1.21 (1.21 to 1.22)</td>
<td>0.001</td>
<td>1.21 (1.21 to 1.30)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.99 (0.82 to 1.20)</td>
<td>0.94</td>
<td>1.41 (1.10 to 1.82)</td>
<td>0.01</td>
<td>1.76 (1.32 to 2.33)</td>
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<tr>
<td>2nd trimester EFW ratio</td>
<td>1.7E-4 (0.6E-4 to 4.8E-4)</td>
<td>&lt;0.001</td>
<td>1.7E-4 (0.4E-4 to 7.1E-4)</td>
<td>&lt;0.001</td>
<td>1.7E-7 (0.3E-7 to 8.9E-7)</td>
</tr>
<tr>
<td>3rd trimester EFW ratio</td>
<td>3.7E-7 (1.1E-7 to 13E-7)</td>
<td>&lt;0.001</td>
<td>1.5E-7 (0.3E-7 to 8.9E-7)</td>
<td>&lt;0.001</td>
<td>1.5E-7 (0.2E-7 to 3.8E-7)</td>
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<tr>
<td>2nd trimester AC ratio</td>
<td>1.0E-12 (0.9E-12 to 11.4E-12)</td>
<td>&lt;0.001</td>
<td>1.0E-12 (0.9E-12 to 11.4E-12)</td>
<td>&lt;0.001</td>
<td>1.0E-12 (0.9E-12 to 11.4E-12)</td>
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<tr>
<td></td>
<td>AUC (95%CI)</td>
<td></td>
<td>AUC (95%CI)</td>
<td></td>
<td>AUC (95%CI)</td>
</tr>
<tr>
<td></td>
<td>0.71 (0.70 to 0.76)</td>
<td></td>
<td>0.87 (0.85 to 0.89)</td>
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<td>0.87 (0.85 to 0.89)</td>
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</table>

SGA, small for gestational age; OR, odds ratio; 95% CI, 95% confidence interval; AUC, area under the curve; BMI, body mass index; EFW, estimated fetal weight; AC, abdominal circumference.
Chapter 9

Potential improvement of pregnancy outcome through antenatal small for gestational age detection

Bart Jan Voskamp, Daphne H Beemsterboer, Corine JM Verhoeven, Katrien Oude Rengerink, Anita CJ Ravelli, Jannet J.H. Bakker, Ben Willem J. Mol, Eva Pajkrt

American Journal of Perinatology, 2014
Abstract

Objective: To assess differences in mode of delivery and pregnancy outcome between antenatally-detected and not-antenatally-detected small for gestational age (SGA) neonates born at term.

Study design: We performed a retrospective multicenter cohort study. All singleton neonates born SGA in cephalic position between 36°0 and 41°0 weeks gestation were classified as either antenatally-detected-SGA or not-antenatally-detected-SGA. With propensity score matching we created groups with comparable baseline characteristics. We compared these groups for composite adverse perinatal outcome, labor induction and cesarean section rates.

Results: We included 718 SGA infants, of whom 555 [77%] were not-antenatally-detected. Composite adverse neonatal outcome did not differ statistically significant between the matched antenatally-detected and the not-antenatally-detected group (5.5% versus 7.4%, odds ratio (OR) 0.74, 95% confidence interval (CI) 0.30-1.8). However, perinatal mortality only occurred in the not-antenatally-detected group (1.8% [3/163] in the matched cohort, 1.3% [7/555] in the complete cohort. In the propensity matched antenatally-detected SGA group both induction of labor (57% versus 9%, OR 14.0, 95%CI 7.4-26.2) and cesarean sections (20% versus 8%, OR 2.9, 95%CI 1.5-5.8) were more often performed compared to the not-antenatally-detected SGA group.

Conclusion: Antenatal SGA detection at term allows timely induction of labor and cesarean sections thus potentially preventing stillbirth.
Introduction

Small for gestational age (SGA) neonates are defined as neonates with a birth weight below the 10th percentile of the growth curve for a given gestational age. In the Netherlands annually approximately 18,000 neonates are born SGA, the majority at term.1-2 This is a heterogeneous group comprising neonates that are constitutionally small and neonates that have failed to achieve their growth potential because they are growth restricted based on utero-placental insufficiency, congenital anomalies or infection.3-5 SGA is associated with an increased risk of adverse pregnancy outcome and adverse events in the postpartum phase.6-9 The more pronounced the SGA, the higher the risk of antepartum death.10

It is assumed that early detection of SGA could improve fetal outcome by close fetal monitoring and the possibility for timely induction of labor or instrumental delivery when fetal condition seems compromised.11 At present, no effective intervention is available to improve the outcome of SGA infants at term.6 Ohel et al. and Verlijsdonk et al. both assessed differences in management of labor and perinatal outcome between antenatally detected SGA and not antenatally detected SGA at term.12-13 While both studies showed more labor inductions and cesarean sections in the antenatally detected SGA group, pregnancy outcome differed between the two studies. Ohel et al. and colleagues showed a higher rate of adverse neonatal outcome in antenatally detected SGA12, whereas Verlijsdonk and colleagues concluded that antenatal suspected SGA was associated with lower rates of adverse neonatal outcome compared to not antenatally detected SGA (3.8% versus 9.0%, p=0.056).13 Both studies were small and likely biased by confounding because results were not adjusted for severity of growth restriction. This resulted in comparison of more severely growth restricted - antenatally detected - infants to generally milder SGA infants that were detected after birth. The actual impact of the antenatal detection of SGA remains uncertain.

The aim of this study was to assess, in groups with a comparable possibility of antenatal SGA detection, whether antenatal SGA detection in term infants improves perinatal outcome and whether this detection influences the timing and mode of delivery.

Methods

Study design
We conducted a retrospective cohort study of women with a singleton SGA child born at home or in the hospital between 36th and 41th weeks of gestation, between April 1st 2005 and December 31st 2008. We classified infants as being antenatally-detected SGA and not-antenatally-detected SGA. Classification of antenatal SGA detection was based on ultrasonographically measured abdominal circumference <p10, estimated fetal weight <p10, flattening of the growth curve in the third trimester (as judged by a clinician) or the presence of all three factors. Subsequently, we created comparable groups of antenatally detected SGA and not antenatally detected SGA infants by propensity score matching and compared pregnancy outcome and mode of delivery between these two groups.

Inclusion and exclusion criteria
We included pregnant women ≥ 18 years with a singleton pregnancy who gave birth to SGA neonates at a gestational age between 36th and 41th weeks in the catchment area of one of the following two hospitals and seven midwifery practices. The Academic Medical Center in Amsterdam, the Maxima
Medical Center in Veldhoven, or one of seven independent midwifery practices referring to these two medical centers.

To warrant comparability of pregnancies with an antenatally detected SGA and not antenatally detected SGA infants, we excluded women with a breech presentation at birth, women with a child with fetal structural or chromosomal anomalies, women with a previous cesarean section, and women with pregnancies with uncertainty about duration of pregnancy.

SGA was defined as a birth weight below the 10th percentile for gestational age.\textsuperscript{14} The Dutch reference curves for birth weight by gestational age stratified for parity, sex and ethnic background were used to calculate birth weight percentiles on a continuous scale for all infants.\textsuperscript{14} Pregnancy dating was performed by last menstrual period, or ultrasound measurements before 20 weeks of gestation (crown-rump-length) or head-circumference measurement.

Data collection
We searched the perinatal databases from the two participating hospitals and seven midwifery practices, to identify pregnancies with an antenatally detected SGA infant. Antenatally detected SGA infants had previously been eligible for inclusion in the DIGITAT study, an RCT that was performed to compare the effect of induction of labor with a policy of expectant monitoring for intrauterine growth restriction near term.\textsuperscript{6} We used the same gestational age criteria as in the DIGITAT study to avoid loss of cases through a cut-off at term (37\textsuperscript{th} weeks gestation) instead of 36\textsuperscript{th} weeks gestation. To ensure inclusion of all not antenatally detected SGA infants in the study period, we used the Netherlands Perinatal Registry (PRN), to complement data that could not be retrieved from the medical files. The PRN is a national database that contains linked maternal and neonatal data entered by midwives, gynecologists, and pediatricians.\textsuperscript{15} It contains information on 96\% of all pregnancies, home and hospital births, and re-admissions until 28 days after birth. It does not contain information on whether SGA is detected antenatally.\textsuperscript{16} We collected information on maternal characteristics: body mass index (BMI), smoking, parity, gestational hypertension; delivery characteristics: start of labor, mode of delivery, gestational age at delivery; and neonatal characteristics: Apgar score, birth weight, sex, neonatal complications, intra-uterine fetal death and neonatal death.

Outcome measures
Outcomes of this study were adverse perinatal outcomes, intra-uterine fetal death, neonatal death, neonatal complications, and a composite of these adverse outcomes. We also assessed whether there were differences in induction of labor and instrumental delivery rates between both groups.

Intra-uterine fetal death was defined as spontaneous fetal demise between 36\textsuperscript{th} and 41\textsuperscript{th} weeks gestation and neonatal death was defined as a live birth resulting in infant death within 28 days of life. Neonatal complications were defined as five minute Apgar score < 7, asphyxia, infant respiratory distress syndrome (IRDS), meconium aspiration, pneumothorax or pneumomediastinum, necrotizing enterocolitis (NEC), convulsions, sepsis and meningitis. Instrumental delivery was divided into primary cesarean section, cesarean section in labor and instrumental vaginal delivery.

Analysis
We used propensity score matched-pairs analyses to determine the association between antenatal-SGA detection and the primary and secondary outcomes, while balancing potentially important confounders between both groups. The rationale and methods underlying the use of propensity scores for proposed causal exposure variables have been previously described.\textsuperscript{17,18}
The propensity scores were generated by logistic regression, based on all covariates that were known to be associated with perinatal outcome and that existed before the start of labor. We considered the continuous covariates maternal age, maternal BMI and birth weight percentile as well as the dichotomous covariates primiparity, maternal smoking, gestational hypertension, birth weight <p2.3 and birth weight <p5. Since propensity scores cannot be calculated if one of the variables is missing, single imputation was used to replace missing values.19

The standardized difference was used to assess the balance of the covariates, as unlike significance testing it is not dependent of the size of the sample.17 A standardized difference greater than 10% points was used to indicate that the samples were meaningfully different.20 After generation of propensity scores, pairs were matched on their propensity score, using one-to-one nearest neighbor matching without replacement.21-25 We matched not antenatally detected SGA infants to the smallest group (antenatally detected SGA), to ensure that as many matches as possible could be made.

To compare baseline and pregnancy characteristics of antenatally and not antenatally detected SGA pregnancies we used Student’s t tests, χ2 tests, and Fisher’s exact tests. In the matched cohort, the standardized difference was used to assess the balance of the covariates of the propensity scores. We also assessed the baseline characteristics of both groups to ensure that matching increased comparability.

To compare outcomes between antenatally detected and not detected SGA infants, odds ratios with 95% confidence intervals (CIs) were computed for all dichotomous outcomes using logistic regression. Mean differences and 95% CIs were calculated for continuous variables with the independent T-test for normally distributed data. The Mann-Whitney U Test was used to assess differences in continuous variables that were not normally distributed.

In a sensitivity analysis, we performed the analyses on a propensity score matched cohort of the original (non-imputed) dataset. We also used multivariable logistic regression analysis in the original dataset to determine the adjusted association of antenatally detected SGA with adverse outcome and mode of delivery in the entire sample.

Statistical analyses were conducted with SPSS version 19.0 for Windows. Propensity score calculation and matching were performed in R with the SPSS R-plugin.26 The following R packages were invoked: Matchit,23-24 Rtools,22 and cem.26 A two-tailed p-value < .05 was considered statistical significant.

Results

In the study period, 11,142 women delivered in one of the selected centers. Figure 1 displays all our exclusions to arrive at a final cohort of 718 SGA infants. Table 1 shows the baseline pregnancy characteristics for antenatally detected SGA and not antenatally detected SGA pregnancies in the unmatched cohort. The majority of SGA infants, 77% [555/718] remained undetected until after birth.

Characteristics of the antenatally detected SGA group and the not antenatally detected SGA group are presented in table 1. In the antenatally detected SGA group 51% of infants were <p2.3 versus 21% in the not antenatally detected SGA group. Smoking and primiparity were more prevalent in the antenatally detected SGA group (OR [95%CI] 2.8 (1.9-4.2), and 1.6 (1.2-2.4) respectively).

We know of 234 women in the cohort that they were referred for ultrasound growth assessment in the third trimester of pregnancy. Nineteen percent [45/234] of these women were reassured
about fetal growth but gave birth to an SGA infant. Because SGA was no longer suspected after the ultrasound, infants delivered by these women are classified as not antenatally detected SGA infants.

Five of the six predefined baseline variables used for propensity score matching contained no missing data because these variables were required fields that caregivers are used to register. The sixth variable BMI lacked in 44% [316/718] of the women. Distribution plots of propensity scores in the 2 groups are shown in figure 2. Overall, as a function of baseline characteristics, the antenatally detected SGA group had a higher probability of antenatal SGA detection, as indicated by a higher mean propensity score (0.315 ±0.156 vs. 0.201 ±0.127; P < .001).

### Table 1. Baseline characteristics of the total cohort in antenatally detected and non-detected SGA neonates.

<table>
<thead>
<tr>
<th></th>
<th>SGA detected antenatally (n=163)</th>
<th>SGA not detected antenatally (n=555)</th>
<th>P-value</th>
<th>Standardized difference (%)</th>
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<tbody>
<tr>
<td><strong>Maternal characteristics</strong> *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age years, mean (SD)</td>
<td>29.3 (5.7)</td>
<td>30.1 (5.8)</td>
<td>0.11</td>
<td>-14.6</td>
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<td>BMI*, median (range)</td>
<td>22.5 (16-44)</td>
<td>22.2 (16-43)</td>
<td>0.69</td>
<td>-2.6</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
<td>90 (55)</td>
<td>237 (43)</td>
<td>&lt; 0.01</td>
<td>25.1</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>53 (33)</td>
<td>82 (15)</td>
<td>&lt; 0.01</td>
<td>37.8</td>
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<td>Gestational hypertension, n (%)</td>
<td>9 (5.5)</td>
<td>26 (4.7)</td>
<td>0.67</td>
<td>3.7</td>
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<td><strong>Infant characteristics</strong></td>
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<tr>
<td>Birth weight percentile, median (range)</td>
<td>1.6 (0-9.9)</td>
<td>5.1 (0-10)</td>
<td>&lt;0.01</td>
<td>-63.9</td>
</tr>
<tr>
<td>Birth weight &lt;p2.3, n (%)</td>
<td>83 (51)</td>
<td>118 (21)</td>
<td>&lt;0.01</td>
<td>59.1</td>
</tr>
<tr>
<td>Birth weight &lt;p5, n (%)</td>
<td>124 (76)</td>
<td>270 (49)</td>
<td>&lt;0.01</td>
<td>64.1</td>
</tr>
</tbody>
</table>

* The body-mass index is the weight in kilograms divided by the square of the height in meters. SGA: small for gestational age (birth weight <p10)
The initial difference in the two groups was further supported by the standardized difference criterion, which revealed that six of the eight baseline covariates (75%) had a standardized difference of >10% and therefore were imbalanced by this criterion. The identified differences and the inherent selection bias they represent, supported the need for further adjustment with propensity matching. This matching process resulted in the creation of 163 matched antenatally detected SGA and not antenatally detected SGA pairs.

**Figure 2.** Distribution of propensity scores before and after matching. Pregnancies were stratified by antenatal SGA detection

![Unmatched adSGA](image1.png) ![Matched adSGA](image2.png)

![Unmatched nadSGA](image3.png) ![Matched nadSGA](image4.png)

Figure 2 displays the distributions of the two matched groups’ propensity scores. In contrast to the distributions of the unmatched groups, it reveals a high degree of overlap and similarity of shape between the two groups. This improved covariate balance was also reflected as the reduced difference in the means of the propensity scores reduced from 0.114 before matching, to 0.004 after matching (0.315 ± 0.156 in the antenatally detected SGA group and 0.311 ± 0.150 in the not antenatally detected SGA group; p = 0.80). The standardized difference criterion analysis confirmed the groups’ similarity, as the highest standardized difference was 7.9%, where <10% is deemed acceptable (Table 2).

The distribution of the outcomes in the matched pairs of antenatally detected SGA and not antenatally detected SGA is presented in table 3. Composite adverse neonatal outcome occurred in 5.5% [9/163] of infants in the antenatally detected SGA group and 7.4% [12/163] in the not antenatally detected SGA group (OR 0.74, 95% CI 0.30-1.8). Perinatal death occurred in none of the 163 antenatally detected SGA neonates and in three (1.8%) of the 163 not antenatally detected SGA neonates (OR not calculable, p= 0.996). Birth weights of these three infants were below the first
percentile. The cohort was too small to detect differences in subcategories of adverse neonatal outcome, but no obvious differences between the two groups were observed.

Table 2. Baseline characteristics of matched cohort in antenatally detected and non-detected SGA neonates.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>SGA detected antenatally (n=163)</th>
<th>SGA not detected antenatally (n=163)</th>
<th>P-value</th>
<th>Standardized difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years, mean (SD)</td>
<td>29.3 (5.7)</td>
<td>29.3 (6.1)</td>
<td>0.99</td>
<td>-0.1</td>
</tr>
<tr>
<td>BMI*, median (range)</td>
<td>22.9 (16-44)</td>
<td>22.8 (16-43)</td>
<td>0.45</td>
<td>7.9</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
<td>90 (55)</td>
<td>91 (56)</td>
<td>0.91</td>
<td>-1.2</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>53 (33)</td>
<td>52 (32)</td>
<td>0.91</td>
<td>1.3</td>
</tr>
<tr>
<td>Gestational hypertension, n (%)</td>
<td>9 (5.5)</td>
<td>9 (5.5)</td>
<td>1.00</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* The body-mass index is the weight in kilograms divided by the square of the height in meters. SGA: small for gestational age (birth weight <10th percentile)

In the complete (unmatched) cohort (n=718), perinatal mortality did not occur among 163 antenatally detected SGA infants and in 1.3% [7/555] of the not antenatally detected SGA infants. These comprised six fetal deaths before the onset of labor (detected at 374+4, 381+1, 391+2, 401+2, and 401+5 weeks GA), and one fetal death during labor (401+6 weeks GA).

To show a statistical significant difference (with alpha 0.05) in composite adverse neonatal outcome with 80% power, a sample size of 2727 per group is needed. To show a statistical significant difference in perinatal death, a sample size of 422 per group is needed.

Labor was more often induced if SGA was detected antenatally (57% of women versus 9% of women, OR 14, 95% CI 7.4-26). There were more cesarean sections performed in the antenatally detected SGA group (20%) than in the not antenatally detected SGA group (8%) (OR 2.9, 95% CI 1.5-5.8), mostly all for suspected fetal distress. Failure to progress was never the indication for a cesarean section in labor in the antenatally detected SGA group and once (0.6%) in the not antenatally detected SGA group.

The rate of vaginal instrumental delivery in the antenatally detected SGA group (6%) was lower than in the not antenatally detected SGA group (12%) although this did not reach statistical significance (OR 0.50, 95% CI 0.22-1.1, p=0.09). There were no significant differences in indication for vaginal instrumental delivery between the antenatally detected SGA and not antenatally detected SGA group (Table 3). On average, antenatally detected SGA neonates were born 7.4 days earlier than not antenatally detected SGA neonates (381+5 vs. 391+5 weeks, 95% CI -9.3 to -5.6, p<.001), and antenatally detected SGA neonates weighed on average 223 grams less than not antenatally detected SGA neonates (median 2410 vs. 2640 grams, 95% CI -293 to -153, p<.001).

Sensitivity analyses
Both the percentages and p-values of the multivariable logistic regression analysis on the complete cohort (n=718) (Appendix 1), and the analyses on the non-imputed cohort after propensity score matching (Appendix 2 and 3), were comparable to the results of the propensity score analysis.
Table 3. Propensity score matched (1:1) analysis of the association between antenatal SGA (BW<10th percentile) detection and adverse pregnancy outcome and perinatal interventions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SGA detected antenatally (n=163)</th>
<th>SGA not detected antenatally (n=163)</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction of labor</td>
<td>93 (57)</td>
<td>14 (9)</td>
<td>&lt;0.001</td>
<td>13.95</td>
<td>(7.43 to 26.19)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>43 (26)</td>
<td>32 (20)</td>
<td>0.15</td>
<td>1.46</td>
<td>(0.87 to 2.5)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>33 (20)</td>
<td>13 (8)</td>
<td>0.02</td>
<td>2.93</td>
<td>(1.48 to 5.80)</td>
</tr>
<tr>
<td>Primary cesarean section</td>
<td>7 (4.3)</td>
<td>1 (0.6)</td>
<td>0.07</td>
<td>7.27</td>
<td>(0.88 to 59.77)</td>
</tr>
<tr>
<td>Cesarean section in labor</td>
<td>26 (16)</td>
<td>12 (7.4)</td>
<td>0.02</td>
<td>2.39</td>
<td>(1.16 to 4.92)</td>
</tr>
<tr>
<td>Failure to progress</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>0.996</td>
<td>Not calculable</td>
<td></td>
</tr>
<tr>
<td>Fetal distress</td>
<td>26 (16)</td>
<td>11 (6.7)</td>
<td>0.03</td>
<td>2.27</td>
<td>(1.07 to 4.83)</td>
</tr>
<tr>
<td>Vaginal instrumental delivery</td>
<td>10 (6.1)</td>
<td>19 (12)</td>
<td>0.09</td>
<td>0.50</td>
<td>(0.22 to 1.10)</td>
</tr>
<tr>
<td>Failure to progress</td>
<td>2 (1.2)</td>
<td>7 (4.3)</td>
<td>0.11</td>
<td>0.28</td>
<td>(0.06 to 1.35)</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>8 (4.9)</td>
<td>12 (7.4)</td>
<td>0.36</td>
<td>0.65</td>
<td>(0.26 to 1.63)</td>
</tr>
<tr>
<td><strong>Neonatal outcome, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gestational age at birth (days), mean (SD)</td>
<td>270.6 (9.6)</td>
<td>278.0 (6.6)</td>
<td>&lt;0.001</td>
<td>-7.4*</td>
<td>(-9.3 to -5.6)</td>
</tr>
<tr>
<td>Birth weight (g), median (range)</td>
<td>2410 (1420-3080)</td>
<td>2640 (1765-3250)</td>
<td>&lt;0.001</td>
<td>-223*</td>
<td>(-293 to -153)</td>
</tr>
<tr>
<td>Composite adverse neonatal outcome</td>
<td>9 (5.5)</td>
<td>12 (7.4)</td>
<td>0.50</td>
<td>0.74</td>
<td>(0.30 to 1.80)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>0 (0.0)</td>
<td>3 (1.8)</td>
<td>0.996</td>
<td>Not calculable</td>
<td></td>
</tr>
<tr>
<td>5min Apgar Score &lt;7</td>
<td>4 (2.5)</td>
<td>4 (2.5)</td>
<td>1.00</td>
<td>1.00</td>
<td>(0.25 to 4.07)</td>
</tr>
<tr>
<td>Neonatal complications&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (1.8)</td>
<td>4 (2.5)</td>
<td>0.70</td>
<td>0.75</td>
<td>(0.16 to 3.38)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRDS</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td>0 (0.0)</td>
<td>2 (1.2)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (0.6)</td>
<td>3 (1.9)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> mean difference and 95% confidence interval (CI); <sup>b</sup> number of infants with neonatal complications, some infants have more than one complication; OR, odds ratio; n.c., not calculated; inf, infinite; IRDS, infant respiratory distress syndrome; NEC, necrotizing enterocolitis; SGA, small for gestational age (birth weight <10<sup>th</sup> percentile)
Chapter 9

Discussion

This study confirms that in a system without routine 3rd trimester growth screening ultrasounds, the large majority of women with a term SGA pregnancy remain undetected until birth. However, severe SGA was more likely to be detected antenatally than mild SGA, although even in women with a child below the 2.3th percentile the diagnosis FGR was missed in 60%.\textsuperscript{12,13} Obviously, antenatal SGA detection is associated with induction of labor and cesarean section\textsuperscript{12,13}. Women with antenatally detected SGA gave birth more than a week earlier, and birth weight of antenatally detected SGA infants is more than 200 grams lower. In the whole not antenatally detected SGA group there were seven fetal deaths (of which three in the propensity score matched group), while none of the antenatally detected SGA infants died. The composite poor neonatal outcome occurred less often in the antenatally detected SGA group, although the difference was not statistically significant.

Strengths

Our study has several strengths. First, we assessed outcomes of antenatally detected SGA and not antenatally detected SGA pregnancies balanced for propensity score, and therefore balanced for the covariates used to estimate the propensity score. These balanced covariates will no longer confound the relation between antenatal SGA detection and the outcome. Therefore, in contrast to two previous studies on the same subject where propensity score matching has not been performed to create comparable groups, the estimation will be theoretically unbiased, or at least less bias will have occurred.\textsuperscript{12,13}

Second, we incorporated severity of SGA into the model as a continuous variable (birth weight percentile), instead of adjusting for birth weight and gestational age at delivery. Failure to do so in other studies might have biased the association between SGA detection and perinatal outcome.\textsuperscript{12,13} The reliability of our results is further supported by the completeness and accuracy of antenatal and postnatal data of mother and child. Complete data were available for all pregnancies because data were extracted from the original patient files and complemented with use of the PRN registry if needed.

Limitations

A first limitation of this study is its sample size combined with the low incidence of adverse pregnancy outcome, specifically regarding perinatal mortality. Given the low incidence of adverse pregnancy outcome at term, a very large sample is required to show a difference. Although this study does not have enough power to detect a statistically significant difference in rare adverse neonatal outcomes, to our knowledge this is the largest study that compared outcome of antenatally detected SGA with not antenatally detected SGA infants. The precision of the results is quite limited due to the sample size, but the propensity score matching has resolved most of the bias that would be present in larger samples that are unmatched for relevant baseline variables.

Second, there is a possible a priori risk selection of antenatally detected SGA pregnancies. Women with an increased a priori risk of adverse pregnancy outcome receive regular ultrasound growth assessment. As a result, SGA infants in this high-risk population will likely be detected antenatally, whereas SGA is more likely to remain undetected until birth in low-risk pregnancies. We expect to have minimized this effect by the propensity score matching of the potential confounding maternal characteristics that were available and severity of SGA. However, we cannot fully exclude the possibility of residual confounding.
Third, in case of fetal death, there was no certainty about the moment of demise. This might have led to an overestimation of SGA severity in these infants. We expect this overestimation to be limited because - according to the Dutch protocol - all pregnant women undergo weekly checkups including Doppler auscultation of the fetal heart rate.

Fourth, unfortunately we did not know for all pregnancies if third trimester growth ultrasound had been performed. Consequently, we cannot report sensitivity and specificity of growth ultrasounds. The false reassurance about fetal growth in 19% of women that were referred for suspicion of SGA makes us suspect that the sensitivity of prenatal ultrasound especially in high-risk pregnancies can be improved. Due to propensity score matching we could not take the majority of not antenatally detected SGA infants into account in the analyses. We first performed one-to-two matching to limit the data loss but the matching process did not yield comparable groups, mainly due to considerable difference in SGA severity between antenatally detected SGA and not antenatally detected SGA infants. We have chosen one-to-one matching to warrant optimal comparability of antenatally detected SGA and not antenatally detected SGA infants and thus to obtain more reliable results. Additional sensitivity analyses on the entire imputed sample of 718 SGA neonates and on the original, non-imputed, cohort after propensity score matching showed results similar to the propensity-score analysis.

Considerations about results
This study confirms the low antenatal detection rates of SGA.\textsuperscript{12,13,27} The majority of pregnancies with an SGA infant remained undetected until birth, severe SGA is more likely to be detected antenatally. This is in concordance with literature which showed that the results of ultrasounds are unreliable to estimate the fetal weight <P10 correctly.\textsuperscript{28,29} Previous studies have also shown high false positive rates (30%) of antenatal SGA detection.\textsuperscript{6} Since we only assessed infants with a birth weight below the 10\textsuperscript{th} percentile for gestational age, we could not rule on specificity of prenatal growth ultrasound.

Maternal smoking was more prevalent in the antenatally detected SGA group. This might be caused by awareness of caregivers for the potentially adverse effect of maternal smoking on fetal growth.\textsuperscript{6,30-33} The statistically significant lower gestational age at birth and lower birth weight of the infants in the antenatally detected SGA group can be explained by the higher incidence of obstetrical interventions in this group.\textsuperscript{12,13,28,33}

The study by Verlijlsdonk et al. concluded that suspicion of SGA was associated with a more active management of labor and delivery, resulting in a better neonatal outcome at birth.\textsuperscript{13} We observed a similar trend as Verlijlsdonk et al. that antenataly detected SGA fetuses have a better perinatal outcome. Combining the cohort of Verlijlsdonk et al. with our matched cohort results in 0.6% [2/321] perinatal deaths among antenatally detected SGA infants and 2.3% [10/435] perinatal deaths among not antenatally detected SGA infants (OR 0.27, 95% CI 0.06-1.22, p0.09). Suggesting improved perinatal outcome of antenatally detected SGA infants compared to not antenatally detected SGA infants.

Our study also confirms the more active management of labor among antenatally detected SGA infants. Increased induction of labor in the antenatally detected SGA group did not lead to higher rates of cesarean sections for failure to progress (stage I and II), but it led to more cesarean sections for suspected fetal distress, and less vaginal instrumental deliveries. The increased rate of cesarean sections and decreased rate of vaginal instrumental deliveries in antenatally detected SGA pregnancies might be caused by earlier intervention in case of suspected fetal distress - in view of the suspected SGA -, or possible preference of the caregiver not to perform vaginal instrumental
delivery if severe SGA is suspected. This assumption is supported by the trend towards more vaginal instrumental deliveries in the not antenatally detected SGA group.

Choosing the 10th percentile as SGA cut-off causes inclusion of a relatively large group of low-risk constitutionally small infants into the study population, by definition 10% of the population. Previous research has shown an association between the severity of SGA and perinatal outcome. A study by Unterschneider et al. showed that an estimated fetal weight <p3 is strongly and consistently associated with adverse perinatal outcome. Our population consisted of a heterogeneous group of SGA infants. However, after propensity score matching, the median birth weight percentiles were 1.6 and 1.9 among antenatally detected SGA and not antenatally detected SGA infants, indicating selection of mainly infants who are severely SGA.

Although this study was underpowered to show a difference in the incidence of perinatal mortality between not antenatally detected SGA and antenatally detected SGA infants, there were no perinatal deaths among antenatally detected SGA infants and seven among not antenatally detected SGA infants in the complete cohort of 718 infants.

In the propensity-matched cohort, these numbers were zero and three respectively. Six out of seven fetal deaths occurred before the onset of labor, versus one fetal death during labor. Considering the fact that death only occurred in SGA infants that were not detected antenatally, in which SGA was relatively milder than in the antenatally detected SGA group, it is not unlikely that death could have been avoided with fetal monitoring and induced labor if SGA had been detected before birth. However, we are not sure how antenatal SGA detection can be improved.

The low antenatal SGA detection rate in our study has several potential causes. First, the absence of 3rd trimester ultrasound growth assessment as part of standard pregnancy care might play a role. Although it seems logical that 3rd trimester ultrasound as part of standard pregnancy care improves SGA detection rates, this has to our knowledge not been proven. Unfortunately our data do not allow quantification of how many women underwent 3rd trimester ultrasound growth assessment.

Second, inaccuracy of ultrasound growth assessment in the 3rd trimester might play a role. Antenatal ultrasound growth assessment is usually performed prior to 36-40 weeks gestation because diagnostic accuracy decreases with advancing gestational age.

A third possibility is that growth impairment starts after a reassuring 3rd trimester growth ultrasound has been performed. We do not know if severe SGA always originates gradually and that poor detection is caused by inaccurate ultrasound measurements, or that growth of properly grown infants slows and comes to a halt after a–proper– ultrasound measurement in the third trimester.

Implications for clinical practice
This study shows that in the Dutch care system term SGA often remains undetected until birth and that prenatal SGA detection might prevent neonatal deaths. Caregivers and especially ultrasonographers should be aware of this to avoid as much as possible false reassurance of fetal growth.

If in any doubt about fetal growth, women should be followed-up with umbilical artery measurements. This allows for intervention if fetal condition is compromised and might prevent unnecessary interventions on constitutionally small infants that are not growth restricted. Also, it is rational to choose induction after 38-40 weeks GA in case of suspected SGA to prevent possible neonatal morbidity and stillbirth.

Women should be informed that in case of suspected SGA at term the risk of adverse pregnancy outcome is very small, but follow-up might be beneficial for them. The potential benefit for mother and child clearly outweighs the relatively light burden of follow-up ultrasounds.
Confirmation of SGA suspicion allows intervention, but caregivers should realize that intervention does not always improve outcome and does always bear risks for mother and child. Therefore, potential harm to mother and child in case of intervention should be weighed against the potential risk of expectant management on the other hand.
References


(37) Alfirevic Z, Stampalija T, Gyte GML. Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database of Systematic Reviews 2010;(8).

### Appendix 1. Multivariable analysis of association between antenatal SGA (birth weight <10\textsuperscript{th} percentile) detection and adverse pregnancy outcome and perinatal interventions in the original dataset.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SGA detected antenatally (n= 163)</th>
<th>SGA not detected antenatally (n=555)</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction of labor</td>
<td>93 (57)</td>
<td>50 (9)</td>
<td>&lt;0.001</td>
<td>16.61</td>
<td>(10.15 to 27.17)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>43 (26)</td>
<td>82.15</td>
<td>0.07</td>
<td>1.56</td>
<td>(0.97 to 2.50)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>33 (20)</td>
<td>40 (7.3)</td>
<td>&lt;0.001</td>
<td>2.68</td>
<td>(1.54 to 4.64)</td>
</tr>
<tr>
<td>Primary cesarean section</td>
<td>7 (4.3)</td>
<td>4 (0.7)</td>
<td>&lt;0.001</td>
<td>8.34</td>
<td>(2.07 to 33.66)</td>
</tr>
<tr>
<td>Secondary cesarean section</td>
<td>26 (16)</td>
<td>36 (6.5)</td>
<td>0.02</td>
<td>2.06</td>
<td>(1.14 to 3.74)</td>
</tr>
<tr>
<td>Vaginal instrumental delivery</td>
<td>10 (6.1)</td>
<td>42 (7.6)</td>
<td>0.12</td>
<td>0.54</td>
<td>(0.25 to 1.17)</td>
</tr>
<tr>
<td><strong>Neonatal outcome, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gestational age at birth (days), mean (SD)</td>
<td>271 (9.6)</td>
<td>277 (6.0)</td>
<td>&lt;0.001</td>
<td>-6.5*</td>
<td>(-7.9 to -5.2)</td>
</tr>
<tr>
<td>Birth weight (g), median (range)</td>
<td>2410 (1420-3080)</td>
<td>2770 (1765-3250)</td>
<td>&lt;0.001</td>
<td>-343*</td>
<td>(-392 to -294)</td>
</tr>
<tr>
<td>Composite adverse neonatal outcome</td>
<td>9 (5.5)</td>
<td>27 (4.9)</td>
<td>0.36</td>
<td>0.67</td>
<td>(0.29 to 1.57)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>0 (0)</td>
<td>7 (1.3)</td>
<td>0.995</td>
<td>Not calculable</td>
<td></td>
</tr>
<tr>
<td>5min Apgar Score &lt;7</td>
<td>4 (2.5)</td>
<td>9 (1.6)</td>
<td>0.96</td>
<td>1.04</td>
<td>(0.29 to 3.74)</td>
</tr>
<tr>
<td>Neonatal complications(^*)</td>
<td>3 (1.8)</td>
<td>10 (1.8)</td>
<td>0.21</td>
<td>0.40</td>
<td>(0.09 to 1.67)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>1 (0.6)</td>
<td>3 (0.5)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRDS</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td>0 (0)</td>
<td>4 (0.7)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (0.6)</td>
<td>4 (0.7)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) mean difference and 95\%Confidence interval (CI); \(^*\) number of infants with neonatal complications, some infants have more than one complication; OR, Odds Ratio; n.c., not calculated; inf, infinite; IRDS, infant respiratory distress syndrome; NEC, necrotizing enterocolitis; SGA, small for gestational age (birth weight <10\textsuperscript{th} percentile)
### Appendix 2. Baseline characteristics of the matched original cohort. Pregnancies are stratified by antenatal SGA detection.

<table>
<thead>
<tr>
<th></th>
<th>SGA detected antenatally (n=163)</th>
<th>SGA not detected antenatally (n=163)</th>
<th>P-value</th>
<th>Standardized difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age years, mean (SD)</td>
<td>29.3 (5.7)</td>
<td>29.0 (5.9)</td>
<td>0.71</td>
<td>4.2</td>
</tr>
<tr>
<td>Maternal BMI*, median (range)</td>
<td>22.5 (16-44)</td>
<td>22.4 (16-40)</td>
<td>0.51</td>
<td>9.5</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
<td>90 (55)</td>
<td>90 (55)</td>
<td>1.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>53 (32)</td>
<td>50 (31)</td>
<td>0.72</td>
<td>3.9</td>
</tr>
<tr>
<td>Gestational hypertension, n (%)</td>
<td>9 (5.5)</td>
<td>8 (4.9)</td>
<td>0.80</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Neonatal outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight percentile, median (range)</td>
<td>1.6 (0-9.9)</td>
<td>1.9 (0-9.9)</td>
<td>0.82</td>
<td>-2.5</td>
</tr>
<tr>
<td>Birth weight &lt;p2.3, n (%)</td>
<td>83 (51)</td>
<td>84 (52)</td>
<td>0.91</td>
<td>-1.2</td>
</tr>
<tr>
<td>Birth weight &lt;p5, n (%)</td>
<td>124 (76)</td>
<td>123 (76)</td>
<td>0.90</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* The body-mass index is the weight in kilograms divided by the square of the height in meters; SGA, small for gestational age (birth weight <10th percentile)
Appendix 3. Propensity score analyses of antenatal SGA (BW<p10) detection as predictor of adverse pregnancy outcome and perinatal interventions after 1:1 propensity score matching in the original dataset

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SGA detected antenatally (n= 163)</th>
<th>SGA not detected antenatally (n=163)</th>
<th>P-value</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction of labor</td>
<td>93 (58)</td>
<td>16 (9.9)</td>
<td>&lt;0.001</td>
<td>12.04</td>
<td>(6.59 to 21.99)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>43 (26)</td>
<td>28 (17)</td>
<td>0.045</td>
<td>1.73</td>
<td>(1.01 to 2.95)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>33 (20)</td>
<td>11 (6.7)</td>
<td>0.002</td>
<td>3.51</td>
<td>(1.71 to 7.22)</td>
</tr>
<tr>
<td>Primary cesarean section</td>
<td>7 (4.3)</td>
<td>0 (0.0)</td>
<td>inf.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary cesarean section</td>
<td>26 (16)</td>
<td>11 (6.7)</td>
<td>0.01</td>
<td>2.62</td>
<td>(1.25 to 5.51)</td>
</tr>
<tr>
<td>Vaginal instrumental delivery</td>
<td>10 (6.1)</td>
<td>17 (10)</td>
<td>0.16</td>
<td>0.56</td>
<td>(0.25 to 1.27)</td>
</tr>
<tr>
<td><strong>Neonatal outcome, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gestational age at birth (days), mean (SD)</td>
<td>270.6 (9.6)</td>
<td>278.1 (6.8)</td>
<td>&lt;0.001</td>
<td>-7.5*</td>
<td>(-9.3 to -5.7)</td>
</tr>
<tr>
<td>Birthweight (g) median, (range)</td>
<td>2410 (1420-3080)</td>
<td>2650 (1765-3090)</td>
<td>&lt;0.001</td>
<td>-225*</td>
<td>(-295 to -156)</td>
</tr>
<tr>
<td>Composite adverse neonatal outcome</td>
<td>9 (5.5)</td>
<td>13 (8.0)</td>
<td>0.38</td>
<td>0.67</td>
<td>(0.28 to 1.62)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>3 (1.8)</td>
<td>0.996</td>
<td>Not calculable</td>
<td></td>
</tr>
<tr>
<td>5min Apgar Score &lt;7</td>
<td>4 (2.5)</td>
<td>4 (2.5)</td>
<td>1.00</td>
<td>1.00</td>
<td>(0.25 to 4.07)</td>
</tr>
<tr>
<td>Neonatal complications*</td>
<td>3 (1.8)</td>
<td>5 (3.1)</td>
<td>0.48</td>
<td>0.59</td>
<td>(0.14 to 2.52)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRDS</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td>0 (0.0)</td>
<td>3 (1.9)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (0.6)</td>
<td>4 (2.5)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* mean difference and 95%Confidence interval (CI); * number of infants with neonatal complications, some infants have more than one complication; OR, Odds Ratio; n.c., not calculated; inf, infinite; IRDS, infant respiratory distress syndrome; NEC, necrotizing enterocolitis
Chapter 10

Summary and concluding remarks
Summary

Since the discovery of the association between abnormal growth and adverse pregnancy outcome, fetal growth has been the subject of research. This has focused on unraveling pathophysiologic mechanisms that underlie growth restriction, identification of factors associated with growth restriction, and prenatal detection of SGA pregnancies. Since growth restriction cannot be prevented or cured, studies have focused on detection of abnormal growth because antenatal detection is thought to reduce adverse pregnancy outcome and perinatal death.\textsuperscript{1} Despite all efforts, the majority of SGA infants remain undiagnosed until delivery.\textsuperscript{2} 50% of unanticipated stillbirths at term are attributed to SGA.\textsuperscript{3} Methods to detect SGA fetuses include antenatal clinical examination, symphys-fundal height measurement, and ultrasound biometry. In this thesis we investigated the association between several risk factors and SGA, we compared two methods to express fetal growth, and discussed the relation between antenatal SGA detection, timing of delivery and pregnancy outcome in SGA pregnancies.

In this final chapter, I will outline our main findings within the context of the current literature. I will also discuss directions for further investigations in the area of SGA.

SGA risk factors

Several risk factors for SGA and growth restriction have been discovered and quantified in previous research.\textsuperscript{4-24} However, some of these risk factors have only been assessed in general and their relation with other risk factors and interaction to gestational age have not been assessed yet. In the first part of this thesis we investigated factors that might be associated with abnormal fetal growth.

In chapter two we assessed in the first two subsequent singleton pregnancies the recurrence rate and incidence of SGA in women with and without SGA in their first pregnancy. We found that women with SGA in their first pregnancy have a strongly increased risk of SGA in the subsequent pregnancy, and that women with an appropriately grown infant in the first pregnancy have a very low SGA risk in the second pregnancy. We also found that the risk of SGA, both in the first and second pregnancy is significantly higher in women with an HTD than in women without an HTD.

With the increase in ultrasound examinations being performed in pregnancy, there is a growing amount of information available to clinicians, with often-unclear relevance. The association between isolated single umbilical artery as a sonomarkers seen on second trimester ultrasound and pregnancy outcome has been described in many studies, but these studies had not yet been reviewed and meta-analyzed. Chapter three is a systematic review and meta-analysis of the association between a single umbilical artery -as an isolated finding during the mid-term anomaly scan- and pregnancy outcome. Our meta-analysis of published data indicates that iSUA is associated with a non-significant trend for increased risk of SGA and perinatal mortality. However, well-designed and properly powered studies are lacking. Therefore we should consider screening for SGA only in a research setting to form a scientific basis for future management.

In chapter four we assessed if fetal sex is independently associated with adverse pregnancy outcome. The risk of fetal and neonatal death is - after correction for gestational age at delivery - comparable for males and females, and males have - regardless of growth and gestational age at birth - a higher risk of neonatal morbidity than females.
Methods to detect and classify SGA pregnancies and perinatal outcome

Expressing growth in percentiles was introduced in the 1970’s to assess birth weight by gestational age and enabled defining standards of normality. Despite the usefulness in research and clinical practice, it also has some disadvantages that are caused by the properties of the percentile distribution. In chapter five we compared birth-weight-ratio and birth-weight-percentile to express infant weight when assessing pregnancy outcome. We found that discriminative ability of birth weight ratio to identify cases at risk of perinatal death or adverse pregnancy outcome is comparable to that of birth weight percentile. Birth weight ratio is - for smaller and larger than average infants - a more discriminative instrument to identify infants at risk of perinatal death and adverse pregnancy outcome than birth weight percentile. In this chapter we also showed an association between abnormal fetal growth and prematurity.

In chapter six we assessed if fetal sex is associated with abnormal growth. We found that after correction for observed physiological differences in birth weights between males and females, a male infant born at a given gestational age is not more likely to have a low birth-weight-ratio than a female born at the same gestational age.

The majority of SGA infants are still not diagnosed until delivery. In chapter seven we evaluated if prenatal SGA detection could be improved. We found that adding information on relative growth between 2nd and 3rd trimester ultrasound does not enhance the ability of 3rd trimester ultrasound to detect infants at risk of SGA at birth. Furthermore, we confirmed the low antenatal SGA detection rate - even in a high risk population -, and showed that changing 3rd trimester cut-offs for follow-up can increase SGA detection from 39.0% to 60.8% and still being 86.3% specific.

Outcome of SGA pregnancies: Timing of delivery and influence of antenatal SGA detection

In chapter eight we investigated the optimal timing of delivery in SGA and non-SGA pregnancies. Therefore, risks of intrapartum/neonatal death and neonatal morbidity were analysed and compared using the fetus/neonate-at-risk approach. We found that the optimal timing of delivery according to mortality risk in SGA<p5 as well as the SGA p5-10 group is at 38 to 39 weeks, whereas for non-SGA pregnancies this is at 39 to 40 weeks.

Finally, research has been done to evaluate the influence of prenatal SGA detection on pregnancy outcome and come with conflicting results. In chapter nine we assessed differences in mode of delivery and pregnancy outcome between antenatally detected and not-antenatally detected SGA neonates born at term. The study confirmed the low antenatal SGA detection rate that was found in previous research. Antenatal SGA detection was associated with induction of labor and cesarean sections leading to earlier delivery and significantly lower birth weight. However, it potentially also prevents stillbirth. In case of detected SGA, fetal monitoring is warranted to detect compromised fetal condition to allow delivery if fetal condition is compromised.

Concluding remarks

Since SGA detection potentially improves pregnancy outcome, we should continue the search for ways to detect SGA pregnancies prenantly. However, at the same time we should also keep in mind that in the past decades the use of ultrasound in pregnancy has increased dramatically, and little has been done to reduce its adverse collateral effect on costs of pregnancy care and its influence on pregnancy management.

To date, third trimester ultrasound screening has been suggested to be ineffective in improving
pregnancy outcome in a low risk population, but evidence suggests that the use of Doppler ultrasound in high-risk pregnancies reduced the risk of perinatal deaths and resulted in less obstetric interventions. Information provided in this thesis can contribute to classification of pregnancies as high-risk and low-risk and thus potentially enables more specific use of resources to detect SGA. Since the risk of SGA in women who delivered a non-SGA infant in their first pregnancy is low, routine US does not seem warranted in this group. Finally, considering gestational age and growth - defined as birth weight percentile or birth weight ratio - instead of gestational age and birth weight, could improve accuracy of counseling and deciding about perinatal management in - especially very premature - infants.

With regard to the low antenatal SGA detection rate we should keep searching for ways to improve antenatal detection. There are four domains of interest: (1) mode of detection, (2) timing of detection, (3) test-threshold, and (4) desire of normalcy.

(1) Regarding mode of detection, a randomized trial is currently being performed to compare the effectiveness of two - third trimester - ultrasound growth assessments with standardized fundal-symphyse measurements.

(2) When considering the low-sensitivity of 3rd trimester ultrasound for term-SGA detection and the possibility of onset of growth restriction after 34 weeks, late 3rd trimester ultrasound for SGA detection should in my opinion also be investigated. Although ultrasound accuracy decreases with advancing gestation, no large studies have investigated the sensitivity of late 3rd trimester ultrasound biometry to detect term SGA.

(4) When considering test characteristics and cut-off values for follow up, prospective research could assess the influence of different cut-off values at third trimester ultrasound for SGA detection and its influence on pregnancy outcome. Changing cut-off values for follow-up seems promising in retrospective research showing much higher detection rates than currently achieved, with acceptable false positive rates.

(5) We should be aware of our desire of normalcy. Caregivers do not want fetuses to be SGA or LGA. This leads to deflection of non-blind measurements to the mean, resulting in underestimation of LGA infant weight and overestimation of SGA infant weight. Awareness among caregivers, and taking measures to avoid false reassurance about fetal growth (e.g. by blind measurement) might decrease this tendency.

Prenatal SGA detection also has disadvantages such as screening costs and - often needlessly - worried parents. Therefore, detection of SGA infants should be as effective as possible with the best possible differentiation between constitutionally small and growth restricted infants. The use of customized growth curves - that take maternal- (age, ethnicity, length, weight), pregnancy- (parity) and fetal- (gender) characteristics into account - shows promising results and should be at least investigated in the Netherlands to increase the identification of infants that are pathologically small and to enable reassurance in case of constitutional smallness.
References


Chapter 11

Nederlandse samenvatting

Portfolio

Dankwoord

Curriculum Vitae
Nederlandse samenvatting

Achtergrond
In een ongestoorde zwangerschap wordt foetale groei niet beperkt door verminderde werking van de placenta of andere ongunstige omgevingsfactoren. De meeste kinderen groeien volgens hun genetische groeipotentieel en worden geboren met een gewicht dat als normaal wordt beschouwd. Sinds de eerste helft van de vorige eeuw is bekend dat extreem kleine kinderen vaker sterven rond de geboorte of ziek worden na de geboorte dan kinderen met een gemiddeld gewicht voor de zwangerschapsduur.

Oorspronkelijk werd absoluut geboortegewicht gebruikt om groei te classificeren en te bepalen of een pasgeborene te licht, normaal gegroeid, of te zwaar was. Sinds de jaren 70 van de vorige eeuw wordt groei uitgedrukt als gewicht in relatie tot zwangerschapsduur. Hierdoor kunnen subgroepen met een hoger risico op slechte zwangerschapsuitkomst worden gedefinieerd. De 10% kleinste kinderen (voor iedere zwangerschapstermijn) worden sindsdien dysmatur genoemd. Deze groep bevatt zowel kinderen die genetisch klein zijn als kinderen die groeivertraagd zijn. In tegenstelling tot de genetisch kleine kinderen, hebben de kinderen die groeivertraging hebben opgelopen tijdens de zwangerschap een grotere kans op sterfte en ziekte rond de geboorte. Tot nu toe is het niet goed mogelijk om antenataal binnen de groep van dysmature onderscheid tussen deze twee soorten kinderen te maken.

Incidentie en oorzaken
Hoe vaak dysmaturiteit voorkomt hangt af van de gebruikte definitie. Wanneer de meest gebruikte definitie wordt gehanteerd, is rond de 10% van de pasgeborenen dysmatur. Er is veel onderzoek gedaan naar de ontstaanswijze van groeivertraging. Een aantal factoren die dit kunnen veroorzaken staat in tabel 1. Er wordt een onderverdeling gemaakt in maternaal, foetale en placentaire oorzaken van groeivertraging.

Gevolgen van groeivertraging
Dysmaturiteit is verantwoordelijk voor 20-25% van de perinatale sterfte en 2-13% van de neonatale morbiditeit (ziekte van de pasgeborene). De gevolgen van groeivertraging en de daaraan gerelateerde slechte zwangerschapsuitkomst strekken zich uit over het hele leven van deze kinderen en diens familie. De aan dysmaturiteit gerelateerde zorgkosten zijn van invloed op de hele maatschappij.

Detectie van abnormale groei
Tot de jaren 80 werd foetale groei geschat door het voelen aan de buik van de zwangere en door het uitwendig meten van de afstand tussen schaambeen en bovenkant van de baarmoeder. Het was niet mogelijk om metingen te doen die informatie verschaften over de foetale conditie om daarmee het optimale moment voor de baring te bepalen.

Tegenwoordig maakt echocopisch onderzoek het mogelijk om een betrouwbare termijnbepaling te verrichten in het 1e trimester en om de foetus gedurende de hele zwangerschap te meten. Hierdoor kan de grootte van de foetus worden beschouwd in relatie tot de zwangerschapsduur. Echoscopie maakt ook evaluatie van de foetale conditie mogelijk doordat bloedstroomsnelheden kunnen worden gemeten met behulp van Doppler. Voor- en tijdens de bevalling kan cardiotocografie worden gebruikt om continu de foetale conditie in de gaten te houden.

Belang van prenatale detectie
Verslechtering van de foetale conditie vaak vooraf wordt gegaan door afwijkende groei, daarom kan prenatale detectie van groeivertraging de zwangerschapsuitkomst verbeteren. Er is veel onderzoek gedaan naar abnormale groei en de opsporing hiervan.
Met de huidige screeningmethodes wordt slechts 28%-46% van de dysmature kinderen voor de geboorte opgespoord. Standaard echoscopisch onderzoek in het 3e trimester bij alle zwangere vrouwen is niet effectief gebleken in het verbeteren van de zwangerschapsuitkomst. In hoog-risico zwangerschappen is dit wel het geval. Daarom zal zowel een betere inschatting van het risico op abnormale groei, als het verbeteren van de opsporing van groeivertraging kunnen leiden tot betere zwangerschapsuitkomsten.

Dit proefschrift
Dit proefschrift bestaat uit drie delen. Het eerste deel richt zich op de associatie tussen verschillende risicofactoren en dysmaturiteit. In het tweede deel onderzoeken wij verschillende methodes om de groei van de foetus in uit te drukken en opsporing van dysmaturiteit te verbeteren. In het laatste gedeelte ligt de focus op de relatie tussen prenatale detectie van abnormale groei, het moment van de partus en de zwangerschapsuitkomst in zwangerschappen met een dysmatuur kind.

Deel 1: Risicofactoren voor dysmaturiteit
In hoofdstuk twee analyseren we de herhalingskans van dysmaturiteit in de eerste twee opeenvolgende zwangerschappen. Tevens wordt het verband tussen de herhalingskans op dysmaturiteit en de aanwezigheid van hoge bloeddruk in de eerste zwangerschap onderzocht. Onze studie laat zien dat vrouwen met een dysmatuur kind in de eerste zwangerschap een sterk verhoogde kans hebben op een dysmatuur in de tweede zwangerschap. Vrouwen met een normaal gegroeid kind in de eerste zwangerschap hebben een zeer laag risico op dysmaturiteit in de volgende zwangerschap. De kans op dysmaturiteit is sterk verhoogd in vrouwen met hypertensie.

Hoofdstuk drie omvat een systematische review en meta-analyse van de invloed van de aanwezigheid van een enkele navelstrengarterie (in plaats van twee) op de zwangerschapsuitkomst. We tonen hierin aan dat een enkele navelstrengarterie - als geïsoleerde bevinding bij de 20 weken echo - geen significante toename van dysmaturiteit en perinatale sterfte geeft. We moeten echter ook concluderen dat er te weinig goed opgezette populatie-studies zijn over dit onderwerp.

In hoofdstuk vier onderzoeken we of foetaal geslacht een onafhankelijke voorspeller is van slechte zwangerschapsuitkomst. Het risico op foetale en neonatale sterfte blijkt -na correctie voor zwangerschapsduur ten tijde van de bevalling- vergelijkbaar voor jongens en meisjes. Mannelijke foetus blijken een hogere kans op neonatale morbiditeit te hebben, ongeacht de zwangerschapsduur ten tijde van de geboorte.

Deel 2: Methodes om foetale groei uit te drukken en dysmaturiteit op te sporen

In hoofdstuk zes onderzoeken we of foetaal geslacht is geassocieerd met abnormale groei. We tonen hier aan dat -na correctie voor natuurlijke verschillen tussen jongens en meisjes-, een mannelijke pasgeborene bij een bepaalde zwangerschapsduur geen grotere kans heeft om dysmaturiteit te zijn dan een vrouwelijke pasgeborene bij dezelfde termijn. De meerderheid van de dysmature kinderen wordt echter niet voor de geboorte opgespoord.

Hoofdstuk zeven bevestigt de lage prenatale detectie van prenatale en beschrijft het onderzoek naar een manier om deze opsporing te verbeteren. We vonden echter dat het toevoegen van informatie over de relatie groei tussen de 20-weken echo en de 30-weken echo geen bijdrage
levert aan de prenatale detectie van dysmaturiteit. Het hanteren van andere afkapwaarden kunnen de detectie van dysmaturiteit verhogen van 39% naar 61%, zonder veel onterechte verdenkingen op abnormale groei. Deze bevindingen bieden een nieuw perspectief voor nader onderzoek.

Deel 3: Uitkomst van dysmature kinderen: moment van de bevalling en invloed van prenatale detectie
In hoofdstuk acht onderzoeken we het optimale geboortetijdspanne van dysmature kinderen. Het laagste risico op prenatale sterfte en neonatale morbiditeit is voor dysmature kinderen tussen 38 en 39 weken. Dit is een week eerder dan voor niet dysmature kinderen.

Ten slotte analyseren we in hoofdstuk negen de invloed van prenatale dysmaturiteits-detectie op de zwangerschapsuitkomst en op de manier van bevallen. Deze studie toont aan dat prenatale detectie van dysmaturiteit leidt tot het vaker opwekken (inleiden) van de bevalling en het vaker verrichten van een keizersnede. We vonden tevens dat prenatale detectie van dysmaturiteit mogelijk doodgeboortes voorkomt. De studie bevestigt wederom de lage prenatale detectie van dysmaturiteit.
PhD Portfolio

PHD TRAINING

General courses
2011  Oral presentation in English (0.8 ECTS)
2012  Scientific writing in English (1.5 ECTS)
2013  Entrepreneurship in Health and Life Sciences (1.5 ECTS)

Specific courses
2012  Practical biostatistics (1.1 ECTS)
2011  Fetal medicine foundation: 1st trimester ultrasound Nuchal Translucency measurement
2011  Fetal medicine foundation: 20-22 weeks scan
2011  Fetal medicine foundation: Fetal echocardiography
2011  PAOG Counseling prenatal screening and invasive testing

Seminars
2011-2013  Weekly department seminars (3.3 ECTS)
2013  Masterclass Medical Business (0.5 ECTS)
2013  Practicum foetale hartafwijkingen AMC (0.5 ECTS)

Presentations
2011  Oral presentation ISUOG 2011 Los Angeles: Reproducibility of three methods to evaluate the volume of intracavitary abnormalities using 3D Gel Instillation Sonohysterography (GIS) (0.5 ECTS)
2013  Oral presentation SMFM 2013 San Francisco and presentation “Pijlerdag Foetomaternale Geneeskunde”: SGA recurrence: analysis of first and subsequent singleton pregnancies (0.5 ECTS)
2013  Presentation at WFE annual meeting: Degree of isolated hydronephrosis in the second trimester of pregnancy as a predictor of renal pathology after birth (0.5 ECTS)
2014  Poster presentation SMFM 2014 New Orleans: Association between fetal gender and adverse perinatal outcome (0.5 ECTS)
2014  Poster presentation SMFM 2014 New Orleans: Association between fetal gender and abnormal fetal growth (0.5 ECTS)

(International conferences
2011  International society of ultrasound in obstetrics and gynecology (ISUOG), Los Angeles (0.75 ECTS)
2013  Society of maternal fetal medicine (SMFM), San Francisco (0.75 ECTS)

Other
2011-2013  Journal Club (2.3 ECTS)

TEACHING

Tutoring/mentoring
2011-2013  Tutoring/teaching ultrasound in pregnancy: practicum for 2nd year medical students (3.0 ECTS).
2012  Student coaching/mentoring scientific research project (1.0 ECTS)
2013  Student coaching/mentoring scientific research project (1.0 ECTS)
Dankwoord

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Dankwoord

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Curriculum vitae
