Prenatal detection of small for gestational age pregnancies
Voskamp, B.J.

Citation for published version (APA):
Voskamp, B. J. (2014). Prenatal detection of small for gestational age pregnancies

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
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

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\(^7\). 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\(^2\,^6\). 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\(^8\,^9\).

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\%)\(^9\,^11\). However knowledge gaps persist, particularly in the area of defining etiology-specific risks\(^12\). 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\(^13\). 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\(^14\,^15\). 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\(^16\).

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.
Chapter 2

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, 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 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. 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. 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<sup>0</sup>-31<sup>6</sup> weeks’ gestation), late preterm (32<sup>7</sup>-36<sup>6</sup> weeks’ gestation) and term (37<sup>0</sup>-42<sup>6</sup> 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) \( \text{PAR} = \frac{\text{P}(\text{RR}-1)}{(\text{P}(\text{RR}-1)+1)}\times 100 \) for each factor.\(^{19}\)

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 1. Study population

<table>
<thead>
<tr>
<th>Factor</th>
<th>First pregnancy birth weight (percentile for gestational age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5p (n=12,943)</td>
</tr>
<tr>
<td><strong>Maternal characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Maternal age (mean, SD)</td>
<td>28.2 (4.6)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>83.6</td>
</tr>
<tr>
<td>Spontaneous onset of labour (%)</td>
<td>50.1</td>
</tr>
<tr>
<td>Low social economic status (&lt;p25)</td>
<td>27.7</td>
</tr>
<tr>
<td>Hypertensive disorder (%)</td>
<td>22.0</td>
</tr>
<tr>
<td>Preterm delivery before 37weeks GA (%)</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>Neonatal characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>51.2</td>
</tr>
</tbody>
</table>

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>Risk Factor</th>
<th>Prevalence of risk factor (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>p-value</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA 1st pregnancy</td>
<td>23.15</td>
<td>8.5 (8.1-8.9)</td>
<td>&lt;0.0001</td>
<td>22.2</td>
</tr>
<tr>
<td>HTD 1st pregnancy</td>
<td>5.56</td>
<td>1.3 (1.3-1.4)</td>
<td>&lt;0.0001</td>
<td>3.7</td>
</tr>
<tr>
<td>Low SES</td>
<td>5.81</td>
<td>1.5 (1.4-1.5)</td>
<td>&lt;0.0001</td>
<td>8.2</td>
</tr>
<tr>
<td>Non-western ethnicity</td>
<td>6.89</td>
<td>1.7 (1.6-1.8)</td>
<td>&lt;0.0001</td>
<td>6.8</td>
</tr>
<tr>
<td>Maternal age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>6.89</td>
<td>1.7 (1.6-1.8)</td>
<td>&lt;0.0001</td>
<td>4.1</td>
</tr>
<tr>
<td>25-34</td>
<td>4.21</td>
<td>ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>4.34</td>
<td>1.0 (1.0-1.1)</td>
<td></td>
<td>-0.5</td>
</tr>
</tbody>
</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 3.** SGA recurrence rate in total and in women with and without HTD in the first pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Birth weight ≤5% recurrence N (%)</th>
<th>De novo birthweight ≤5% 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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Hypertensive disorder in first pregnancy (SGA (n=2,844), no-SGA (n=29,898))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA in second pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm delivery: (GA 24+0 - 31+6 wks)</td>
<td>598 (21.0)</td>
<td>1.223 (4.1)</td>
<td>6.2 (5.6-7.0)</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: (GA 32+0 - 36+6 wks)</td>
<td>115 (24.0)</td>
<td>233 (7.3)</td>
<td>4.0 (3.1-5.1)</td>
<td>&lt;0.0001</td>
<td>4.1 (3.2-5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Term delivery: (GA 37+0 - 42+6 wks)</td>
<td>467 (20.6)</td>
<td>895 (3.5)</td>
<td>7.3 (6.4-8.2)</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm delivery: (GA 24+0 - 31+6 wks)</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>Late preterm delivery: (GA 32+0 - 36+6 wks)</td>
<td>137 (30.2)</td>
<td>535 (4.3)</td>
<td>9.6 (7.7-11.2)</td>
<td>&lt;0.0001</td>
<td>9.1 (7.3-11.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Term delivery: (GA 37+0 - 42+6 wks)</td>
<td>2.232 (23.4)</td>
<td>6.618 (3.3)</td>
<td>9.1 (8.6-9.6)</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. 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. 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, identification of growth restriction is more accurately performed using the individual growth potential (IGP) and placental characteristics. 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 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 5th percentile than when it is set at the 10th percentile. (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 5th percentile than when it is set at the 10th 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 10th 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. Therefore very preterm neonates with a birth weight above the 5th centile for gestational age might have a birth weight far below the 5th 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. However, cohorts were smaller (4,623 up to 152,827 women), less uniform, or included anomalous fetuses and/or twins. Moreover, due to a different cutoff value for SGA (10th percentile or 2,500gr), 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 5th 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. 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. 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 etiologic 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.


(33) Bricker L, Neilson JP, Dowswell T. Routine ultrasound in late pregnancy (after 24 weeks’ gestation. Cochrane Database Syst Review 2008; 8:CD0001451

