Prenatal detection of small for gestational age pregnancies
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Chapter 7

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

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In preparation
Chapter 7

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 the 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 (2.5th, 5th or 10th 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. SGA severity is associated with (perinatal) death risk. 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.

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.

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 2nd and 3rd 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 3rd 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 360 and 426 weeks of gestation, between January 1st 2001 and December 31st 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 18-23 weeks GA) and at least one ultrasound growth assessment during the third trimester (between 28-33 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 360 and 426 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 2nd trimester (between 18-23 weeks)
and 23\textsuperscript{rd} weeks gestation), and in the 3\textsuperscript{rd} trimester (between 28\textsuperscript{rd} 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 (Log\textsubscript{10} EFW = 1.3596 + 0.0064(HC) + 0.0424(AC) + 0.174(FL) + 0.00061(BPD)(AC – 0.00386(AC)(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\textsubscript{ratio} - 2\textsuperscript{nd} trimester BW\textsubscript{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 two-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>Cohort (n=5,180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (± SD)</td>
</tr>
<tr>
<td>BMI*, median (range)</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
</tr>
<tr>
<td>Fetal male sex, n (%)</td>
</tr>
<tr>
<td>GA at 2nd trimester US, median days (range)</td>
</tr>
<tr>
<td>GA at 3rd trimester ultrasound, median days (range)</td>
</tr>
<tr>
<td>GA at delivery, mean days (SD)</td>
</tr>
<tr>
<td>Birthweight, median grams (range)</td>
</tr>
<tr>
<td>SGA &lt;p10, n (%)</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 (<10th) at birth

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>BMI*, median (IQR)</td>
<td>23.7 (6.5)</td>
<td>24.6 (7.5)</td>
</tr>
<tr>
<td>Primiparity, n (%)</td>
<td>308 (35.5)</td>
<td>1,635 (37.9)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>426 (49.1)</td>
<td>2,191 (50.8)</td>
</tr>
<tr>
<td>2nd trim EFW ratio, mean (SD)</td>
<td>0.93 (0.10)</td>
<td>1.00 (0.10)</td>
</tr>
<tr>
<td>3rd trim EFW ratio, mean (SD)</td>
<td>0.88 (0.11)</td>
<td>1.02 (0.12)</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>
</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**

<table>
<thead>
<tr>
<th>Model Description</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, BMI, Primiparity, Sex, 2nd trimester EFW ratio</td>
<td>0.69</td>
<td>(0.67-0.72)</td>
</tr>
<tr>
<td>Age, BMI, Primiparity, Sex, 3rd trimester EFW ratio</td>
<td>0.84</td>
<td>(0.83-0.86)</td>
</tr>
<tr>
<td>Age, BMI, Primiparity, Sex, 3rd trimester EFW ratio, 2nd3rd EFW ratio diff</td>
<td>0.84</td>
<td>(0.83-0.86)</td>
</tr>
<tr>
<td>Age, BMI, Primiparity, Sex, 3rd trimester AC ratio</td>
<td>0.82</td>
<td>(0.80-0.84)</td>
</tr>
</tbody>
</table>

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 and 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 3rd 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.\textsuperscript{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.\textsuperscript{2,14,15} 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 operator characteristics of different SGA predicion models.
<table>
<thead>
<tr>
<th>Proportion of population (%)</th>
<th>2nd trimester EFW ratio</th>
<th>3rd trimester EFW ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.85 (7.4%)</td>
<td>&lt;0.90 (19.1%)</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 2<sup>nd</sup> to 3<sup>rd</sup> trimester growth does not add discriminative ability to a model based on 3<sup>rd</sup> trimester ultrasound to detect pregnancies at risk of SGA and provides an answer to the clinical question what to do if normal 3<sup>rd</sup> trimester biometry is observed but EFW ratio/percentile has declined between the 2<sup>nd</sup> and the 3<sup>rd</sup> trimester scan.

This study also quantifies, and gives insight to the low antenatal detection rates of SGA, and shows that if third trimester ultrasound is used with cut-off values for referral/follow up at the 10<sup>th</sup> 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 3<sup>rd</sup> trimester cut-off values for follow-up, as earlier suggested by de Reu and colleagues. In our population using a 3<sup>rd</sup> 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 (<10<sup>th</sup> percentile), two women without fetal growth deviation are unnecessary intensively investigated and probably worried. Given the potential risks of unidentified SGA in late pregnancy 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. 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 36weeks). 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 3<sup>rd</sup> 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 2<sup>nd</sup> to 3<sup>rd</sup> trimester growth does not add discriminative ability to a model based on 3<sup>rd</sup> 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 3<sup>rd</sup> trimester (28<sup>th</sup> - 33<sup>rd</sup> 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 2<sup>nd</sup> trimester ultrasound for follow-up.
References


Chapter 7

97