Prenatal detection of small for gestational age pregnancies
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Chapter 1

General introduction
Chapter 1

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.\textsuperscript{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.\textsuperscript{3-6} 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\textsuperscript{th}, 5\textsuperscript{th}, or 10\textsuperscript{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.\textsuperscript{7}

Prevalence and etiology
The prevalence of fetal growth restriction depends on the definition used. If the 10\textsuperscript{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.\textsuperscript{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,\textsuperscript{9} and because it often presents itself with maternal morbidity.\textsuperscript{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\textsuperscript{11} and subtler Doppler and biophysical abnormalities. It often remains unrecognized and contributes to over 50\% of unanticipated stillbirths at term.\textsuperscript{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 (<10\textsuperscript{th} percentile) deliveries are responsible for 20-25% of perinatal death and 2-13% of severe neonatal morbidity.\textsuperscript{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.\textsuperscript{14-16}

Since the emergence and increased use of ultrasound, reliable pregnancy dating with 1\textsuperscript{st} 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.\textsuperscript{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.\textsuperscript{18} The reported sensitivity of third trimester ultrasound to detect SGA (<10\textsuperscript{th} percentile) in a low risk population is low - between 28% and 46%.\textsuperscript{19-21} and routine late pregnancy ultrasound is reported not to be associated with improvements in overall perinatal mortality.\textsuperscript{22} However, the use of Doppler ultrasound in high-risk pregnancies reduces the risk of perinatal deaths and results in less obstetric interventions.\textsuperscript{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

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Environmental</th>
<th>Fetal</th>
<th>Placental</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Previous SGA pregnancy</td>
<td>- Low socio economic status</td>
<td>- Aneuploidy</td>
<td>- Placental disorders and umbilical cord abnormalities</td>
</tr>
<tr>
<td>26-28</td>
<td>38</td>
<td>43 (eg. Trisomy 13, trisomy 18)</td>
<td></td>
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<tr>
<td>- Diabetes mellitus</td>
<td>- Malnutrition</td>
<td>- Structural abnormalities 44 (eg. congenital heart disease, or gastroschisis)</td>
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<tr>
<td>29</td>
<td>39</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>- Renal disease</td>
<td>- Smoking</td>
<td>- Multiple gestation</td>
<td></td>
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<tr>
<td>30</td>
<td>40</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>- Sytemic lupus erythematous</td>
<td>- Alcohol</td>
<td>- IVF conception</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bowel disease</td>
<td>- Teratogen exposure (eg. Cyclophosphamide, valproic acid, or antithrombotic drugs)</td>
<td></td>
<td></td>
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<tr>
<td>(Celiac 32, Crohn 33)</td>
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<tr>
<td>Pregnancy-related hypertensive diseases (eg. Chronic hypertension, gestational hypertension, or preeclampsia) 34</td>
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<td></td>
<td></td>
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<tr>
<td>- Thrombophilia 35</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age &gt;35 36</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Weight (BMI&lt;20) 37</td>
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</tbody>
</table>

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


