Prenatal detection of small for gestational age pregnancies
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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. Despite all efforts, the majority of SGA infants remain undiagnosed until delivery. 50% of unanticipated stillbirths at term are attributed to SGA. Methods to detect SGA fetuses include antenatal clinical examination, symphysiofundal 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. 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 prenatally. 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


