Prenatal detection of small for gestational age pregnancies
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Citation for published version (APA):
Voskamp, B. J. (2014). Prenatal detection of small for gestational age pregnancies
Chapter 6

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

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Submitted
Chapter 6

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\textsuperscript{th} and 42\textsuperscript{nd} 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\textsuperscript{rd} weeks (25\textsuperscript{th}-28\textsuperscript{th} weeks: Odds Ratio (OR) 0.91, 95% confidence interval (CI) 0.80-1.03, and 29\textsuperscript{rd}-32\textsuperscript{nd} 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\textsuperscript{rd} weeks GA (33\textsuperscript{rd}-36\textsuperscript{th} weeks: OR 0.96 95% CI 0.92-1.00 and 37\textsuperscript{th}-42\textsuperscript{nd} 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\textsuperscript{1} with males being on average heavier than females. Associations between male sex and poor pregnancy outcome such as preterm birth,\textsuperscript{2-8} perinatal death and morbidity have been described in literature.\textsuperscript{9-12} This may be explained by higher rates of spontaneous preterm delivery of males,\textsuperscript{7} and by the association between male sex and placental insufficiency and pre-eclampsia, although studies on this latter subject show conflicting results.\textsuperscript{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.\textsuperscript{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\textsuperscript{0} and 42\textsuperscript{6} 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.\textsuperscript{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{rd} 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 42nd 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    | Female infants  | 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                        |                 |                 | <0.001           |
| Induction of labor, %                         | 35.6            | 35.1            |                 |
| 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                      |                 |                 | <0.001           |
| Gestational age at delivery (weeks), median (IQR) | 39.2 (1.92) | 39.3 (1.83) |                 |
| 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>OR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Birth-weight-ratio &lt; 0.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-28 weeks GA</td>
<td>691/2192</td>
<td>31.5</td>
<td>0.88 (0.77 - 1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>29-32 weeks GA</td>
<td>1148/5609</td>
<td>20.5</td>
<td>1.00 (0.90 - 1.10)</td>
<td>0.94</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>3799/34067</td>
<td>11.2</td>
<td>0.92 (0.88 - 0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>27781/624115</td>
<td>4.5</td>
<td>1.00 (0.98 - 1.01)</td>
<td>0.66</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>OR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Birth-weight-ratio &gt; 1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-28 weeks GA</td>
<td>339/2192</td>
<td>15.5</td>
<td>0.85 (0.72 - 1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>29-32 weeks GA</td>
<td>920/5609</td>
<td>16.5</td>
<td>0.75 (0.68 - 0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>33-36 weeks GA</td>
<td>2530/34067</td>
<td>7.4</td>
<td>0.75 (0.71 - 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37-42 weeks GA</td>
<td>41139/624115</td>
<td>6.6</td>
<td>0.98 (0.97 - 1.00)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for: GA at delivery
Late preterm (33\textsuperscript{w0}-36\textsuperscript{w6} weeks) and term (37\textsuperscript{w0}-42\textsuperscript{w6} 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\textsuperscript{w0}-36\textsuperscript{w6} 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\textsuperscript{w0}-36\textsuperscript{w6} 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 \textsuperscript{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\textsuperscript{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
restriction.\textsuperscript{25,26} 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.\textsuperscript{22} 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.\textsuperscript{5} 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.\textsuperscript{6,9,27-31}

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 8\textsuperscript{th} and 12\textsuperscript{th} week of gestation.\textsuperscript{32} 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^{th}-28^{th} weeks) and very preterm (29^{st}-32^{nd} 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


