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Effect of fetal gender on pregnancy outcomes in Northern China

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Abstract

Purpose: Several studies have demonstrated that fetal gender has a significant effect on the pregnancy outcomes and pregnancy-related complications. However, results differ as the race and population changes. The aim of our study was to test whether the recorded phenomenon of adverse pregnancy outcomes associated with a male fetus applies to women in northern China.

Methods: This was a multi-centered, cross-sectional study. The study population included women who delivered babies in 25 different hospitals in 9 provinces in northern China, from 1 January 2011 to 31 December 2011. For our analysis, we selected 65,173 singleton birth deliveries at or after 28 weeks that occurred during the year 2011.

Results: Male fetal gender was associated with an increased incidence of preterm delivery (8.33% for males; 7.19% for females), gestational diabetes mellitus (4.58% for males; 4.26% for females), fetal macrosomia (9.41% versus 5.78%), lower Apgar score (2.05% versus 1.78%), perinatal death (0.92% versus 0.76%), placenta previa (0.95% versus 0.81%), increased cesarean section delivery (54.87% versus 52.31%), and operative delivery (1.34% versus 1.19%) (p < 0.05).

However, female fetuses were associated with an increased risk of preeclampsia at an advanced gestational age (15.86% for males; 17.53% for females), fetal growth restriction (0.74% for males; 1.09% for females), malpresentation (3.6% for males; 4.31% for females), postpartum hemorrhage (2.92% for males; 3.19% for females) (p < 0.05).

Conclusions: The recorded phenomenon of adverse pregnancy outcomes associated with a male fetus applies to our population regardless of some different results.

Keywords

Obstetrics complication, perinatal outcome, sex ratio

Background

Several studies have demonstrated that fetal gender has a significant effect on the pregnancy outcome and on the development of pregnancy-related complications [1,2]. A male fetus can increase the risk of many adverse perinatal complications such as preterm delivery [3–5], gestational diabetes mellitus (GDM) [2], fetal distress [6,7], low Apgar scores [6], perinatal mortality [6], fetal macrosomia, failure to progress during the first and second stages of labor, cord prolapse, nuchal cord, true umbilical cord knots [8,9], placental abruption [10] and placenta previa [11]. Male fetal gender was also associated with significantly higher rates of cesarea delivery and instrumental vaginal delivery [2,12,13].

On the other hand, some results varied with different races and populations. Cooperstock and Campbell interestingly found a 7.2% excess of males among white singleton preterm newborns, which was significantly greater than the 2.8% excess of males in a comparable black newborn population (p < 0.001) [14]. Furthermore, conclusions on the association between fetal gender and pregnancy-induced hypertension (PIH) and preeclampsia have been contradictory [2,15,16]. To date there are several possible explanations for this situation. However, there is still a lack of clear understanding of the mechanisms by which fetal gender interacts with pregnancy outcome. What is more, although most studies have focused on specific aspects of the association (i.e. preterm delivery, mode of delivery and so on), only few reports have examined the relationship in a more broad perspective [1,8,9]. To determine whether fetal gender affects pregnancy outcomes in a more broad perspective in China, we surveyed the generation delivered from 1 January 2011 to 31 December 2011 in northern China.

Methods

This was a multi-centered, cross-sectional study. The data were obtained from nine provinces, municipalities and autonomous regions within China (Beijing, Jilin, Liaoning, Shanxi, Hebei, Inner Mongolia, Shandong, Shanxi, and Xinjiang), covering 25 hospitals of different levels. The hospitals included nine tertiary care general hospitals, three tertiary care specialty hospitals, five secondary care general hospitals, and eight secondary care specialty hospitals (in Chinese hospital classification system, tertiary care is the...
most specialized, and primary care is the least specialized), covering mainland China but not Hong Kong, Taiwan, or Macao. The study contained 68,048 babies delivered in 25 hospitals in nine provinces in China, from 1 January 2011 to 31 December 2011. Inclusion criteria were singleton pregnancies that completed 28 weeks of gestation. Miscarriages, termination of pregnancy and labor induction before 28 gestational weeks due to stillbirths, neonatal deaths, and infants with congenital anomalies, births born after assisted reproductive technology, incomplete data were excluded. So 2875 records were excluded from the study, leaving 65,173 singleton birth deliveries at or after 28 weeks that occurred during the year 2011 for our analysis. Gestational age was determined by the mother’s last menstrual period and was confirmed by an ultrasound examination within 20 weeks of gestation or by first trimester ultrasound measurement of the crown-rump length of the fetus.

**Data collection**

Questionnaire: The questionnaire included the mother’s age, ethnic group, level of education, marital status, employment status, medical history, parity, history of pregnancy, pregnancy comorbidity and complications, method of delivery, and maternal and neonatal outcomes, and so on. The questionnaire was designed by obstetric and statistical experts and finalized after many discussions regarding its feasibility.

Training of investigators: The head of each sub-center in each province, municipality, or autonomous region accompanied 2–3 investigators to attend face-to-face training on questionnaire entry and completion. Instructions for completing the questionnaire were also sent out to the investigators.

Data entry: Investigators from each province, municipality, and autonomous region were responsible for training personnel for data entry. Data were collected and recorded by specially trained medical staff (obstetrics and gynecology doctors and students). Data were first entered in hardcopy format and then entered into computer network databases.

Data collection: Data were collected and entered into a computer network database. Case collection and hardcopy data entry were carried out from January–April 2012. Then, data were entered into network database from May–June 2012, and data quality control was carried out during the same period. Each participating hospital was responsible for its own case collection and data entry, and all personnel that participated in data entry received training beforehand. Data included birth outcomes of each hospital throughout 2011.

Quality control: In each sub-center 1–2 specialized personnel were trained in data quality control, and were responsible for their entire region. After the data were sent to the survey headquarters, specialized personnel at the headquarters were responsible for the second round of quality control assessment.

The primary indications for caesarean section were divided into three categories: maternal indications, fetal indications, maternal request with no obstetric reasons. Maternal indications include previous cesarean delivery, elderly primigravida, cephalo-pelvic disproportion, prolonged labor (dystocia), maternal infection, complications of pregnancy such as preeclampsia, oligohydramnios, placenta praevia, placental abruption, presence of cardiac disease, or other maternal pathologies. Fetal indications included precious infant, malpresentation, fetal distress, macrosomia and multiple fetuses.

**Statistical analysis**

Statistical analysis was conducted using SPSS 19.0 version. Quantitative data were presented as the mean± standard deviation (SD). The Student t test was used to compare continuous variables between the groups. The Fisher exact test and the chi square test were performed to detect differences in the proportions of categorical variables between two or more groups. Logistic regression analysis was performed to assess the association between the fetal gender and pregnancy outcome and pregnancy-related complications. To control the impact of possible confounding, the factors were added to the logistic model. Multivariate logistic regression models were constructed in order to find independent associations between male gender and pregnancy outcome and pregnancy-related complications. A two-tailed p<0.05 was considered significant.

**Results**

**The correlation between fetal gender and different pregnancy outcomes**

To compare the association between fetal gender and pregnancy outcomes, we selected singleton deliveries at 28 completed weeks. Of the leaving 65,173 singleton deliveries at or after 28 completed weeks, 35,491 (54.46%) deliveries were male infants and 29,682 (45.54%) deliveries were female infants. Among all births, there were 8.92% more males than females (sex ratio of 1.2). As Figures 1 and 2 show, there is a strong male dominance for each gestational age category from 28 to 40 weeks. The sex ratio for each age (from 28 weeks to 40 weeks) was 1.48, 1.55, 1.78, 1.53, 1.25, 1.50, 1.30, 1.54, 1.25, 1.36, 1.34, 1.20 and 1.12. However, at week 41 there were slightly fewer male babies than female babies (sex ratio, 0.97). After 41 weeks, there was still a male predominance (sex ratio, 1.09).

In our study, 78.40% of all the deliveries were primiparous women. Female infants had a higher chance of delivery by primiparous women, compared to male infants (80.42% versus 76.71%, OR = 1.247, 95% CI: 1.201–1.295, p<0.001). Women with high gravidity and parity were more likely to deliver male fetuses; both of these differences were significant (p<0.001). There were no significant differences between the groups regarding residence location, age or obesity.

**Maternal outcomes**

Premature delivery was increased among male-bearing pregnancies, compared to female-bearing pregnancies (8.33% for males, 7.19% for females, adjusted OR = 1.206, 95% CI: 1.131–1.287, p<0.001) (Table 1), even after adjustment for resident, maternal age, maternal education, gravity, parity, HDCP, GDM, DM, placenta previa, placenta abruption other medical disorders. To show the situation clearly, we selected the 20–28 week abortions for the analysis.
Table 1. Comparison of pregnancy-related risk factors neonatal outcomes and delivery mode.

<table>
<thead>
<tr>
<th>Pregnancy-related risk factors</th>
<th>Males</th>
<th>Females</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature delivery n (%)</td>
<td>2958 (8.33%)</td>
<td>2134 (7.19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDM n (%)</td>
<td>1625 (4.58%)</td>
<td>1265 (4.26%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Placenta previa n (%)</td>
<td>337 (0.95%)</td>
<td>239 (0.81%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDCP n (%)</td>
<td>2263 (6.38%)</td>
<td>1954 (6.58%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia n (%)</td>
<td>1296 (3.65%)</td>
<td>1129 (3.80%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Preeclampsia at an early gestational age n (%)</td>
<td>593 (20.05%)</td>
<td>477 (22.35%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Premature rupture of membranes n (%)</td>
<td>5364 (15.11%)</td>
<td>4480 (15.09%)</td>
<td>0.94</td>
</tr>
<tr>
<td>ICP n (%)</td>
<td>111 (0.31%)</td>
<td>81 (0.27%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Polyhydramnios n (%)</td>
<td>447 (1.26%)</td>
<td>332 (1.12%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Oligohydramnios n (%)</td>
<td>1561 (4.40%)</td>
<td>1283 (4.32%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Postpartum hemorrhage n (%)</td>
<td>1037 (2.92%)</td>
<td>946 (3.19%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Malpresentation n (%)</td>
<td>1279 (3.60%)</td>
<td>1278 (4.31%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placental abruption n (%)</td>
<td>228 (0.64%)</td>
<td>185 (0.62%)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Neonatal outcomes

| Birth weight ≤25 00g n (%)                                   | 2440 (6.87%)   | 2224 (7.49%)   | <0.001|
| Birth weight ≥40 00g n (%)                                  | 3338 (9.41%)   | 1717 (5.78%)   | <0.001|
| Apgar score <7 at 1 min n (%)                               | 729 (2.05%)    | 527 (1.78%)    | <0.05 |
| Apgar score <7 at 5 min n (%)                               | 313 (0.88%)    | 249 (0.84%)    | 0.55  |
| Fetal distress n (%)                                        | 3712 (10.46%)  | 3170 (10.68%)  | 0.36  |
| Perinatal death n (%)                                       | 328 (0.92%)    | 226 (0.76%)    | <0.05 |

Mode of delivery

| Vaginal delivery n (%)                                      | 16018 (45.13%) | 14155 (47.69%) | <0.001|
| Non-instrumental n (%)                                      | 15543 (43.79%) | 13802 (46.50%) | <0.001|
| Instrumental n (%)                                          | 475 (1.34%)    | 343 (1.16%)    | <0.001|
| Cesarean section n (%)                                      | 19473 (54.87%) | 15527 (52.31%) | <0.001|
| Elective n (%)                                              | 13395 (37.74%) | 10647 (35.87%) | <0.001|
| Emergency n (%)                                             | 6067 (17.09%)  | 4872 (16.41%)  | 0.021 |

Figure 1. Distribution of gestational age at delivery by fetal gender.

Figure 2. Sex ratio of different gestational age at delivery.
of sex ratio. In Figure 2, the sex ratio decreases from 4 to nearly 1 as the gestational age increases.

As Table 1 showed, the incidence of GDM was increased among male-bearing pregnancies (4.58% for males, 4.26% for females, \( \text{OR} = 1.078, 95\% \text{ CI:} \ 1.002–1.162, \ p < 0.05 \)). Placenta previa was more frequent among the male-bearing mothers (0.95% for males, 0.81% for females, \( \text{OR} = 1.081, 95\% \text{ CI:} \ 1.003–1.398, \ p < 0.05 \) (Table 1).

The overall incidence of preeclampsia showed no correlation with fetal gender (\( p = 0.31 \)). As Table 1 shows, however, the incidence of preeclampsia was higher in female-bearing pregnancies with preterm labor (20.05% for males, 22.35% for females, \( p = 0.048 \)).

The incidence of postpartum hemorrhage was also higher among female-bearing pregnancies (3.19%) than among male-bearing pregnancies (2.92%) (adjusted \( \text{OR} = 0.867, 95\% \text{ CI:} \ 0.792–0.948, \ p < 0.05 \) (Table 1), even after adjustment for maternal age, gravity, parity, HDCP, placenta previa, delivery mode, fetus weight, other medical disorders, as well as malpresentation.

In contrast to the findings of other studies, our study found no significant correlation between the fetal gender and the following complications: HDCP (6.38% for males, 6.58% for females, \( p = 0.29 \)), preeclampsia/eclampsia (3.65% for males, 3.80% for females, \( p = 0.31 \)), premature rupture of membranes (15.11% for males, 15.09% for females, \( p = 0.94 \)), ICP (0.31% for males, 0.27% for females, \( p = 0.35 \)), polyhydramnios (1.26% for males, 1.12% for females, \( p = 0.099 \)), oligohydramnios (4.40% for males, 4.32% for females, \( p = 0.64 \)), and placental abruption (0.64% for males, 0.62% for females, \( p = 0.76 \) (Table 1).

## Fetal outcomes

The percentage of fetal macrosomia (i.e. birth weight greater than 4 kg) was higher among male neonates (9.41%) than among female neonates (5.78%) (adjusted \( \text{OR} = 1.768, 95\% \text{ CI:} \ 1.639–1.908, \ p < 0.001 \) (Table 1), even after adjusting for significant confounders (adjusted for resident, maternal age, education, gravity, parity, GDM, DM, pre-pregnancy BMI, pre-labor BMI). On the other hand, as Table 1 showed the incidence of GDM was increased among female-bearing women (7.49%) than male-bearing women (5.78%) (adjusted \( \text{OR} = 1.068, 95\% \text{ CI:} \ 0.633–0.741, \ p < 0.001 \), even after adjusting for significant confounders (adjusted for resident, maternal age, education, HDCP, GDM, DM, placenta previa, perinatal death, and increased chance of cesarean and operative deliveries).

To our surprise, our study did not show an association of male fetus with premature rupture of membranes, ICP, HDCP, preeclampsia/eclampsia, polyhydramnios, oligohydramnios or placenta abruption, as other studies have demonstrated [2,8,10,11]. The reason for this situation is unclear. On the contrary, our study showed an association of female fetuses with an increased incidence of preeclampsia at an advanced gestational age, FGR, postpartum hemorrhage, and malpresentation. The reason to the different result may be heterogeneity that comes from different races and populations.

### Discussions

The results presented in the study support previous reports of an adverse effect of a male fetus on pregnancy and labor. Our study, which was conducted in northern China, a developing country, similarly showed that male gender is an independent risk factor for increased preterm labor, GDM, higher birth weight, fetal macrosomia, placenta previa, lower Apgar score, perinatal death, and increased chance of cesarean and operative deliveries.

The association of fetal gender with PIH and preeclampsia has been studied; however, the results are contradictory. Data from several studies indicate an increased risk for the development of preeclampsia in pregnancies with male fetuses [17]. By contrast, several studies have found a
predominance of female fetuses in preterm preeclamptic pregnancies, compared to preterm normotensive pregnancies [2,15,16,18].

The results also varied with different races and populations. Cooperstock and Campbell interestingly found that the 7.2% excess of males among white singleton preterm newborns was significantly greater than the 2.8% excess of males among a comparable population of black newborns ($p<0.001$) [14]. Their study shows that gender does matter and the degree of association can change to some extent with different populations. This variation may be because of differences in racial and ethnic backgrounds or racial differences in the immunological response. As Figure 1 shows, there was a strong male dominance for each gestational age category from 28 to 40 weeks. The sex ratio for each age (from 28 weeks to 40 weeks) was 1.48, 1.55, 1.7862, 1.53, 1.257, 1.5046, 1.3023, 1.540, 1.257, 1.369, 1.343, 1.220, and 1.121. However, at week 41 there were slightly fewer male babies than female babies (sex ratio, 0.9795). After 41 weeks, there was still a male predominance (sex ratio, 1.2009).

Physiological basis of the phenomena

To date, the physiological basis of these phenomena remains obscure. There are several possible explanations for this situation.

At birth the number of male fetuses exceeds the number of female fetuses by a small percentage; however, substantially more male embryos may be needed to produce a live born infant [16,19]. This is because the risk of spontaneous abortion in early pregnancy or miscarriage at later stages of pregnancy is higher if the offspring is male [19,20]. As shown in Figure 2, the sex ratio of abortion at 20 weeks can be as high as 5. As the gestational age increases, the sex ratio decreases from 5 to nearly 1. Sex differentiation is believed to begin at conception [21]. The failure of implantation contributes to as much as 75% of lost pregnancies. This suggests that pregnancies with male embryos may be more vulnerable to the process of implantation, compared to females [16,22]. In murine and bovine embryos, Bourgoyn found that the Y chromosome accelerates the growth and development of XY embryos [23]. The acceleration of growth and development result from a higher metabolic rate. The Bourgoyn study demonstrated that in preimplantation bovine embryos, the total glucose metabolism was twice as high in male embryos as in female embryos [23]. This indicates that an XY embryo has an advantage in development and thus male fetuses seem to be more advanced than female fetuses before the gonads have differentiated [21,23]. It is the increased metabolic rate in male embryos that increases the vulnerability of male infants during critical and subsequent stages of development [6,24].

Some researchers hypothesize that fetal sex-specific differences in the human placenta cause the different effects. Edwards and Megens found that the placenta of the male fetus is more prone to severe dysfunction in the form of absent or reversed end-diastolic umbilical artery flow, compared to the placenta of the female fetus [25]. They also found that mothers with pregnancies that are complicated by severe placental dysfunction have smaller-than-normal placentas in comparison to the infant’s birth weight [25]. Furthermore, male fetuses have smaller placentas than female fetuses relative to their birth weight [25]. In addition, maternal serum concentrations of human chorionic gonadotropin (HCG), a biochemical marker of placental function, are lower in pregnancies with male fetuses than with female fetus [26–29]. High maternal serum HCG levels can result in lower amniotic fluid angiogenin levels [28,29]. Ghidini and Salafia found that a more aggressive maternal immune response against the invading interstitial trophoblast is present in pregnancies with male fetuses, compared to female fetuses [28]. One hypothesis is that abnormal hormone concentrations at conception may affect infiltration by extravillous trophoblasts into the placental bed and thus cause the abnormal sex ratios [10,28]. Other researchers suggest that the sex of the fetus may affect maternal blood volume expansion and blood flow in early gestation via the different production of HCG and testosterone in males, compared to female fetuses [28,30]. It may be that placental origins, rather than fetal origins, lead to male adverse effects on the pregnancy outcome and the development of pregnancy-related complications.

The physiological basis of the adverse effects of male gender on pregnancy outcome remains still obscure. Further investigations of the exact mechanisms underlying this association are needed. The well-established statistical data confirm adverse pregnancy outcomes with male fetuses; however, we should not change our obstetric management simply based on the gender of a fetus until further research determines whether gender-based decisions would improve the pregnancy outcomes.

Strengths and limitations

As a multicenter clinical epidemiological research, we had the large number of 68 048 babies from 25 hospitals of 9 provinces and regions over the northern Chinese country, while most other studies present a smaller number of babies from one hospital or from a local area. The generalization of the results to the world is limited despite the large amount of data. Because only northern Chinese people were included and this resulted in a relatively homogeneous, mainly Chinese sample. Different results might be obtained for other ethnic groups. As a retrospective study, part of the clinical data was not completed and undetected deviations can exist. Some data such as income, personality, diet, drug abuse, etc., cannot be obtained from cases, so it can not represent all of the risk factors. However, it is important to bear in mind that selection bias and undetected deviations don’t necessarily influence the results when associations between variables are investigated in northern China. Further study would be continued.

Conclusions

In the northern Chinese population male gender is an independent risk factor for adverse pregnancy outcome. However, the results differ from the previous studies to some extent as the populations and races change. Regardless of the well-established statistical data, we should not change our obstetric management simply based on the gender of a
fetus until further research determines whether gender-based decisions would improve the pregnancy outcomes.

Compliance with ethical standards

This study was approved by the human ethics committees of the Beijing Obstetrics and Gynecology Hospital (Beijing, China) and the Capital Medical University (Beijing, China), and the appropriate institutional ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards.

Declaration of interest

The authors report no conflicts of interest.

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