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Effects of Fetal Gender on Occurrence of Placental Abruption

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Summary

A multicenter retrospective cohort study was conducted to clarify the differences in occurrence of placental abruption between placenta with and without the Y chromosome. We reviewed the chart records from the database of the Japan Perinatal Registry Network during the period from January to December 2009. 348 women were included. Risk factors were compared to those of pregnant women with a female fetus. The fetal sex ratio was 1.22: 191 male cases and 157 female cases. There were no significant differences in maternal background factors, perinatal or neonatal and infantile outcomes between the two groups. In terms of risk factors, pregnant women with a male fetus had a significantly lower incidence (30/191, 15.7%) of pregnancy-induced hypertension as compared with female fetuses (44/157, 28.0%, p = 0.0052) (relative risk: 0.48 [95% confidence intervals: 0.29-0.80]). Placental abruption occurred in pregnancies with a male fetus even in the absence of reported risk factors for placental abruption.

Keywords: *Fetal sex; Placental abruption; Pregnancy-Induced hypertension; Sex bias*

Introduction

There has been clear evidence that gender or human sex difference contributes to the pathogenesis of many diseases based on many epidemiological studies. However, there are little evidences accounting for this sex bias. The same phenomenon is seen in pregnancy complications. Fetal sex, especially the male fetus, is one of the risk factors for higher morbidity in preterm delivery, preeclampsia, and placental dysfunction [1]. A male fetus bias is also seen in placental abruption [2-6]. In light of these epidemiological facts, it is reasonable to assume that a male fetus will be prone to impaired placental development or function. A recent study demonstrated a strong relationship between a certain haplotype of the Y chromosome and morbidity of coronary arterial disease [7]. In this study, we have investigated differences in occurrence of placental abruption between placenta with and without the Y chromosome, i.e., placenta with male fetus and placenta with female fetus.

Materials and Methods

A multicenter retrospective cohort study was conducted after being approved by our Institutional Review Board (certification number 2301). This cohort study was analyzed as another cohort study from our previous study [8]. We reviewed the computerized chart records from the database of the Japan Perinatal Registry Network, which is managed by the Japan Society of Obstetrics and Gynecology, during the period from January 1 to December 31, 2009. This database, derived from 131 tertiary and/or secondary perinatal hospitals, including 76 university hospitals, 11 national hospitals, 11 Red Cross hospitals, and 33 other hospitals, covered 76,113 births after 22 gestational weeks, 7.1% of all deliveries (1,073,680 births in same period) in Japan. In this database, 570 pregnant women were diagnosed with placental abruption. Exclusion criteria included the following: unclear estimated confinement date provided by last menstruation period supported by early trimester ultrasound, twin gestation, chronic abruption oligohydramnios sequence (CAOS), and infants lost to

follow-up at 2 years of age. The remaining 348 cases (0.46%) were included as subjects in this study, and were divided into two groups: male or female, i.e., pregnant women with male fetus or pregnant women with female fetus, respectively. Background factors, risk factors for abruption, perinatal outcomes, and neonatal and infantile outcomes were compared between these two groups. Placental abruption, pregnancy-induced hypertension (PIH), chronic hypertension, and CAOS were defined according to our previous report [8]. Briefly, placental abruption as defined by Ananth and Kinzler [9]and CAOS by Elliott ., *et al.* [10].

Statistical analyses were performed with a computer program: Statflex 6.0 (Artech Co., Ltd., Osaka, Japan. URL: http://www.statflex.net/). Values were shown as the mean ± standard deviation (SD). Mann- Whitney U test or kai square test was performed as an evaluation of the mean difference or proportional difference, respectively. A p value less than 5% was considered to be significant. Relative risk was presented as the risk ratio with 95% confidence intervals (RR [95%CI]).

Results

The fetal sex ratio was 1.22:191 male cases and 157 female cases. The background of the two groups are shown in Table 1. There were no significant differences in maternal age, parity, maternal ambulance transfer to tertiary care hospital after occurrence of abruption, delivery gestational weeks, delivery route, birth weight, and administration of tocolytic agent before delivery. Table 2 shows the differences between male and female fetuses in terms of maternal risk factors for occurrence of abruption, and perinatal and neonatal outcomes. In terms of risk factors, pregnant women with a male fetus had a significantly lower incidence (30/191, 15.7%) of PIHas compared with female fetuses (44/157, 28.0%, p = 0.0052) (RR: 0.48 [95% CI: 0.29-0.80]).The incidence of other risk factors, including trauma, smoking habit, previous abruption, light for date infant, and chorioamnionitis, were much lower in the case of male fetusesas compared with female fetuses, but not significantly. The above results do not directly demonstrate that pregnancy with a male fetus is a risk factor for occurrence of abruption, but they do show that the frequency of other known risk factors is low in pregnancies with a male fetus. There were no significant differences in perinatal or neonatal and infantile outcomes between the two groups.

	Male fetus	Female fetus
Number	191	157
Age [year]	31.9 ± 5.2	32.2 ± 5.1
Primipara	107 (56.0%)	79 (50.0%)
Maternal ambulance transfer	118 (61.8%)	97 (61.8%)
Delivery [weeks]	34.0 ± 3.5	33.9 ± 3.7
Extremely preterm birth (24-27 weeks)	2 (1.0%)	2 (1.3%)
Very preterm birth (28-31 weeks)	42 (22.0%)	38 (24.2%)
Preterm birth (32-33 weeks)	30 (15.7%)	25 (15.9%)
Late preterm birth (34-36 weeks)	72 (37.7%)	51 (32.5%)
Term birth (37-42 weeks)	45 (23.6%)	41 (26.1%)
Delivery route		
Normal vaginal delivery	18 (9.4%)	21 (13.4%)
Vacuum extraction or forceps delivery	3 (1.6%)	4 (2.5%)
Cesarean section	170 (89.0%)	132 (84.1%)
Birth weight [gram]	2068 ± 668	1960 ± 666
Administration of tocolytic agent before delivery	28 (14.7%)	34 (21.7%)

Values are shown as mean ± SD or the number with percentage.

Table 1: *Background of women with placental abruption by pregnancy with male fetus and female fetus.*

	Male fetus	Female fetus	*p* value
Risk factors			
One of risk factors	50 (26.2%)	67 (42.7%)	0.0012
Pregnancy-induced hypertension	30 (15.7%)	44 (28.0%)	0.0052
Smoking habit	18 (9.4%)	22 (14.0%)	n.s.
Chronic hypertension	18 (9.4%)	19 (12.1%)	n.s.
Placental abruption of previous pregnancy	4 (2.1%)	5 (3.2%)	n.s.
Trauma	1 (0.5%)	1 (0.6%)	n.s.
Light for date infant	39 (20.4%)	33 (26.6%)	n.s.
Pathological chorioamnionitis	20/120 (16.7%)	16/91 (17.6%)	n.s.
Perinatal outcomes			
Apgar score			
< 7 at 1 minute	126 (66.0%)	110 (70.1%)	n.s.
< 5 at 1 minute	101 (52.9%)	94 (59.9%)	n.s.
< 7 at 5 minutes	82 (42.9%)	79 (50.3%)	n.s.
< 5 at 5 minutes	56 (29.3%)	51 (32.5%)	n.s.
Umbilical arterial pH	7.159 ± 0.185	7.137 ± 0.188	n.s.
< 7.0	23 (12.0%)	19 (12.1%)	n.s.
Fetal death (still birth)	43 (22.5%)	43 (27.4%)	n.s.
Neonatal outcomes			
Intact survival	136 (71.2%)	101 (64.3%)	n.s.
Early neonatal death	5 (2.6%)	1 (0.6%)	n.s.
Neonatal death	1 (0.5%)	0 (0.0%)	n.s.
Infant death	1 (0.5%)	1 (0.6%)	n.s.
Neurological dysfunction at 2 years of age	5 (2.6%)	11 (7.0%)	n.s.

Values are shown as mean ± SD or the number with percentage. Statistical analysis was performed by Mann-Whitney U testor chi-square test. Abbreviations, n. s.: not significant.

Table 2: *Comparison of risk factors and perinatal outcomes by pregnancy with male fetus and female fetus.*

Discussion

The most important finding in this study was that the rate of complications with known risk factors such as PIH was significantly lower in pregnancies with a male fetus as compared with those with a female fetus in cases of placental abruption. And although it was not statistically significant, it was found that the frequency of complications tended to be lower in pregnancies with a male fetus in the case of risk factors such as smoking habit and history of placental abruption. Therefore, there is presumed to be some risk factor for occurrence of placental abruption in pregnancies with a male fetus. Pregnancies with a male fetus are characterized by the presence of the Y chromosome in the villi of placental tissue. It is easy to assume that the Y chromosome contributes to occurrence of placental abruption by being involved in some way in the deciduous membrane, which is comprised of only the X chromosome. A report by Murji., *et al*. is interesting in this respect [5]. They retrospectively investigated the course of pregnancies with siblings of fetuses with severe placental dysfunction (SPD) and found that when SPD occurred in pregnancies with a male fetus, the likelihood of occurrence of SPD was higher in pregnancies with sibling male fetuses. Consequently, we can presume that there is some genetic mechanism underlying occurrence of SPD in pregnancies with a male fetus. A recent report in Lancet [7], pointed out an association between some Y chromosomal haplotypes and occurrence of coronary artery disease, which suggests the involvement of a gene on the Y chromosome in vascular disease.

On the other hand, it has been shown that an immunological mechanism is involved in the occurrence of placental abruption. Baumann., *et al*. retrospectively investigated 170,000 births in Germany [11]. They extracted 874 cases of placental abruption and performed a multivariate analysis of the risk factors for occurrence of abruption. They found a significant increase in occurrence of placental abruption in primiparas, especially those ≥ 35 years of age, and they speculated about the possibility that placental abruption occurs due to inadequate immunological tolerance to paternal antigens. Steinborn., *et al*. found less occurrence of placental abruption in a group with low levels of plasma soluble HLA-G [12]. This means that there is less occurrence of placental abruption in those with immunological tolerance. Vatten., *et al*. investigated the relationship between the length of gestation and fetal sex in cases of preeclampsia [13]. They found that male fetuses were more prone to miscarriage and preterm delivery at an earlier stage, and they touched on the presence of an immunological mechanism for maintaining pregnancy. The same is true for placental abruption, with clinical observation of placental abruption in pregnancies with a male fetus being more likely to occur at an earlier stage of pregnancy. In a large-scale retrospective study conducted by Tikkanen., *et al*. [6], the male-to-female ratio of placental abruption was 1.45 at < 28 weeks, 1.49 at 28-31 weeks, 1.31 at 32-36 weeks, and 1.11 at ≥ 37 weeks, indicating that the earlier the stage of gestation was, the higher the risk (odds ratio was 35.2, 7.13, 4.70, and 1.00, respectively) of placental abruption in pregnancies with a male fetus was. There have been several reports suggesting that PIH is associated with pregnancy with a male fetus. At first glance, the results of the present study appear to contradict such reports. However, if pregnancy with a male fetus causes placental abruption or PIH via an alternative mechanism, the present results would not contradict those studies and all could be explained. Further discussion is impossible at the present time because the cause of the two disorders has not yet been identified.

One known functional gene located on the Y chromosome is the sex-determinating gene, but the number of other functional genes on the Y chromosome is low. In this sense, it is assumed that expression of genes on the Y chromosome has little impact on the occurrence of diseases. In the case of the X chromosome, a part of the function of the chromosome is lost due to X chromosomal inactivation if homozygous. This inactivation mechanism does not affect the Y chromosome. These facts support the hypothesis that expression of the paternal Y chromosome is the cause of placental abruption. This would suggest that expression of genes on the paternal X chromosome that were not inactivated causes occurrence of placental abruption in pregnancies with a female fetus. To prove this hypothesis, we need to demonstrate that the degree of X chromosomal inactivation in the placenta comes from the parents.

A limitation of the present study was the fact that we could not statistically directly prove that pregnancy with a male fetus is a risk factor for occurrence of placental abruption. A large-scale case control study is needed to demonstrate that gender difference is a risk factor for occurrence of disease. Another limitation was the fact that we could not investigate psychophysiology factors and socioeconomic factors surrounding the mother as risk factors for placental abruption. However, we did find circumstantial evidence pointing to involvement of genetic and immunological factors as causes of placental abruption in other reports in the literature.

In conclusion, we showed in the present study that placental abruption occurred in pregnancies with a male fetus even in the absence of reported risk factors for placental abruption. Consequently, we need to identify specific factors in pregnancies with a male fetus in future studies. For example, it will be necessary to investigate the involvement of expression of one or more specific genes on the Y chromosome in occurrence of placental abruption in cases of placental abruption in pregnancies with a male fetus. It will also be necessary to shed light on inactivation patterns of paternal X chromosome genes by means of epigenetic analysis, etc.

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Declaration of interest statement

The authors state no conflict of interest.

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