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The effects of fetal gender on pregnancy induced hypertension in twin pregnancy

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Summary

Purpose of investigation: To determine whether pregnancy induced hypertension (PIH) is associated with fetal gender. *Materials and Methods:* The authors reviewed the records of 26,026 pairs of twins from the US 1995-2004 Matched Multiple Birth Dataset (the largest multiple dataset available for multiple births). Logistic regression model was applied to estimate the odds ratio (OR) between different sex groups of twins. *Results:* The authors found that compared with male-male group (7.60%), the incidence of PIH in female-female and female-male groups are 8.25% (adjusted odds ratio (aOR) 1.10, 95% confidence interval 1.06-1.13 and 8.14% (aOR 1.08, 95% confidence interval (CI) 1.05-1.11), respectively. Comparably, the incidence of eclampsia has no significant difference among three groups. *Conclusion:* The present finding confirms that the fetal gender has partially influenced on the incidence of PIH, while having no effects on eclampsia.

Key words: Fetus; Gender; Pregnancy induced hypertension; Twin pregnancy.

Introduction

Pregnancy induced hypertension (PIH) is one of the most common complications during pregnancy with hypertension or/and proteinuria, and it is one of the leading causes of maternal and fetal mortality and morbidity. PIH affects approximately 5-10% of all pregnancies [1], and its onset is associated with many influence factors. Previous studies, which focused on the maternal factors of PIH, found that the risk factors of PIH included primipara, multiple gestation, maternal age, low social economic situation, etc. However, PIH is a special disease which associated with pregnancy and the exact cause is not clear. The present authors infer that some fetal factors may be related with the onset of PIH.

The placenta is a fetus-related organ, its capacity to secrete hormones would be affected by the fetal genome, raising the possibility that there may be a differential sex-specific fetal impact on PIH [2]. Molecular mechanism driving the sexual dimorphism in blood pressure activity may provide insight into sex differences in blood pressure regulation, so studies have focused on the effects of fetal gender on gestational diseases. Some studies have reported the effects of fetal gender on PIH, while they used the singletons as the study subjects. For example, Toivanen *et al.* reported that the ratio of males to females in babies born to mothers with PIH was 1:24 and the ratio increased up to 1:72 according to the severity of the disease [3]. There's a wide spectrum of opinions on this problem whether the fetal gender has the effect on PIH or not. Therefore the present authors analyzed this problem using the data in the U.S. matched multiple dataset (1995-2004). The advantage of this database is that it is the largest linked dataset available for multiple births. Moreover, the present authors have divided the twins into three groups, which can give us the clear trend of the incidence PIH of in different gender groups.

The aim of the present study is to analyze the effects of fetal gender on PIH in twin pregnancy.

Materials and Methods

This was a retrospective cohort study of twin births, using the U.S. matched multiple dataset (1995-2004), of the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS). The twin data were abstracted from live birth and infant death certificates. The three-stage matching algorithm develops the twin data resources. The algorithm was verified and was confirmed reliable. The accurate of this dataset was more than 99%. The identifying information of mother includes age, race, purity, education, married status, and excludes mothers' name and address.

The primary outcome is the incidence of PIH recorded in the Matched Multiple Birth Data files. PIH is classified as two or more occasions in blood diastolic pressure ≥ 90 mmHg or sys-

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Table 1. — *Baseline characteristics in the different sex twin pregnancies, the US Matched Multiple Birth Data, 1995-2004.*

	Male-male group	Female-female group	Male-female group	*p* value
N	109,722	107,756	108,067	
Race (n, %)				< 0.0001
White	86,966 (79.3)	85,059 (78.9)	84,234 (78.0)	
Black	17,919 (16.3)	18049 (16.8)	20,392 (18.9)	
Others	4837 (4.4)	4652 (4.3)	3441 (3.2)	
Age (n, %)				0.19
< 20 years	8500 (7.8)	8479 (7.9)	5696 (5.3)	
20-34 years	81,718 (74.5)	80,446 (74.7)	79,188 (73.3)	
> 34 years	19,504 (17.8)	18,831 (17.5)	23,183 (21.5)	
Marital status (n, %)				< 0.0001
Married	78,559 (71.6)	76701 (71.2)	78,612 (72.7)	
Unmarried	30,390 (27.7)	30,280 (28.1)	29081 (26.9)	
Unknown	773 (0.7)	775 (0.7)	374 (0.4)	
Education (n, %)				< 0.001
0-8 years	4753 (4.4)	4780 (4.2)	3353 (3.1)	
9-12 years	46,962 (42.8)	46,532 (43.2)	43751 (40.5)	
13-15 years	24,829 (22.6)	24,471 (22.7)	24,592 (22.8)	
16 years and over	31,381 (28.6)	30,122 (28.0)	34,590 (32.0)	
Not stated	1977 (1.8)	1851 (1.7)	1763 (1.6)	
Smoking during pregnancy (n, %)				< 0.001
No	80,174 (73.1)	78,685 (73.0)	78,992 (73.1)	
Yes	9219 (8.4)	8707 (8.0)	9867 (9.1)	
Unknown	20,329 (18.5)	20,364 (18.9)	19,208 (17.8)	

tolic pressure ≥ 140 mmHg, taken ≥ 4 hours apart and occurring after 20 weeks of gestation without proteinuria.

Previous studies have showed the mothers' age, ethnic, married status, and education were the risk factors of PIH, so these variables were adjusted in the multiple logistic regression analysis.

The subjects included in the present study should meet the following criteria: (1) birth with twin pregnancy, (2) maternal without missing information for PIH, (3) pregnancy without chronic hypertension, (4) each one in every twin without missing information for gender.

All outcomes were coded as dichotomous variables. A multiple logistic regression analysis was used to calculate the odds ratio (OR) of the outcomes. The results of the logistic models were expressed as OR and 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant. All analyses were carried out using SAS version 9.3.

Results

Baseline characteristics in the different fetal gender groups are shown in Table 1. PIH was reported in 26,026 out of 325,545 twin pregnancies (8.0%); among these pairs, there were 8,892 (34.2%) female-female pairs, 8,793 (33.8%) female-male pairs, 8,839 (32.0%) male-male pairs. There were significant differences in maternal and pregnancy characteristics among different fetal gender groups (Table 2). Some maternal factors seem to relate with the gender of the fetuses, such as maternal race and marital status, while maternal age, educational status, and smoking during pregnancy have no relationship with it.

There is no markedly distribution of three gender groups. Compared to the incidence of PIH in male-male group (7.60%), the incidence of PIH in female-female group and female-male group were 8.25% (adjusted OR 1.10, 95%CI 1.06-1.13) and 8.14% (adjusted OR 1.08, 95%CI 1.05-1.11), respectively. It has statistical significance. On the contrary, there was no significant difference of the incidence of eclampsia among three groups. (Table 3)

Discussion

The results suggest that fetal gender has effects on the incidence of PIH. Compared to the male-male group, the incidence of PIH in female-female group and female-male group are 8.25% (adjusted OR 1.10, 95%CI 1.06-1.13) and 8.14% (adjusted OR 1.08, 95%CI 1.05-1.11), respectively. It seems that female fetus is at higher risk for PIH in pregnant women. Nevertheless, the present outcome is inconsistent with some previous reports. Previous studies reported that female fetus had higher eostriol that is a protective factor in the development of hypertension than male fetus in singleton pregnancy from the experiments [4-7]. Testosterone plays the absolutely opposite role in the regulation of the blood pressure compared to estrogen. There are also a number of reports that women with preeclampsia have higher plasma testosterone levels compared to those of healthy pregnant women [8-19]. So there may be a possibility that in twin pregnancy, female-female twin has

Table 2. — *Baseline characteristics in the different sex twin pregnancies with pregnancy induced hypertension, the US Matched Multiple Birth Data, 1995-2004 (n = 26,025 pairs).*

Pregnancy induced hypertension	Female-female group	Female –male group	Male-male group	*p* value
N	8892	8794	8339	
Race (n, %)				< 0.001
White	7120 (80.1)	7027 (79.9)	6765 (81.1)	
Black	1413 (15.9)	1513 (17.2)	1267 (15.2)	
Others	359 (4.0)	254 (2.9)	307 (3.7)	
Age (n, %)				0.87
< 20 years	823 (9.2)	496(5.6)	774 (9.3)	
20-34 years	6427 (72.3)	6206 (70.6)	6008 (72.0)	
> 34 years	1642 (18.5)	2092 (23.8)	1557 (18.7)	
Marital status (n, %)				< 0.001
Married	6478 (72.9)	6636 (75.5)	6033 (72.3)	
Unmarried	2384 (26.8)	2140 (24.3)	2278 (27.3)	
Unknown	30 (0.3)	18 (0.2)	28 (0.4)	
Education (n, %)				0.07
0-8 years	326 (3.7)	242 (2.8)	263 (3.1)	
9-12 years	3708 (41.7)	3188 (36.3)	3430 (41.1)	
13-15 years	2123 (23.9)	2150 (24.5)	1945 (23.3)	
16 years and over	2619 (29.4)	3118 (35.4)	2585 (31.0)	
Not stated	116 (1.3)	96 (1.1)	116 (1.4)	
Smoking during pregnancy (n, %)				0.95
No	6889 (77.6)	6837 (77.8)	6450 (77.4)	
Yes	553 (6.2)	556 (6.3)	524 (6.3)	
Unknown	1440 (16.2)	1401 (15.9)	1365 (16.4)	

Table 3. — *Odds ratio of pregnancy induced hypertension and eclampsia in the different sex group Twins, the US Matched Multiple Birth Data, 1995-2004.*

	OR	95% CI	OR[a]	95% CI
Pregnancy induced hypertension				
Male-male	1.00		1.00	
Female-female	1.09	1.06-1.13	1.10	1.06-1.13
Female-male	1.08	1.04-1.11	1.08	1.05-1.11
Eclampsia				
Male-male	1.00		1.00	
Female-female	1.06	0.97-1.15	1.06	0.97-1.15
Female-male	1.03	0.94-1.12	1.03	0.95-1.13

a: adjusted by race, marital status, age, education of mother, and maternal smoking during pregnancy; CI: confidence interval; OR: odds ratio

the lowest incidence of the PIH. However, the present data analysis is opposite to this inference.

There is also evidence that supports the present analysis. There is a report in Japan that is consistent with this study that the incidence of PIH rank is female-female, female-male, and male-male respectively. Their analysis showed in both monochorionic diamniotic (MD) and dichorionic diamniotic (DD) twin pregnancies, compared with mothers carrying male–male fetuses, and those carrying female–female fetuses had significantly higher incidences of PIH and preeclampsia; at the same time those with male–female fetuses were intermediate [20]. They explained the outcome with the immune theory, one of the pathology mechanisms of PIH as above. Shiozaki *et al.* thought the amount of fetal antigens led to the pathogenesis of preeclampsia [20].

Higher insulin resistance is another mechanism of PIH. As women with gestational hypertension exhibited metabolic features similar to the patients with insulin resistance syndrome, this suggests that similar abnormalities could be involved in the pathogenesis of these disorders. The more severe the insulin resistance, the higher incidence of the PIH. Indeed, a study has found that maternal with female has more serious insulin resistance than maternal with male [21]. There is also evidence that it is consistent with the current research in that the female-female twins have the highest incidence of PIH, the male-male twins have the lowest incidence, and the female-male twin have an intermediate one.

The main limitation of the present study is that a variety of the factors can affect the outcome of this analysis. The fetal and maternal information is limited in the dataset. For example, we cannot distinguish between gestation hypertension and preeclampsia. The types of chorionicity and amniosity information are not included. The onset and duration of the hypertension are also not recorded in this dataset. In different stage of gestation, the result and inci-

dence of PIH is different, because the hormones have different peak times to affect blood pressure. A study has shown preeclampsia with early term is a low risk factor, and preeclampsia with full term is a high risk factor [22]. As mentioned above, the present authors also cannot validate the previous study postulation like immune theory, insulin resistance in this data study. Thus, further researches should be taken to precisely understand the accurate mechanism.

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