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Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan

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ABSTRACT

The male antigen (HY), the elevated level of fetal antigen in twin pregnancies, and the increased number of MHC mismatches in dizygotic twin pregnancies might affect immunological tolerance during pregnancy. Using the Perinatal Database of the Japanese Society for Obstetrics and Gynecology, we studied the occurrence of pregnancy-induced hypertension (PIH) and preeclampsia in mothers delivering singleton babies and in those delivering monochorionic diamniotic (MD) twin pregnancies and dichorionic diamniotic (DD) twin pregnancies at 125 centers of the perinatal network in Japan from 2001 through 2005. In singleton pregnancies, pregnant women carrying female fetuses had a significantly higher incidence of PIH and preeclampsia compared with those carrying male fetuses. In MD twin pregnancies, compared with mothers carrying male–male fetuses, those carrying female–female fetuses had significantly higher incidences of PIH and preeclampsia and a marked difference was observed in primiparous cases. In DD twin pregnancies, the incidences of PIH and preeclampsia were significantly higher in mothers with female–female fetuses than those with male–male fetuses, while those with male–female fetuses had intermediate values. The incidence of PIH and preeclampsia in MD twin pregnancies was similar to that in DD twin pregnancies with male–male fetuses or female–female fetuses. The male antigen and the increased number of MHC mismatches in DD twin pregnancies were not a risk factor for PIH and preeclampsia. Female fetal sex was a risk factor for PIH and preeclampsia.

1. Introduction

Preeclampsia (preeclampsia) is a pregnancy complication affecting pregnant women and one of the major causes of maternal mortality and morbidity, perinatal death, preterm birth, and fetal growth restriction. Several risk factors for preeclampsia have been identified such as nulliparity, prolonged interpregnancy interval, short cohabitation, condom user, and use of donated embryos (Robillard et al., 2003; Dekker, 2002; Saito et al., 2007).

The embryo (fetus) and placenta are a semi-allograft to the maternal immune system because half of the embryonal (fetal) genes are paternally derived. In general, the risk of preeclampsia is greatest in primiparous women. Pathogenesis of preeclampsia in primiparous women may differ from that in multiparous women, multifetal gestation, or previous preeclampsia. Subsequent pregnancy with the same partner reduces the risk of preeclampsia (Trupin et al., 1996). Moreover, the risk of preeclampsia seems to be partner-dependent. Subsequent pregnancy with a new partner increases the risk of preeclampsia (Robillard et al.,

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2003; Dekker, 2002). Conversely, prolonged exposure to a partner's semen may reduce the risk of preeclampsia (Einarsson et al., 2003; Robillard et al., 2003). These phenomena suggest that immunological mechanisms such as induction of tolerance may contribute to the pathogenesis of preeclampsia.

Several studies have identified the association of fetal gender with PIH and preeclampsia, while their results are contradictory. In singleton pregnancies, Toivanen and Hirvonen (1970) 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. On the other hand, Hsu et al. (1994) found a predominance of female fetuses in preterm preeclamptic pregnancies compared with preterm normotensive pregnancies ($p = 0.043$), but not those in term preeclamptic and normotensive pregnancies ($p = 0.989$). In multifetal pregnancy, there is no difference in the male/female ratio between normotensive mothers and preeclamptic mothers (Makhseed et al., 1998). However, the sample size in this twin study was very small (<70 cases). Caution is needed when evaluating this result.

There are three hypothesized types of pathogenesis for the risk of preeclampsia in male–male and female–female twins (Tables 1A and 1B). The first hypothesis speculates that immune-incompatibility between mother and fetus ('major histocompatibility complex [MHC] mismatch') contributes to the pathogenesis of preeclampsia (Stevenson et al., 1971). If this were the case, the incidence of preeclampsia should be higher in dichorionic diamniotic (DD) twins compared with monochorionic diamniotic (MD) twins and should be similar in MD twins and in singletons, because all the MD twins are derived from monozygotic twins and 80–90% of the DD twins are derived from dizygotic twins in Japan.

The second hypothesis suggests that increased levels of fetal antigen lead to the pathogenesis of preeclampsia. If this were the case, the incidence of preeclampsia should be twice as high in twins compared with singletons and should be similar in DD twins and MD twins.

The third hypothesis is related to the HY antigen. Recent data suggested that the chance of a subsequent live birth in secondary recurrent miscarriage patients with first-born boys compared with first-born girls was significantly lower in women with HY-restricting HLA class II alleles (Nielsen et al., 2009). Most patients with recurrent placental abruptions had first-born boys and significantly more of these patients carried HLA haplotypes with HY-restricting class II alleles compared with controls (Christiansen et al., 2010). A maternal immune reaction against fetal HY antigens might break the maternal tolerance to semiallograftic fetuses. If this were the case, the male–male twins should have the highest rate of preeclampsia, the female–female twins and female singletons should have the lowest rate, and the male–female twins and male singletons should have an intermediate rate.

The aim of the present study was to evaluate the effects of fetal sex on the pathogenesis of PIH/preeclampsia. To demonstrate that any of the hypotheses above contribute to preeclampsia, we examined the incidence of preeclampsia in twin pregnancies as well as singleton pregnancies and analyzed the relationship among fetal gender, fetal number, and PIH/preeclampsia.

2. Materials and methods

This study was approved by the Tokyo Women's Medical University Ethics Committee.

Detailed descriptions of the database have been published elsewhere (Matsuda et al., in press). Briefly, the attendant physicians at 125 tertiary perinatal centers of Perinatal Research Network in Japan collected yearly data for women in an off-line clinical database with a common format. Data were sent to the Perinatal Committee of the Japanese Society of Obstetrics and Gynecology, and quality control was assessed for the database.

There were 241,672 singleton births and 20,050 twin births (10,025 mothers) that resulted in live birth or fetal death. Fetal death was defined as follows: fetal death before complete expulsion or extraction from the mother of a product of conception with a gestation of at least 22 weeks. All measurements reported in the database were obtained as the usual care provided to high-risk obstetric patients at tertiary perinatal centers. Determination of chorionicity was performed non-invasively during the first trimester of pregnancy by ultrasound examination of the base of the inter-twin membrane for the presence or absence of the lambda sign (Sepulveda et al., 1996).

Gestational age was determined based on the menstrual history, prenatal examination and ultrasound findings during early pregnancy (gestational sac diameter, crown rump length, and biparietal diameter).

Women were classified as having pregnancy-induced hypertension when they had hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic $\geq$ 90 mmHg) on two occasions. Women were considered to have preeclampsia when they had hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic $\geq$ 90 mmHg) on two occasions and proteinuria defined as either $\geq$300 mg/24 h urine collection or $\geq$1+ on a dipstick on at least two separate occasions without urinary tract infection. Women were stratified to have severe preeclampsia when they had hypertension (systolic blood pressure $\geq$ 160 mmHg and 100 mmHg) on two and proteinuria defined as either $\geq$2 g/24 h urine collection or $\geq$3+ on a dipstick on at least two separate occasions without urinary tract infection. Women with chronic hypertension were excluded. Variables considered to be of potential importance in the analysis included maternal age, parity, gestational age at delivery, maternal smoking.

We compared numbers and rates of PIH, preeclampsia, preeclampsia with fetal death, severe preeclampsia, and severe preeclampsia with fetal death among mothers (mothers carrying male fetuses; mothers carrying female fetuses; mothers carrying male–male MD fetuses; mothers carrying female–female MD fetuses; mothers carrying male–male DD fetuses; mothers carrying male–female DD fetuses; mothers carrying female–female DD fetuses) and compared background