Gender Differences of Placental Dysfunction in Severe Prematurity

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Abstract

Background: Several obstetric complications have been reported to be related to fetal gender such as prematurity, preeclampsia and placental abruption.

Objective: To investigate whether a sex difference exists in findings at placental histology of extreme prematurity.

Design: Cross-sectional.

Setting: Gynecology and Obstetrics department, Al-Kadhimyia Teaching Hospital, Baghdad, Iraq

Patients and Methods: Fifty deliveries before 32 weeks of gestation of singleton, liveborn, non-anomalous infants were included in the study. Placental histological findings were compared between male (n=25) and female (n=25) neonates.

Results: Male fetuses had distributions rate of nulliparity, maternal age , gestational age at delivery as female fetuses , but higher birth weight centiles ([55.09±11.3] vs. [43.09±8.2]). Placental histology showed no association between fetal gender and lesion of acute inflammation (p=0.09) , intraplacental vascular pathology (p=0.2) or uteroplacental vascular pathology (p=0.5).However ,lesion of chronic inflammation had a significantly higher score in male than in female fetuses (p=0.01).when we examined the distribution of chronic placental inflammation ,significantly more severe lesions were noted in male than in female fetuses at the implantation site (i.e the area of interstitial trophoblast invasion of the maternal decidua and maternal endovascular trophoblast remodeling),than within the placental villi (chronic villitis) or in the amniochorionic membranes (where interstitial trophoblast invasion is minimal).

Conclusion: In premature deliveries at <32 weeks ,male fetal gender is associated with placental lesions suggestive of a maternal immune response against the invading interstitial trophoblast .The immunological basis of these findings deserves further studies.

Key wards: Gender difference, prematurity, placental histology.

Introduction:

Rates of several obstetric complications have been reported to vary with fetal gender. Male neonate weight approximately 200 gm more than female at term so they are more prone to shoulder dystocia than female. Also male fetuses are more prone to be post-term than female so induction of labour is more with male fetuses [1]. The risk of pre-term labour , and placental abruption are increased in male fetuses while hyper emesis gravid arum , hypertension related growth restriction and placenta accreta are more common in female fetuses [2,3,4,].

Fetal gender observed on maternal serum multiple markers with higher alkaline phosphatase levels in females fetuses than in those with male fetuses [5] and a significant lower angiogenin levels in second trimester amniotic fluid of male fetuses than female fetuses , including those women delivering preterm [6].

Male fetuses are more likely to have a positive placental membrane cultures than female infants[7] and a decidual lymphoplasmacytic cells infiltrations where more common in male versus female placentas , suggesting that a maternal immune reaction to fetal tissue may be more common in male fetuses [8].

The association of fetal gender on placental histology has undergone limited serutiny todate. In preeclamptic pregnancies an excess of syncytial knots, a characteristic villous manifestation of low uteroplacental blood flow has been reported in female compared with male fetuses [9].

There were more males among pre-term and early pre-term births in most populations, including IVF births. The proportion of male births declines with increasing gestation, even when time of conception is known. This male excess appears to be strongest for spontaneous preterm births. The greater mortality risks for males during pregnancy and infancy are well known. Boys have higher rates of fetal and neonatal mortality and are more vulnerable to long term neurological and motor impairments after pre-term births. The higher proportion of pre-term births among males could contribute to an explanation for their higher mortality in infancy. A greater male excess for spontaneous onset pre-term births would add support to an explanation based on labour inducing processes associated with fetal sex , whereas a greater male excess among medically indicated pre-term births would favor an explanation base on greater male susceptibility to certain complications of pregnancy such as hypertension or growth restriction. Labour-

inducing effects of fetal sex hormones or the effects of fetal weight were most likely causal mechanisms [8].

Aim of the study:

Dose sex difference exists in findings of placental histology of extreme prematurity.

Patients & methods:

A cross sectional study was done at the department of obstetrics and Gynecology in cooperation with the department of histopathology at Al-Kadhymia Teaching hospital, Informed consent was obtained from all participating women Fifty women who expected to deliver preterm were enrolled in this study, Twenty five women were delivered male fetuses and twenty five were delivered female fetuses.

The inclusion criteria include non-anomalous, Singleton, live born infants delivered between 22-32 weeks of gestation. The gestational age was established by a reliable last menstrual period or early ultrasonographic assessment and was confirmed by neonatal examination, Cases of maternal diabetes mellitus, chronic hypertension, Rh sensitization, placenta praevia, and hydrops were excluded from the study, The diagnosis of preeclampsia was made prior to delivery. Birth weight centile were calculated using customized birth weight percentile.

After delivery samples of the placentas are taken and put in previously prepared containers and then sent to the department of histopathology for examination,

Placental pathology examinations were performed following a standard protocol. The same pathologist reviewed the slides, blinded to the clinical data with the exception of gestational age at delivery. For each case, at least 2 samples of umbilical cord, 2 samples of extra placental membranes and 4 samples of grossly normal chronic villi were available for review.

Briefly histologic lesions identified at histopathologic examination were classified into four primary pathophysiologic groups:-

Group I (lesion of acute inflammation)

Acute amnionitis, acute chorionitis and diciduitis, acute chorionic plate inflammation, acute umbilical vasculitis, and acute vasculitis of chorionic plate vessels.

Group II (uteroplacental vascular pathology)

Uteroplacental vessel fibrinoid necrosis or atherosis, absence of physiologic conversion and presence of endovascular trophoblast, haemosidren histologic features of placental abruption, syncytio-trophoblastic knotting, cytotrophoblast (x-cell) proliferation, circulated nucleated erythrocytes, uteroplacental vessel thrombosis, intervillus thrombus, perivillus fibrin deposition, and intervillus thrombosis with peripheral infarct.

Group III (intraplacental vascular pathology)

Villus infarct, villus stromal mineralization, chorionic vessel thrombus, fetal stem vessel thrombus , hemorrhagic endovasculitis, and a vascular terminal villi.

Group IV (lesion of chronic inflammation)

Chronic uteroplacental vasculitis, dicidual eosinophilia basal plate plasma cell infiltration, chronic basal plate inflammation, chronic villitis of anchoring villi, chronic intervillositis, chronic villitis and chronic inflammation of examination.

Statistical analysis

Data were collected and described by using number, percentage, mean ± (SD). The association was considered to be statistically significant when $p<0.05$ or relative risk (RR) with (95%) confidence (CI) not inclusive of the unity was considered significant.

Results:

A total 50 neonates fulfilled the inclusion and exclusion criteria of which 25 (50%) were male and 25 (50%) female.

Table (1) shows demographic characteristics of the study, there was no significant difference regarding maternal age p-value (0.6), neonatal weeks of gestation – p value (0.9), and parity (nulliparity p-value 0.4 and multiparty p- value 0.6).

The birth-weight centiles were significantly higher for male than female fetuses (P value 0.04).

Table 1: Demographic characteristics and birthweight centiles in relation to fetal gender, values are presented as mean ±SD and n (%).

Variable	Male fetuses (n=25)	Female fetuses (n=25)	P value
Maternal age (years)	25.6±6	25±8	0.6 NS
Gestation age (weeks)	25.5±3	26.6±2.9	0.9 NS
Nulliparity	10(40%)	12 (48%)	0.4
Multiparty	15 (60%)	13 (52%)	0.6
Birth weight centiles	55.09 ± 11.3	34.09 ± 8.2	0.04

Table (2) shows the indications for pretetm delivery in relation to fetal gender.There was no significant difference in between male and female gender in preterm labour, PROM, and placental abruption (p-value 0.6) in preeclampsia there is lower rate [2(8%)] for male versus [3 (12%)] for female (p value 0.7).

Table 2:- Indications for preterm delivery in relation to fetal gender. Values are presented as n (%).

Indications for preterm delivery	Male fetuses (n=25)	Female fetuses (n=25)	P value
Spontaneous Preterm labour	15 (60%)	13 (52%)	0.6 NS
PROM	5 (20%)	6 (24%)	
Placental Abruption	3 (12%)	3 (12%)	0.7 NS
Preeclampsia	2 (8%)	3 (12%)	

Table (3) shows the distribution of chronic inflammatory lesions of male and female placentas. We found that those at the placental site (the area of interstitial trophoblast invasion of the maternal decidua and maternal endovascular trophoblast remodelling represented by anchoring villi and basal plate) were significantly more common in the placenta of male than female fetuses.

While there were no significant difference between male and female placentas in rate of chronic inflammatory lesions within the placental villi. (chronic villitis and chronic intervillositis). Or the amniochorionic membranes where the trophoblast invasion is minimally seen.

Table 3:- Individual lesions of chronic inflammation in relation to fetal gender presented as n (%).

Location of placental lesions	Male fetuses (n=25)	Female fetuses (n=25)	Relative Risk (95% CI)	Odds ratio
Chronic inflammation at the basal plate	2 (8%)	1 (4%)	1.4 (0.7-2)	2.1 (1.7-3)
Chronic inflammation of amniochorion	2 (8%)	2 (8%)	1 (0.3-1.4)	1 (0.7-1.7)
Chronic intervillositis	3 (12%)	4 (16%)	0.8 (0.4-1)	0.7 (0.3-1)
Chronic villitis	1 (4%)	2 (8%)	0.7 (0.4-1.2)	0.5 (0.1-2)
Chronic uteroplacental vasiculitis	6 (24%)	4 (16%)	1.3 (1.1-1.7)	1.7 (1.3-2)
Deidual eosinophilia	6 (24%)	4 (16%)	1 (0.5-1.3)	1 (0.7-1.8)

95% CI = 95 Confidence interval

Discussion:

There are several complications of pregnancy that have a significant association with fetal gender, one of them is preterm labour ,it is an important obstetric problem which may lead to perinatal morbidity and mortality.

More frequent lesion of chronic inflammation have been reported in female with recurrent miscarriage as small series of cases with chronic chorioaminionitis is reported with high rate of prematurity [10].

Antonio Farina in Italy found spontaneous preterm labour is thought to result from the pathological and untimely activation of the common terminal pathway of parturition (uterine contractility, cervical repining, and membrane/decidual activation) suggest that preterm parturition is a syndrome that is caused by multiple pathogenic process such as infection, inflammation, bleeding and over distention[11]. Our findings suggest that in very preterm fetuses male gender is associated with significantly higher rate of chronic inflammatory lesions at the level of interface between placenta and maternal tissues.

This result is consistent with that of Jacques et al who report that inflammatory cells in the chronic chorioamnionitis have distribution in the membrane similar to that seen in acute chorioamnionitis including involvement of free (exetraplacental) fetal membrane or chorionic plate and there was tendency toward low birth weight and high frequency of preterm labour [12].

In our study we found excess of basal plate plasma cells infiltration as well as tendency to increased uteroplacental chronic vasculitis and each correlate with male gender while the chronic inflammatory lesions involving intervillous space such as villitis or exetraplacental membrane are not. Our findings thus suggest that a more maternal immune response against the invading interstitial trophoblast is present in male compared with female fetuses.

These results were in agreement with that of Khong et al who found that chronic basal deciduitis could be a normal modulation of the placental allograft or an abnormal immune response to it and found that basal diciduitis is associated with TORCH infections which reflects an abnormal immune response such as systemic lupus erythematosis or that it might be a part of chronic inflammatory disease , and found the diagnosis of chronic deciduitis was almost identical to the assessment of the severity of the inflammation which depend on the extent and plasma cell infiltration [13].

Our study population of pregnancies delivered at < 32 weeks confirms an excess of male fetuses and

higher birth-weight centiles associated with male gender as already associated with term pregnancies.
However, our findings of lower rates of preeclampsia and no significant differences in rate of placental abruption for male fetuses are at variance with those previously reported. This may be due to modest effect of fetal gender on placental abruption and the presence of several statistical confounders (including prematurity, chorioamnionitis, hypertensive complications of pregnancy and cigarette smoking), thus indicating complex interaction between fetal gender, pregnancy complications and gestational age at delivery [14] .

Conclusion:

The present study demonstrate that in premature deliveries at < 32 weeks, male fetal gender is associated with placental lesions in the form of chronic inflammation at the level of the interface between placenta and maternal tissue higher than female, which may suggest the presence of a maternal immune response against the invading interstitial trophoblast, The immunologic basis of these findings deserves further studies.

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