ORIGINAL ARTICLE

Impact of Sex of The Previous Child on the Out Come of Subsequent Pregnancy

Amita Gupta, Deepali Raina, Aakriti Gupta, Tania Kakkar

Abstract

Survival of the semi allogeneic fetus in uterus without rejection is an immunological paradox . The antigenic dissimilarity is pronounced when XX mother Carries an XY fetus Pervious birth of a boy negatively affects the obstetrical future in female where these has been a supposed failure of immunological tolerance of pregnancy. Out of all the obstetrical complication assessed, IUGR turned out to be the most strongly associated with pervious Male Baby. PIH turned out to be the most common complication associated with pregnancy. Rate of LBW was also significantly more in women with previous male child. Oligo - hydromnios was also found to be significantly associated with history of having previous male child. PROM was also seen more frequently in cases that had a preceding male child. Pre -Eclampsia was also significantly associated with history of having a previous male child. A total of 1350 cases were studied. As expected, 64.89% of the cases included in the study went uneventful. There were 22.52 % vs. 12.59% eventful pregnancies in women with previous male and previousfemale child respectively (p = 0.0001).27.04% pregnancies went uneventful in women with previous male compared to 37.85% in women with previous female child (p = 0.0001).The study clearly shows that there is a lesser predilection of obstetrical mishaps happening to women whose first child is a female compared to those who have a previous male child.

Key Words

Antigen, Preceding Child , Subsequent Pregnancy

Introduction

Pregnancy is a unique symbiotic union between mother and fetus which contradicts many of the general rules of immunology. The fetus contains an immunological set of paternal antigens that are foreign to mother, acting thereby as a transplant inside the uterus. Foreign transplantation antigens normally generate a cell mediated immune reaction in the recipient, which causes rejection within some weeks. Thus from an immunological point of view the development of a normal pregnancy seems almost impossible. Yet the fetus survives the period of intrauterine gestation without rejection due to inherent fetal and maternal mechanisms for immunological recognition of pregnancy. Incorrect recognition of fetal antigens might result in failed pregnancy.

During pregnancy, fetal cells enter the maternal circulation and in later stages apoptotic syncytiotrophoblast debris is also normally shed in large quantities from the placenta (1). Fetal microchimerism i.e. persistence of fetal cells in the mother after birth is a well-known process too (2).It is presumed that this can lead to maternal sensitization against fetal cells, particularly male-specific minor histocompatibility (H-Y) antigens carried by a male fetus. This may harm embryos and fetuses and cause complications in subsequent pregnancies. Also anti-H-Y

immunity, which may be either humoral or cellular, can be demonstrated up to 22 years after the birth of a boy in mothers (3). The first fetus might escape the immunological attack while memory cells that persist may lodge an immediate and more intense attack on the fetus in the subsequent pregnancy. Maternal immune recognition of the minor HY antigens from male fetuses is considered a well- tolerated status generally, as half of all newborns are healthy boys. However, a potential harmful role for these immune responses in pregnancy has been suggested as well. There are studies suggesting presence of functional H-Y specific CD8+ T cells in women following pregnancy with a male fetus. Exposure to male cells (either through pregnancy or blood transfusion) also results in the development of antibody responses to H-Y proteins.

From the Deptt. Of Obs.& Gynac Govt. Medical College Jammu- J&K India

Correspondence to : Dr. Amita Gupta, Asstt. Prof. Deptt. of Obs.& Gynac Govt. Medical College Jammu, J&K-180001

Studies have been done which provide evidence that in a minority of women, previous birth of a boy may be associated with LBW, still births (4), increased incidence of abruption etc.(5). An explanation for the findings in such studies could be maternal immune responses against H-Y antigens leading to inflammatory processes, which theoretically can reduce the invasion of the placenta in the uterus, leading to insufficient placental function & causing IUGR or a decrease in birth weight. An inflammatory process may also promote liberation of inflammatory cytokines, causing increased prostaglandin production in the uterus that may lead to a shorter gestation i.e. PTL or PROM (6). Compliment mediated immune mechanisms have been implicated in placental dysfunction in patients with IUGR. Such pregnancies are characterized by inflammatory infiltrates and defective development in placenta consequent to inappropriate and injurious recognition of the fetal antigens by the mother's immune system. Egg Donated pregnancy too leads to a hyper-activation of Th1 and Th2 cells, a higher risk of perinatal and maternal morbidity like increased incidence of PIH & eclampsia compared to spontaneously conceived pregnancies, probably as a result of higher degree of antigenic dissimilarity between mother & a fully allogeneic fetus derived from foreign ovum & sperm (7). Indirect evidence for sensitization of maternal immune system against fetal Y-mediated antigens can be seen in the non-physiological situation of Stem cell transfer where male recipients of parous female HLA-matched stem cell grafts are seen to be more prone to develop GvHD than those of nulliparous female grafts or male grafts (8). This increased incidence of GvHD is presumably due to donor immune responses directed against Y-encoded antigens and clonal T-cell responses to at least some of these H-Y proteins suggesting that previous pregnancy of the female stem cell donor sensitizes her to MiHA like H-Y.

Material and Method

The study was conducted in The Department of Obstetrics & Gynecology SMGS Hospital, GMC Jammu over a period of one year.All the consenting women fulfilling the selection criteria were selected as cases on every alternate day (thrice a week) from those who were admitted in the emergency ward of the Hospital.

Inclusion Criteria:

- Parous women -one previous child i.e. GxP1A(x-2)

Exclusion Criteria:

- Parity > 1
- Age < 20 or > 35 years
- Chronic hypertension
- Gestational or pre-gestational diabetes
- Any other chronic or debilitating illness
- Multi-fetal gestation (Previous or current)
- BMI < 19 or > 30
- Anemia Hb< 9 gm%
- Congenitally anomalous fetus (Previous or current)
- Previous unexplained IUD
- Structural uterine & cervical abnormalities including Fibroids
- Uncontrolled hypothyroidism or hyperthyroidism
- Apparent maternal infections
- Placenta previa (All grades)
- Chronic smoker, alcoholic or any other substance abuse
- Rh negative with ICT positive
- TORCH positive
- History of blood transfusion in the past

After selecting the cases, relevant history was sought from them. Sex of the previous child was also asked. General physical and obstetrical examination was done. All routine, case specific and other necessary investigations to rule out conditions falling in the exclusion criteria were done. e.g. Hb; Blood group; Blood sugar; TSH; Obstetrical USG; ICT in Rh negative women; CRP & CBC in women with PPROM or PROM; 24-hour urinary proteins in patients with PIH, pre-eclampsia or eclampsia;Coagulation profile in abruption;TORCH test.

The outcome of present pregnancy was assessed in terms of: Uneventful pregnancy; Placental abruption; IUGR; PTL; PPROM; PROM; PIH; Low birth weight baby (< 2.25 Kg); Eclampsia ; Pre- eclampsia; IUD; Oligohydramnios.

Comparison of the assessed outcome was made with respect to sex of the previous child by applying chi squared test on respective 2x2 tables, performed at a significance level of $p< 0.05$.

Results

A total of 1350 patients fulfilled the inclusion criteria during the period of study. 669 of those (49.6%) had a previous male baby while 681 (50.4%) had a previous female baby. 876 (64.89%) patients had an uneventful course of pregnancy and delivery. 474 (35.11%) patients developed one or the other obstetrical complication under consideration. Many patients suffered from more than one complication. A total of 46 patients (3.41%) gave birth to babies weighting less than 2.25 Kilograms.Of these 34 (2.52%) had a previous male child. Only 12 (0.89%) had given birth to a female previously (p=0.0008).

IUGR was seen in 43 (3.19%) patients.35 (2.59%) out of these had a preceding male child. Only 8 (0.59%) had a previous female child (P = 0.0001).

Table 1. Sex Distribution

Previous child	Number	Percentage
Male	669	49.6%
Female	681	50.4%.
Total	1350	100%

Table3. Comparison of Eventful Vs Uneventful Events in Respect to Sex

Previous child	Eventful (n = 1350)	Uneventful (n = 1350)	P value
Male	304 (22.52%)	365 (27.04%)	0.0001
Female	170 (12.59%)	511 (37.85%)	0.0001

Table 2. Comparison of Assessed Outcome with Respect to Sex of Previous Child

Outcome	No. Of Patients (Total = 1350)	Previous Male Child	Previous Female Child	P Value
Preterm labour	41	22 (1.63%)	19 (1.41%)	0.6
Low birth wt.	46	34 (2.52%)	12 (0.89%)	0.000
IUGR	43	35 (2.59%)	8 (0.59%)	0.000
Oligohydramnios	51	36 (2.67%)	15 (1.11%)	0.002
PPROM	31	18 (1.33%)	13 (0.96%)	0.34
PROM	103	65 (4.81%)	38 (2.81%)	0.004
PIH	197	121 (8.96%)	76 (5.63%)	0.000
Eclampsia	4	2 (0.15%)	2 (0.15%)	N.A
Abruption	10	8 (0.60%)	2 (0.15%)	0.053
IUD	39	22 (1.62%)	17 (1.26%)	0.38
Pre-eclampsia	17	13 (0.96%)	4 (0.30%)	0.029
Uneventful	876	365 (%)	511 (37.85%)	0.000

Oligohydramnios was seen in 51 (3.78%) patients. Of those, 36 patients (i.e. 2.67%) had a previous male while 15 (i.e. 1.11%) had a previous female child (p= 0.002).

PROM occurred in 103patients, i.e. around 7.63%. 65 (4.81%) patients with PROM had given birth to a male firstly. 38 (2.81%) had a first female child (p = 0.004). PIH turned out to be the most common complication associated with pregnancy in the present study. About 197 (14.59%) of the patients had PIH. 121 (8.96%) of these had a previous male child. 76 (5.63%) had a previous female baby (p = 0.0003).

Seventeen (1.26%) pregnancies were complicated by Pre-eclampsia.Of those 13 (0.96%) had a first male child.4 (0.3%) had a previous female child (p = 0.029).

Only 4 (<0.3%) patients had eclampsia. 2 of these had a previous male baby (0.15%). 2 had a female child previously (0.15%). The cases seen during the period of study were too less to draw a valid conclusion.

Abruption was seen in a total of 10 (0.75%) patients only. 8 (0.60%) out of those had a male. 2 (0.15%) had a female child previously (p = 0.053). Thirty nine (2.89%) women had IUD. 22 (1.62%) out of those had a prior male baby. 17 (1.26%) had a prior female baby (p = 0.38). Thirty one patients presented with PPROM, constituting 2.3% of total cases. Of these, 18 had a male child previously (11.33%). 13 had a previous female baby (0.96%) (p = 0.34). PTL was found in a total of 41(3.04%) patients.Of these 22(1.63%) had given birth to a male previously.19 (1.41%) had a female child previously (p = 0.6). *All percentages have been calculated from 1350.

Discussion

There are only a few studies that demonstrate the direct clinical effect of sex of the preceding child on the outcome of subsequent pregnancy, therefore this study has been undertaken keeping in view the paucity of clinical studies related to anti H-Y immunity.

In the present study, a total of 1350 patients with singleton pregnancy were studied. 669 out of those (49.6%) had a previous male and 681 (50.4%) had a previous female baby.

The mean age of women with previous female child was 26.57 years and that of women with previous male child was 26.76 years. The difference between mean ages in both the groups was statistically insignificant. Thus the two groups were comparable in terms of age.

As expected more than half of the pregnancies (64.89%) among the cases included in the study went uneventful because the H-Y antigen recognition by maternal immune system is considered to be a well-tolerated status normally. Percentage distribution of eventful and uneventful pregnancies however clearly shows that there is a lesser predilection of obstetrical mishaps happening to women who have given birth to a female child previously compared to those who have an earlier male child. There were 22.52 % vs. 12.59% eventful pregnancies in women with previous male and previous female child (p = 0.0001) and 27.04% vs. 37.85%

uneventful pregnancies in women with previous male and previous female child, respectively (p = 0.0001). The difference between the two is statistically very significant.

Out of all the obstetrical complications assessed IUGR turned out to be most strongly associated with previous male baby (p = 0.0001).PIH turned out to be the most common complication associated with pregnancy in the present study. It stood second only to IUGR as the most strongly associated with previous male child. The results show that birth of a boy previously significantly increases the occurrence of PIH in subsequent pregnancy when compared to birth of a previous female (p=0.0003). Rate of LBW was also significantly more in women with previous male child (p=0.0008). Nielsen HS *et al* (9) did a similar study from a Danish birth registry to assess the birth weights of subsequently born children of mothers who had given birth to their first-born singleton from 1980 to 1998. It was found that brothers compared with sisters reduced the birth weight of later-born siblings. = Oligohydramnios was also found to be significantly associated with history of having a previous male child. (p=0.002). PROM was also seen more frequently in cases that had a preceding male child than in those who had a previous female child (P=0.004).

Pre-eclampsia was also significantly associated with history of having a previous male child (p=0.029).

Abruption was found to have very less significant association with sex of the preceding baby (p = 0.053). The finding is in contradiction with Nielsen HS *et al* (10), who did a study on recurrent abruptions and found 88% of the patients who developed abruption to have a previous male child. The contradictory results might be because of inadequate number of patients presenting with abruption. In the present study only 10 (0.74%) patients suffered from abruption, 8 out of whom had a previous male child.

Eclampsia was the least frequent complication. Number of patients having eclampsia was also too less to draw any statistical conclusion.The difference between occurrence of PPROM in women with previous male and previous female child was not found to be statistically significant (p = 0.34). The probable explanation for this is the existence of a different etio-pathological mechanism for PPROM which most likely is presence of a sub-clinical chorioamnionitis. Same was true for IUD (p=0.38) and PTL (p = 0.6).

Conclusion

The study suggests that frequency of certain obstetrical mishaps happening to pregnant women drastically lowers in those who have had a previous female child. Previous birth of a boy negatively affects the obstetrical future in females where there has been a supposed failure of immunological tolerance of pregnancy. The possible mechanism that can explain this is the development of anti H-Y immunity in women who are exposed to Y chromosome mediated antigens during pregnancy, which affects the second pregnancy irrespective of the sex of the fetus in subsequent one. Though there are many studies that have demonstrated the presence of anti H-Y immunity at a molecular level or the presence of cells and cellular components or debris of fetal origin in mother, studies showing the clinical effect and practical implication of the above mentioned phenomena are very few in number. Present study was done with the aim to add to the limited information available on clinical significance of anti H-Y immunity. Further research in this regard is warranted in order to have a better understanding of reproductive physiology and immunology and to discover newer immunology based treatments and interventions to improve maternal and fetal outcome.

References

1. Nielsen HS. Secondary recurrent miscarriage and H-Y immunity. *Hum Reprod Update* 2011; 17 (4): 558-74
2. Gammill HS, Nelson JL. Naturally acquired microchimerism. *Int J Dev Biol* 2010; 54:531-43
3. James E, Chai JG, Dewchand H, Macchiarulo E, Dazzi F, Simpson E. Multiparity induces priming to male-specific minor histocompatibility antigen, HY, in mice and humans. *Blood.* 2003; 102:388-93
4. Chen SJ, Liu YL, Sytwu HK. Immunologic Regulation in Pregnancy: From Mechanism to Therapeutic Strategy for Immunomodulation. *Clin Dev Immunol* 2012; 2012: 258391. doi: 10.1155/2012/258391
5. Christiansen OB, Steffensen R, Nielsen HS. Anti-HY Responses in Pregnancy Disorders. *Am J Reprod Immunol* 2011; 66: 93-100
6. Romero R, Espinoza J, Goncalves LF *et al*. The role of inflammation and infection in preterm birth. *Semin Reprod Med* 2007; 25:21-39
7. Van Der Hoorn MLP, Lashley EELO, Bianchi DW, Claas FHJ, Schonkeren CMC, Scherjon SA. Clinical and immunologic aspects of egg donation pregnancies: a systematic review. *Hum Reprod Update* 2010; 16 (6):704
8. Flowers ME, Pepe MS, Longton G, *et al*. Previous donor pregnancy as a risk factor for acute graft-versus-host disease in patients with aplastic anaemia treated by allogeneic marrow transplantation. *Br J Haematol* 1990;74(4):492-96
9. Nielsen HS, Mortensen L, Nygaard U, *et al*. Brothers and Reduction of the Birth Weight of Later-born Siblings. *Am J Epidemiol* 2008; 167 (4):480-84
10. Nielsen HS, Mogensen M, Steffensen R, *et al*. Indications of anti-HY immunity in recurrent placental abruption. *J Reprod Immunol* 2007; 75(1):63-69