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Feto–maternal haemorrhage in parturients: Incidence and its determinants

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Summary

This prospective study of parturients at a tertiary health institution in south-western Nigeria aims to identify the incidence, severity and obstetric factors predisposing to feto–maternal haemorrhage (FMH) in our population. The exclusion criteria were haemoglobinopathy and patient's refusal of consent to participate in the study. The prepared slide was processed as in the acid elution test described by Kleihauer–Betke. The FMH was calculated using Mollison formula (Mollison 1972). Baseline data included maternal biodata, blood group, RhD and haemoglobin electrophoresis, route/mode of delivery, duration of labour, obstetric interventions, fetal blood group and birth weight. Data generated were analysed with Statistical Package for Social Scientists (SPSS) version 11 software. Frequency tables, cross-tabulations and correlations were performed. Pearson's correlation was applied to continuous variables, while Spearman's correlation was utilised for discrete variables. Level of statistical significance was set at $p < 0.05$. A total of 163 parturients were studied, of which eight were multifetal gestations. There were no significant differences in maternal age, parity, estimated gestational age at delivery and birth weight, in both groups of parturients with and without FMH. A total of 17 parturients (10.43%), four of which were multifetal gestations (2.45%), had demonstrable FMH. Large FMH (>15 ml fetal cells) were noted in 10 (6.14%) parturients, of which, four were RhD-negative mothers. A total of 9.8% and 11.5% parturients in the vaginal and caesarean delivery groups, respectively, had significant FMH ($p = 0.736$). Incidence of large FMH was similar with each of the routes of delivery. Antepartum complications of pregnancy, delivery manoeuvres and episiotomy were not significant determinants of FMH. Multiple gestations, fetal birth weight and complications in labour were significantly associated with risk of FMH. Risk-based approach to management, in RhD negative pregnant women, might lead to under-treatment, with attendant increased incidence of isoimmunisation. At least in all RhD-negative women, the cord blood should be tested to determine the baby's blood group and if RhD-positive, Kleihauer–Betke test should be done to determine the degree of FMH and anti-D immunoglobulin dose administered appropriately. Further studies are necessary to establish the determinants/risk factors for FMH.

Keywords

Feto-maternal haemorrhage, transplacental haemorrhage, RhD factor, Kleihauer test

Introduction

Fetal–maternal haemorrhage (FMH) has been of considerable interest and importance to obstetricians for decades, this is because leakage of fetal cells into the maternal circulation is the mechanism through which Rhesus (Rh) sensitisation arises. In addition, studies have shown that when large volumes of fetal blood are lost in this way, then serious and potentially fatal fetal or neonatal outcomes can result (Laube and Schauberger 1982; Sebring and Polesky 1990).

The Rh blood group system is the most common of the antigens capable of causing maternal alloimmunisation and fetal haemolytic disease. In particular, the D antigen of the Rh blood group system (RhD) causes the most cases of severe haemolytic disease.

Fetal–maternal blood group incompatibilities, where the fetus possesses an antigen which the mother lacks, can lead to isoimmunisation of the mother. If no preventative measures are taken, some women will become isoimmunised antenatally, developing specific antibodies through exposure to fetal blood. After sensitisation, any subsequent pregnancy in which the fetus' red cells are incompatible with the mother's red cells can result in the propagation of maternal antibodies that can cross the placenta into fetal circulation, leading to the development of congenital haemolytic anaemia (haemolytic disease of the newborn, erythroblastosis fetalis).

Risk of sensitisation depends largely upon: volume of transplacental haemorrhage, extent of the maternal immune response and concurrent presence of ABO incompatibility.

To assess FMH, the maternal blood is examined for the presence of fetal haemoglobin (HbF). Normal non-pregnant adults can have a low percentage of circulating haemoglobin F cells, generally <0.1%. The commonly used clinical decision point for assessing FMH is 0.6%.

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Results are reported as positive or negative. Positive results will then report the percentage of fetal cells detected. FMH of over 30 ml of fetal blood (15 ml of fetal red cells) occurs in normal pregnancies with a frequency of about 1 in 300 (Giacoia 1997). Massive FMH (loss of >150 ml or approximately 50% of the fetal blood volume), is rarely suspected before fetal death (Cardwell 1987; Elliot 1991). Leakage of fetal red blood cells has been reported from the mid-first trimester onwards. It presumably results from a breach in the integrity of the placental circulation.

The acid elution test described in 1957 by Kleihauer et al. (1957) has been essential to the study of transplacental haemorrhage. Fetal haemoglobin is resistant to acid and, after acid elution treatment, fetal red blood cells (which are rich in haemoglobin F) stain darkly. Maternal red blood cells, which have only small amounts of haemoglobin F, stain lightly (Emery et al. 1995).

Comparison with other more expensive or high-tech methods (e.g. flow cytometry) have shown that the Kleihauer–Betke method is just as accurate (Bayliss et al. 1991; Lubenko et al. 1997; Pelikan et al. 2004). Background counting errors can result in estimates of as much as 5 ml fetal blood loss when there is none, but standard methods available in most laboratories should never result in a false positive for large FMH. It is of importance to identify HbF in maternal blood to confirm and quantify the presence of FMH. Elevated haemoglobin F (HbF) is found in some haemoglobinopathies, in ß-thalassaemias, and in hereditary persistence of fetal haemoglobin. Increased HbF may also be identified in megaloblastic anaemia, myelofibrosis, aplastic anaemia, leukaemia, erythroleukaemia, and others. These causes of false positive do not significantly alter expected result (Letsky and de Silva 1994).

While large volumes of studies of this condition abound in the literature. It is remarkable that there is great paucity of such research in low-resource countries like Nigeria. Whereas, we routinely administer Rh anti-D prophylaxis to our Rh-negative mothers, little effort is made to determine the incidence and severity of feto–maternal blood transfusion among parturients in our population. Through this study, we sought to determine the incidence and severity, and see if risk factors, associated with feto–maternal transfusion/haemorrhage with sufficient reliability in our population could be identified, to allow targeted rather than universal anti-D prophylaxis and make better use of resources in our population.

Method and clinical material

This was a prospective study of all parturients at the Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Osun state, Nigeria and was approved by the institution's ethical review committee. The exclusion criteria were maternal haemoglobinopathy and patient's refusal of consent to participate in the study.

According to the method of Kleihauer–Betke, 2 ml of maternal blood was obtained into EDTA bottle within 2 h of the postpartum period and same quantity of cord blood was similarly collected at delivery. The maternal whole blood sample was diluted 1:2 with normal saline. The diluted sample was mixed well and a standard blood smear was prepared. Each slide was spread evenly and examined under the microscope to ensure that the red cells were touching, but not overlapping each other. An acid bath was then used, which would remove all adult haemoglobin but not the fetal haemoglobin. Subsequent staining made fetal cells (containing fetal haemoglobin) rose pink while adult's cells were only seen as 'ghosts'. A minimum of 25 fields was examined using ×10 objective. Slides giving positive screening results were examined further to estimate the number of fetal cells present. A large number of cells (≥5,000) were counted under the microscope and a ratio of fetal to maternal cells generated. All slides were examined by a Scientist (MAM) and thereafter, independently re-examined by two of the Investigators (AAR and VOM) to confirm the results.

The FMH was calculated using Mollison formula (1972). This assumed that the maternal red cell volume is 1,800 ml, fetal cells are 22% larger than the maternal cells and only 92% of fetal cells stain darkly. The fetal bleed was calculated thus:

$$\text{Uncorrected volume of bleed} = 1,800 \times \text{fetal cells counted (F)}/\text{Adult cells counted (A)}$$

$$\text{Corrected for fetal volume } (1.22) = (1,800 \times \text{F/A}) \times 1.22 = \text{J}$$

$$\text{Corrected for staining efficiency } (1.09) = \text{J} \times 1.09 = \text{Fetal bleed}$$

On each day of our testing, blood from a newborn and blood from an adult male (without any haemoglobinopathy) were used and inspected on the same slide and served as positive and negative controls, respectively. The cord blood collected at birth was processed to determine the baby's blood group.

Baseline data included maternal biodata, blood group, RhD factor and haemoglobin electrophoresis, booking status, route/mode of delivery, duration of labour, obstetrics interventions, fetal blood group and birth weight. Data generated were analysed with the Statistical Package for Social Scientists (SPSS) version 11 software. Frequency tables, cross-tabulations and correlations were performed. Pearson's correlation was applied to continuous variables, while Spearman's correlation was utilised for discrete variables. Level of statistical significance was set at $p < 0.05$.

Results

A total of 163 parturients were studied, of which eight were multifetal gestations. There were no significant differences in maternal age, parity, estimated gestational age at delivery and birth weight, in both groups of parturients with and without FMH (Table I).

A total of 17 parturients (10.43%), four of which were multifetal gestations (2.45%), had demonstrable FMH. Large FMH (>15 ml fetal cells) were noted in 10 (6.14%) parturients, of which, 4 were Rhesus negative mothers (Table II).

Four of the eight parturients (50%) with multifetal gestations had demonstrable feto–maternal haemorrhage, in which half were large FMH, compared with the singleton group in which only 13/155 (8.39%) had any significant FMH ($p < 0.005$) (Table III).

A total of 102 parturients were delivered through the vaginal route (62.6%) and the rest (61) had caesarean delivery. Ten (9.80%) and seven (11.48%) parturients, respectively in these groups, had demonstrable FMH

Table I. Sociodemographic characteristics of study population

Factors	Negative FMH ($n=146$) (mean ± SD)	Positive FMH ($n=17$) (mean ± SD)	Significance	
			p value	F value
Maternal age (years)	28.79 ± 4.27	29.86 ± 1.99	0.19	1.79
Parity	1.73 ± 1.57	1.57 ± 1.34	0.69	0.16
EGA (weeks)	38.00 ± 2.96	37.5 ± 3.42	0.52	0.42
Birth weight (kg)	2.99 ± 0.63	2.70 ± 0.71	0.08	3.12

EGA, estimated gestational age; FMH, fetal–maternal haemorrhage.

Table II. Kleihauer count and maternal blood groups

Mothers blood groups	Negative FMH	Positive FMH (<15 ml fetal cells)	Positive FMH (>15 ml fetal cells)	Total
O+	76	3	5	84
O−	1	–	4	5
A+	30	2	–	32
A−	3	–	–	3
B+	28	2	1	31
B−	4	–	–	4
AB+	4	–	–	4
AB−	–	–	–	–
Total	146	7	10	163

FMH, fetal–maternal haemorrhage.

Table III. Fetal number vs feto–maternal haemorrhage (FMH)

Fetal number	Negative FMH	Positive FMH (<15 ml fetal red cells)	Positive FMH (>15 ml fetal red cells)	p value
Singleton	142	6	7	$p < 0.005$*
Multiple (Twins)	4	2	2	

*Significant.

($p=0.736$). Incidence of large FMH was similar with each of the routes of delivery (6/10 vs 4/6, respectively). Antepartum complications of pregnancy (threatened abortion, pregnancy induced hypertension, premature rupture of fetal membranes, antepartum haemorrhage and intrauterine growth restriction), delivery manoeuvres (assisted breech delivery and vacuum extraction) and episiotomy were explored as possible determinants of FMH and were not found significant (Table IV).

The fetal birth weight ($p=0.008$) and complications in labour (obstructed labour, retained placenta, perineal tear, cervical laceration and retained second twin) ($p < 0.005$) were significantly associated with risk of FMH (Table IV).

While both number of fetuses and complications of labour were positively correlated with FMH, only fetal birth weight was negatively correlated ($-0.194(r)$, $p=0.014$) (Table V). This implied increasing risk of FMH with decreasing fetal birth weight. When however, subjected to multivariable analysis, only the fetal number was significantly associated with FMH ($p < 0.005$, 95% CI 0.194–0.650). The association with fetal birth weight and complications in labour ($p=0.139$, 95% CI −0.123–0.017 and $p=0.691$, 95% CI −0.015–0.030, respectively) were not significant.

Table IV. Determinants of feto–maternal transfusion in group with FMH vs group without FMH

Variables	Values	Significance
Antepartum complications	6.916	0.646*
Route of delivery	0.424	0.736*
Delivery manoeuvres	0.974	0.324*
Episiotomy	0.326	0.568*
Number of fetuses	15.686	<0.005†
Fetal birth weight	17.240	0.008†
Labour complications	52.552	<0.005†

FMH, fetal–maternal haemorrhage; *Not significant; †significant.

Table V. Correlation of significant variables in group with FMH vs group without FMH with the incidence of feto–maternal transfusion

Variables	Correlation	Significance
Number of fetuses	0.277*	0.000‡
Fetal birth weight	−0.194*	0.014‡
Labour complications	0.178†	0.017‡

FMH, fetal–maternal haemorrhage. *Pearson's correlation; †Spearman correlation; ‡Significant.

Discussion

The incidence of significant FMH in this study is 10.43%, while large FMH was 6.14%. These are higher values than traditionally quoted figures of 0.23–1% in the literature (Bowman 1985; Stedman et al. 1986; Ness et al. 1987), but conform to the reports of Devi et al. (1968) and Salim et al. (2005).

Many reports exist regarding the determinants of significant FMH. However, their individual conclusions are contradictory. Cohen et al. 1964, Li et al. (1988) and more recently, Salim et al. (2005) were unable to confirm mode of delivery as a risk factor for FMH. However, this conclusion was at variant with that of Ness et al. (1987) who reported that caesarean delivery was a risk factor for FMH.

From our results, vaginal and caesarean delivery routes were not different in the incidence of FMH. Though slightly higher with caesarean delivery (6.56% vs 5.88%), the incidence of large FMH was not significantly different in the two routes of delivery ($p=0.736$). Salim et al. (2005) had similarly concluded, but reported higher incidence of large FMH among women who delivered vaginally, contrary to the finding in our study. In our study, instrumental vaginal (forceps and vacuum) and assisted vaginal breech (10 and 2 entries, respectively) deliveries were categorised broadly as vaginal deliveries. This was however unlikely to impact much on our conclusion, as only one case of <15 ml fetal cells fetomaternal

haemorrhage, which occurred in an assisted breech delivery, was involved.

Antepartum complications, delivery manoeuvres and episiotomy in labour were also explored as possible determinants of FMH and found not to be significant.

Number of fetuses, labour complications and fetal birth weight were significantly associated with risk of FMH. While number of fetuses and labour complications were positively correlated with this condition, it was surprising that fetal birth weight was observed to correlate negatively. However, the explanation might derive from the result of our multivariate analysis which confirmed only number of fetuses as the strong determinant of FMH. Since pre-term deliveries are known complications of multiple gestations and are associated with low birth weights, it is possible that this influenced the finding of negative fetal birth weight correlation with FMH in our study.

Therefore, it is reasonable to suggest that multiple gestation is a very strong risk factor for FMH. However, we are mindful of conflicting reports in the literature on whether this is the situation or not. Devi et al. (1968), among others, had reported twin delivery as a risk factor, but this was recently disputed by Salim et al. (2005) who concluded that the rate of large FMH is not greater than that of singleton deliveries and went further to state that no significant association were found with other risk factors such as abdominal trauma, placental abruption, operative vaginal deliveries and retained placenta in the vaginal delivery group. These were however, contradictory to our findings in this study.

From conflicts in various reports on FMH, it is likely that a risk-based approach to management, if findings are extrapolated to RhD-negative pregnant women, might lead to under-treatment, with its attendant increased in incidence of isoimmunisation in those missed. We therefore, conclude that on the basis of this study, targeting only certain D-negative women in Nigeria for anti-D prophylaxis is not justified. Therefore, in all RhD-negative women, the cord blood should be tested to determine the baby's blood group and if found to be RhD-positive, the Kleihauer–Betke test should be done to determine the degree of FMH and anti-D immunoglobulin dose administered appropriately. We consequently recommend further studies, preferably multicentred and multi-racial to establish the determinants/risk factors for FMH.

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