

Assessment Of Feto Maternal Hemorrhage In Antenatal Period In Indian Females – Need Of Modifications In Anti D Prophylaxis In India.

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Abstracts: *Objective:* -To assess Feto maternal Hemorrhage in pregnant Indian Females. *Method:* - 516 consecutive antenatal patients attending the Fetal Medicine Department of Vadilal Sarabhai General hospital under NHL Municipal Medical College, Ellis Bridge, Ahmadabad were analyzed for Feto maternal Hemorrhage by Kleihauer Betke test after taking informed consent. *Result:* - All the 516 antenatal patients including those who underwent invasive procedures like Chorionic villus sampling, Amniocentesis, Amnioinfusion and Intrauterine blood transfusion had Feto maternal Hemorrhage less than 2 ml. *Conclusion:* - Study shows that Feto maternal hemorrhage in Indian women is very insignificant even after invasive procedures. Feto maternal Hemorrhage has special importance in Rh Negative Women, carrying an Rh positive fetus. FMH can lead to isoimmunization leading to a wide spectrum of antenatal and postnatal fetal complications ranging from anemia to stillbirth. Answer to this is Antenatal Anti –D prophylaxis which is not a standard practice in our setup due to high cost of Anti D. As we have found FMH to be less than 2 ml even a dose of 50 microgram can suffice if given at 26 and 32 weeks of gestation to prevent isoimmunization thus reducing the cost and encouraging the practice of Antenatal Anti D prophylaxis. [Vaisnav G et al NJIRM 2012; 3(3) : 111-115]

Key words: Andhra Pradesh , Bacteriological Profile , Antibiotic Resistance , Septicaemia , Blood culture.

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Introduction: Feto maternal hemorrhage refers to the entry of fetal blood in to maternal circulation before and during delivery. Antenatal Feto maternal hemorrhage is a pathological condition with wide spectrum of clinical variation. Tran’s placental transfer of fetal erythrocytes in to maternal circulation occurs in most pregnancies with some studies indicating that loss of less than 1 ml of blood occurs in 96 % of all deliveries.

FMH of approximately 30 ml occur in 0.3 % of all pregnancies and often occurs without significant signs and symptoms in either mother or fetus.^{1,4}

Study shows that 3 % pregnant women have FMH in the first trimester, 12 % in the second, and 45 % in the third trimester. Feto maternal hemorrhage may get precipitated by trauma, amniocentesis ,fetal blood sampling, chorionic villus sampling, miscarriage, external cephalic version ,rapid reduction in uterine size , (e.g. following birth of first twin , chorio carcinoma , spontaneous placental abruption of unknown cause) .During intra partum period ventouse ,forceps delivery ,cesarean section, manual

removal of placenta are known to increase the risk of FMH.

FMH has special importance in Rh negative mothers, carrying Rh positive fetus. Isoimmunization can occur from incompatible blood transfusion or Feto maternal hemorrhage.

FMH has considerable importance in Rh-negative females who deliver Rh-positive babies, against whom the mother may form antibodies which pass across the placenta to the fetus. These antibodies destroy the red blood cells inside the fetus. This causes anemia, jaundice, hepatosplenomegaly, fetal hemolytic anemia, hydrops fetalis and severe cases can lead to, brain damage, still birth and death. & ultimately increase the Neonatal Mortality rate, increase in cost of treatment to patients & nation, & increase work load of Pediatricians, compare to the cost of Anti D prophylaxis in ante natal period.

To prevent Hemolytic disease of the newborn, the Rh negative mothers are given an injection of Rho (d) immunoglobulin in a quantity which

destroys all the Rh positive cells that were passed from baby to mother during childbirth. This prevents mother from making anti Rh antibodies that can cause HDN in future pregnancies.

That is why estimation of FMH is important because FMH volume estimation enables calculation of the adequate doses of Rh immunoglobulin in sensitized mother. A number of techniques to detect and quantify FMH with varying degree of sensitivity have been described in the literature. These techniques are based on either detecting cells containing fetal Hb or detecting the presence of Rh D antigen¹

Method:-

The center for study is Fetal Medicine department and Obstetrics and Gynecology department of Sheth Vadilal Sarabhai General Hospital and Sheth Chinai Maternity Home, Ellis Bridge, Ahmadabad, Gujarat.

516 consecutive patients which included Antenatal patients with gestation from 20 to 40 weeks of pregnancy and patients who underwent any invasive procedure like Chorionic villus sampling, Amniocentesis, Amnioinfusion, cordocentesis, Intrauterine transfusion from March 2010 to July 2010 were assessed for the FMH by Kleihauer-Betke acid elution test (KB test) after taking informed consent.

The KB test is the standard method of detecting Feto maternal hemorrhage (FMH). K-B test has been chosen for assessment of FMH as it is cheap, easily available and can be easily done in developing country like ours where most of the patients are poor. Though Flow cytometry is a gold standard to assess FMH but it is very expensive.

In patients with Feto maternal hemorrhage more than 4 ml were, Hb electrophoresis was done to rule out Thalassemia as high fetal

hemoglobin level in Thalassemic patients give false positive test.

Kleihauer Betke technique is based on the fact that acid solution elutes adult but not the fetal Hb from the red cells. This test can detect as small as 0.2 ml of fetal blood diluted in 5 liter of maternal blood. KBT detects fetal Hb in the maternal blood appears to be precise only in small volumes of Trans placental hemorrhage. It gives quantitative results.

The other tests available to assess the volume of Feto maternal hemorrhage¹ are:

- The Flow cytometry
- The Rosette test
- The Gel technology

To date Kleihauer Betke technique {KBT} has stood the test of time and used widely¹. Slide showing dark pink fetal cells surrounded by adult ghost cells.

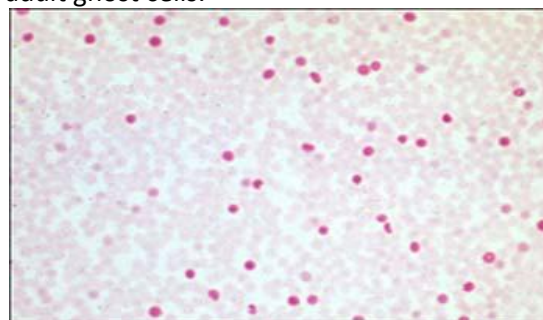


Table 1. Distribution of Antenatal patients according to gestational age

Gestational age	No. of patients	Amount of Feto maternal hemorrhage	
		<2 ml	>4ml
Less than 20 weeks	11	10	0
20-24 weeks	121	121	0
25-28 weeks	97	95	0
29- 32 weeks	109	108	0
33- 36 weeks	130	122	0
37 – 40 weeks	37	37	0

Result:-

We analyzed 516 antenatal patients irrespective of their blood group for Feto maternal hemorrhage by Kleihauer Betke test. None of the patient had FMH more than 4 ml⁵⁻⁹.

Table No. 2 Distribution of patients according to condition predisposing to Feto maternal hemorrhage.

Conditions predisposing to FMH	No. of patients	Amount of Feto maternal hemorrhage	
		<2 ml	> 4 ml
Chorionic villus sampling	2	2	0
Amnioinfusion	2	2	0
Trauma	1	1	0
Intrauterine transfusion	1	1	0
Multiple pregnancy	17	17	0
Ante partum hemorrhage	27	27	0
Cordocentesis	2	2	0
Intrauterine death	9	9	0

There was no difference in Feto maternal hemorrhage in patients with factors supposed to predispose to Feto maternal hemorrhage as compared to patients having no risk factor.

This supports the conclusion that a policy of administering a dose of 300 micrograms of Anti – D to all the patients is not advisable.

So blindly giving a dose of 300 micrograms of Anti D immunoglobulin is wastage of resources as well as decreasing the affordability by the patients who really need it.

Since, decades we are blindly following regimen of giving 300 micrograms Anti D Immunoglobulin postpartum .Antenatal prophylaxis is almost not existent or not practised in our set. So it is important to assess exact amount of Feto maternal

hemorrhage to decide the dose of Anti D antibodies to be administered to the patient to give her optimum protection from isoimmunization at a reasonable cost.

In India almost 4 to 5 % women are Rh negative. Knowledge and importance of Rh immunoprophylaxis, Rh Allo-immunization and hemolytic disease of newborn are lacking, some time neglected and often overlooked possibly due to economic reasons.

K S Joseph from CMC Vellore tried to estimate the extent of the problem. The anti D immunoglobulin requirement for the year 2000 was expected to be 8.03 lacs doses postpartum and 4.43 lacs doses after abortions with total of 12.46 lacs doses. In fact only 1.15 lacs units were sold in to the market, only 9.22 % of required estimate [market research report. Rh immuno globulin market data April 2005].

However, in India a lot still needs to be done .There is gross underutilization of the anti-D prophylaxis in India. Deka D et.al observed that failure to administer post natal anti-D prophylaxis was responsible for the Rh D alloimmunisation in more than 50 % of cases, followed by failure to administer anti D after MTP in 10%.³

The reason behind under utilization is the cost of Anti D, which is 150 micrograms for Rupees @ 1600 approximately and 300 micrograms for 2600. If we can tailor the dose by assessing the exact amount of Feto maternal hemorrhage by Kleihauer Betke Test, we can reduce the cost of Anti D Immunoglobulin for the patient.

It will have a dual benefit of giving Anti D to the patients who can not afford Anti D due to its higher cost. As well as it will also segregate the patients who need more than routine dose of Anti D that is 300 micrograms.

As in our study all the antenatal patients have Feto maternal hemorrhage less than 2 ml .As

we all know around 20 micrograms of Anti D neutralizes around 2 ml of fetal red blood cells. So, we can give a minimum dose of 30 microgram to patients undergoing invasive procedures in first trimester of pregnancy as 30 micrograms would remove from maternal circulation the entire Feto placental blood volume (3 ml) of a 12 weeks pregnancy, 50 micrograms of Anti D to our antenatal patients after first trimester.

Though a study done in U.K by Lee et al in 1995 showed that 50 microgram dose of Anti D immunoglobulin failed to show the desired results. But we should keep in mind that this study was not done in Indian females. Till date there is no large study done to prove that Indian females need same dose as females of white races. But we have data that despite the underutilization of the Anti – D immune globulin , the reported incidence of alloimmunisation in India is low (1.9%) as compared to that in U.S.A (6.8%), the possible reasons for this difference could be attributed to many factors like :

- Varying rate if occurrence of various red cell antigens.
- Their variable antigenicity.
- Insufficient transfer of antigen or antibody.
- Variability of the maternal immune response to the antigen.

Protection from isoimmunization by ABO incompatibility of the fetus and mother.

This confers some protection against D – isoimmunization because of fetal red cells entering the mother usually are rapidly destroyed before they can elicit an immune response viz there is only a 2% chance of D-isoimmunization in all women by 6 months postpartum^[13].

Genetic differences may also play its role in decreased rate of alloimmunisation in Indian population as compared to other races.

So it is possible that we can modify are existing protocols for Anti D administration so that smaller more appropriate doses are given , better utilizing the limited supply of Anti D.

It will encourage the practice of Antenatal prophylaxis in our setup decreasing the incidence of alloimmunisation due to ‘Silent FMH’.

It will decrease the incidence of hemolytic disease of newborn because of Rh-Iso immunization and also bring cost effectiveness in therapy..Last but not least it will reduce the misuse of “less resourceful” drug Anti d immunoglobulin especially polyclonal antibody.

Conclusion:

We can conclude that Kleihauer Betke test should be made mandatory to assess Feto maternal hemorrhage in Rh negative females before subjecting them to Anti D. Though KB test has less accuracy compared to Flow cytometry as proved by various studies but it is more practical and affordable than flow cytometry.

Existing protocol of Anti D administration in India needs modifications and should be revised by carrying out clinical trials .We have evaluated only KB test although this needs to be confirmed by flow cytometry

We can consider starting with 50 microgram of Anti–D to be used during antenatal period at 26 and 32 weeks of gestation to make antenatal Anti D prophylaxis a common practice like our western counterparts.

References:-

1. The estimation of Feto maternal hemorrhage. Anti – D administration in pregnancy for preventing Rhesus Allo immunization (Review); the Cochrane Collaboration.
2. Feto maternal hemorrhage during Antenatal Study – Indian study The incidence of Large Feto maternal Hemorrhage and KBT; Raed Salim, MD. Izhar Ben Shlomo MD.
3. Feto maternal hemorrhage: Treatment by Intrauterine Transfusion; Michael Permezal, MD, Lachlan DE Crespigny MD, Peter England MBBS.

4. Assessment of FMH by Flow Cytometry and KBT in RH negative Pregnancies (Gynecol Obste. Invest 2008 ; 65 : 84- 88)
5. The Kleihauer Test; Section B: Clinical guideline King Edward Memorial Hospital Perth, Western Australia. Prenatal Rh – immunoprophylaxis with 300 micrograms immunoglobulin Anti d in the 28th week of Pregnancy; Acta Obste. Gynecol Scand .1989; 68 (1) : 45-7
6. Feto maternal transfusion after chorionic villus sampling: clinical implications. Human Reproduction. Vol 1. No. 1 pp 37-40; 1986
7. Gel technology: An easy and useful method for estimating Feto maternal hemorrhage in the Blood Banks of Developing Nations. Laboratory Medicine 2010 ; 41 (3) : 147 -149
8. Routine antenatal anti D prophylaxis for women who are Rhesus negative. Review of NICE, technology appraisal guidance 41 . Issue date August 2008.
9. Recommendations for the use of Anti D immunoglobulin for Rh prophylaxis. Transfusion Medicine. 1999; 9: 93-7.
10. Pregnancy in the Rh negative Woman. Author Rehana kausar Vol 1,no.4 (2005-01 – 2005-02)
11. Antenatal prophylaxis of RH Immunization with 250 mcg anti D immunoglobulin. Acta Obste Gynec Scandinavia , Vol 63 :1984 :115
12. Rhesus gam im (solution for intramuscular Injection) Commercial Anti D reagents in Indian market & detection of partial D variants. Indian J Med Res 125, May 2007, pp615-617
13. Feto maternal Hemorrhage. Obste. Gynecol 2010 May; 115 (5) : 1039-51
14. Blood group Systems Prevention of Rh D alloimmunisation in Rh D negative women. Czech republic .2010 Mar ; 154 (1) 3-7
15. Rhoclone (Anti – rho (D) immunoglobulin (monoclonal) 300mcg /150mcg, Feto maternal Hemorrhage detection .Authors Jenny Bryant, ARCBS, Sydney, Peter Hobson, Sullivan Nicolaidis Pathology, Margaret Nelson, Hematology Dept. Royal Prince Alfred Hospital, Sydney.
16. Anti D administration in early pregnancy – A time for a new protocol. Aust. N Z J Obste. Gynecol. 1996 May; 36 (2): 227-8.
17. Measurement of FMH: A comparative study of three Kleihauer techniques and two Flow cytometry methods. National blood `service, Mersey and North Wales, Liverpool, UK.
18. Detection of fetal red cells in Feto maternal hemorrhage using a fetal hemoglobin monoclonal antibody by flow cytometry.