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Role Of Middle Cerebral Artery Doppler In Evaluation Of Fetal Anemia In Rh Isoimmunisation

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Abstract:
Introduction: *Maternal Rhesus isoimmunization occurs when a pregnant woman develops an immunological response to a paternally derived red blood cell antigen (D) foreign to the mother and inherited by the fetus. in subsequent pregnancies these antibodies may cross the placenta, bind to antigens present on the erythrocytes of the foetus, and cause hemolysis which in turns leads to foetal anaemia.*
Material and methods: *77 pregnant mothers with a history of previous Rh isoimmunization attending the USG department were examined. The last MCA PSV measurement was made within 7 days before the termination of pregnancy, and umbilical cord haemoglobin was measured at the termination. MCA, PSV, and haemoglobin were expressed as multiples of the median (MoM). As in India, we don't yet have a reference range for foetal haemoglobin concentration, and for MCA PSV, we adopted the reference ranges suggested by Mari.*
Results: *We found a good correlation between MoM MCA PSV and MoM hemoglobin. Using the threshold values of 1.50 MoM for MCA PSV to diagnose any degree of anaemia (haemoglobin ≤ 0.84 MoM), t the sensitivity and the specificity values were 66.6% and 98.3%, while using the threshold values of ≥1.29 MoM for MCA PSV in the diagnosis of any degree of anaemia, the sensitivity and the specificity values were 94.4% and 88.1%.*
Conclusions: *Based on this, using a threshold of 1.29 for MCA PSV MoM provides much better sensitivity (94.4%, compared to 66.6% for the threshold of >1.5 MoM) and also good specificity (88.1%) in predicting any degree of foetal nemia. Anti-D antibody prophylaxis, especially post-partum prophylaxis, reduces the risk of developing foetal anaemia significantly.*

Keywords: *MCA Doppler, MoM, Fetal anemia, Rh incompatibility*

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I. Introduction

Maternal Rhesus isoimmunization occurs when a pregnant woman develops an immunological response to a paternally derived red blood cell antigen (D) foreign to the mother and inherited by the fetus. These initial anti-D antibodies are of the IgM type, which can't cross the placenta; subsequently, there is the production of IgG antibodies, which cross the placenta. There is usually no complication in the first pregnancy. But in subsequent pregnancies these antibodies may cross the placenta, bind to antigens present on the erythrocytes of the foetus, and cause hemolysis. Hemolysis leads to foetal anaemia, which can cause oedema, hydrops foetalis, and even foetal demise in severe cases. The Rh blood group system includes the C, c, D, E, e, and G antigens; the d antigen is absent. Other antigens of the nonrhesus blood group system, such as Kell, MNS, and others, may also induce hemolytic disease in the foetus or ewborn [1], but these cases are rare. Therefore, the term red cell or Rhesus alloimmunization is more commonly used.

The aim of maternal Rhesus alloimmunization management is to detect anaemic foetuses in utero and treat them with intrauterine transfusions or to terminate the pregnancy by caesarean section or induction of

labour. In earlier days, amniocentesis was used to diagnose foetal anaemia indirectly by assessing the amniotic fluid optical density deviation at 450 nm. But this method showed a lack of accuracy before 27 weeks of gestation [3] and provided poor information regarding the severity of anemia [4]. The only accurate way to measure haemoglobin concentration directly is through cordocentesis. But this is an invasive process linked to complications like infection, bleeding from the puncture site, temporary bradycardia, and feto-maternal haemorrhage [5].

To devise a non-invasive test for the evaluation of fetal anemia h has been the aim of many researchers in the last few cades. Vyas et al. [6] were the first to propose the examination of the blood velocity (mean) in the middle cerebral artery (MCA) of anaemic etuses. Then, Mari et al. (2) proposed that the noninvasive prediction of foetal anaemia in foetuses at risk due to maternal red-cell alloimmunization could be greatly enhanced by measuring the peak systolic velocity (PSV) in the foetal MCA. The foetal MCA PSV correlates well with hematocrit and haemoglobin concentration and is also useful for predicting the severity of foetal anaemia. This method is based on the theory that anaemic foetuses have hyperdynamic circulation, or increased blood flow velocity. V b v The advantage of using the MCA over other vessels is that it improves reproducibility by enabling velocity measurements without the need for an angle adjustment because its angle of insonation is almost 0° in the axial plane.

The aims of this study are to evaluate the reliability of MCA PSV in the diagnosis of foetal anaemia in pregnancies complicated by Rh iso-immunisation, to determine the threshold value of MoM MCA PSV for predicting any degree of anaemia, and to evaluate the outcome and role of other related factors like mode and time termination and an anti-D antibody prophylaxis in Rh iso-immunisation.

II. Material And Methods

This is an institution-based prospective observational study. The study was carried out at the Department of Radiodiagnosis, Medical College Kolkata, between August 2022 and July 2023. 77 pregnant mothers with a history of previous Rh isoimmunization attending the USG department were examined to assess appropriate growth for gestational age and amniotic fluid volume, to perform MCA doppler, and to diagnose foetal hydrops.

Study Design: Prospective observational study

Study Location: This was a tertiary care teaching hospital based study done in Department of Radiodiagnosis, Medical College Kolkata, West Bengal, India.

Study Duration: February 2023 to January 2024.

Sample size: 77 patients.

Ethical clearance: This study has the approval of the institutional ethics committee (IEC) of Medical College, Kolkata.

Inclusion criteria:

1. Second trimester and onwards pregnant females of >18 years age with a history of previous Rh isoimmunization ntervals.

Exclusion criteria:

1. Patients with anaemia (Hb<11gm%).
2. Patient with age <18 years.
3. Patients with first trimester pregnancy.
4. Patient with non-immune hydrops.
5. Patients with any severe systemic disease
6. Patient with history of third-trimester TORCH infection.
7. Patients who did not give written consent were excluded from the study.

Procedure methodology

After taking written informed consent 77 pregnant mothers with a history of previous Rh isoimmunization attending the USG department were examined to assess appropriate growth for gestational age and amniotic fluid volume, to perform MCA doppler, and to diagnose foetal hydrops.

A transverse section of the foetal head was obtained by ultrasonography (2–5 MHz curvilinear probe, GE LOGIQ P9), and a colour doppler was used to identify the circle of Willis and the MCA(Figure I). The

MCA was isolated close to its origin from the internal carotid artery. The angle between the ultrasound beam and the blood flow was kept as close as possible to 0°. At least three consecutive waveforms with the patient in a semirecumbent position in the absence of foetal body or breathing movements were recorded, and the highest point of the Doppler waveform was considered the PSV (cm/s)(Figure II).

In order to adjust for the effect of gestational age on the measurements, we expressed the MCA PSV and the haemoglobin values in multiples of the median (MoM). This was calculated by dividing the measured value (haemoglobin, or MCA PSV) by the expected value for gestational age. As in India, we don't yet have a reference range for foetal haemoglobin concentration, and for MCA PSV, we adopted the reference ranges suggested by Mari [7]. MoM values were obtained using a calculator from Perinatology.com.

Foetal anaemia was defined by Mari [7] as a haemoglobin value of ≤0.84 MoM (≤5th percentile), moderate anaemia as a haemoglobin value between 0.65 and 0.55 MoM, and severe anaemia as a haemoglobin concentration of <0.55 MoM.

After termination of pregnancy, cord blood was examined for hemoglobin, Direct Coombs Test, total bilirubin/direct bilirubin, and blood group. MCA PSV MoM was measured within 7 days before termination of pregnancy, and MoM for haemoglobin was measured from the umbilical cord at birth.

Statistical analysis

Datas were compiled in MS excel worksheet and analysis done in SSPS VERSION 17 statistical software (for windows). Results were statistically analyzed using Chi-square test. P value of <0.05 was considered to be significant and P <0.001 as highly significant.The results were calculated within 95% confidence limits.

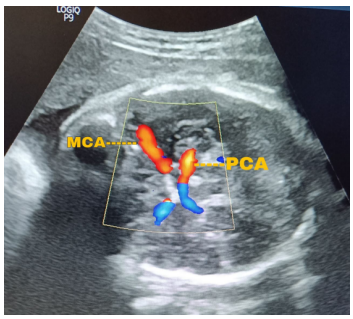


Fig. I: Colour doppler showing bilateralMCA & PCA

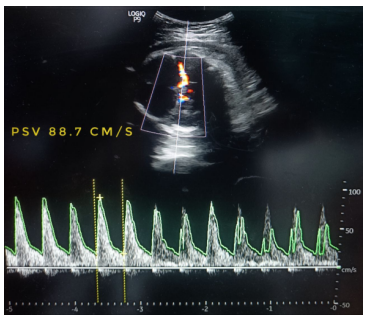


Fig. II: Normal MCA doppler at 36 weeks 4 days(MoM 1.1)

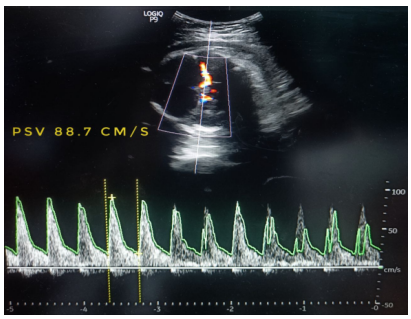


Fig. III: MCA doppler at 35 weeks 1 day (MoM 1.72)

III. Result

We examined 77 pregnant mothers with a history of Rh isoimmunization. 53 foetuses had the last values of MoM MCA PSV before birth below 1.29 MoM, 11 foetuses between 1.29 and 1.50 MoM, and 13 foetuses above 1.50 MoM(Table 1, Figure V). Of 53 foetuses with MCA PSV below 1.29 MoM, only 1 foetus of [illegible] one developed hydrops and died in utero at 26 weeks and 3 days(Figure IIIa-c).

27 patients received only postpartum anti-D antibody prophylaxis in their previous pregnancy; of them, only 2 developed anemia. 15 patients received only antenatal prophylaxis at 28–32 weeks of their current pregnancy; of them, 7 developed anemia. 23 patients received both prophylaxis; of them, only 1 developed anemia. 12 patients received no prophylaxis; of them, only 8 developed anemia(Table 3, Figure VII). All except 3 foetuses were delivered within 36–38 weeks of POG. Two fetuses were delivered between 34 and 36 weeks of POG due to the high risk of nemia. One of them developed severe anaemia (MoM 1.72, Figure IV), another developed moderate anaemia (MoM 1.57), and one was delivered at 26 weeks and 3 days due to IUFD, caused by hydrops.

Out of 18 foetuses with anaemia, one died in utero at 26 weeks and 3 days due to hydrops. Out of the rest, 11 foetuses developed jaundice (cord blood total bilirubin ≥7 mg/dl and total serum bilirubin at 24 hours >95 centile) (Figure IX). Out of them, 3 required phototherapy and exchange transfusions, 6 required only phototherapy, and 2 did not require active treatment except monitoring and follow-up(Figure X).

Using the threshold values of 1.50 MoM for MCA PSV to diagnose any degree of anaemia (haemoglobin ≤ 84 MoM), t the sensitivity and specificity values were 66.6% and .3%, respectively. Using the threshold values of ≥1.29 MoM for MCA PSV in the diagnosis of any degree of anaemia (haemoglobin ≤ 84 MoM), t the sensitivity and specificity values were 94.4% and 88.1%, respectively(Table 4, Figure VIII).

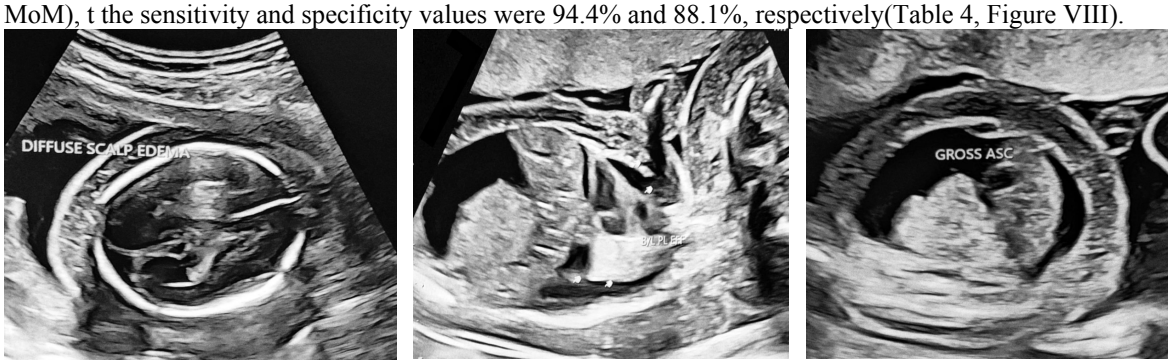


Fig. IV(a-c): Generalized subcutaneous edema with gross ascites and bilateral pleural effusion ---- suggestive of hydrops fetalis

Table 1 : Distributions of fetuses according to MCA PSV MoM (N=77).

MCA PSV MoM Value	No. OF fetus
MoM <1.29	53
MoM1.29-1.49	11
MoM ≥1.50	13

Fig. V: Pie diagram showing distributions of fetuses according to MCA PSV MoM value.

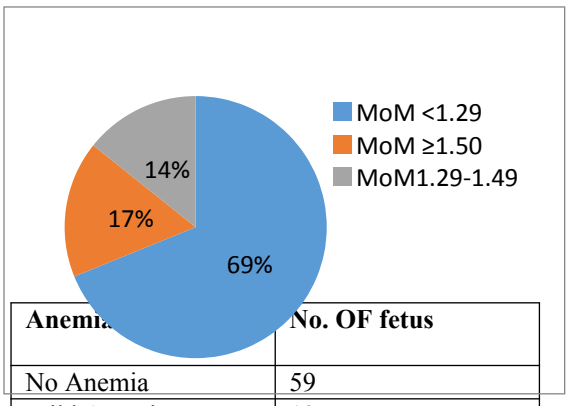


Table 2 : Distributions of fetuses according to anemia(N=77)

Anemia	No. OF fetus
No Anemia	59
Mild Anemia	13
Moderate Anemia	3
Severe Anemia	2

Fig. VI: Pie diagram showing distributions of fetuses according to anemia

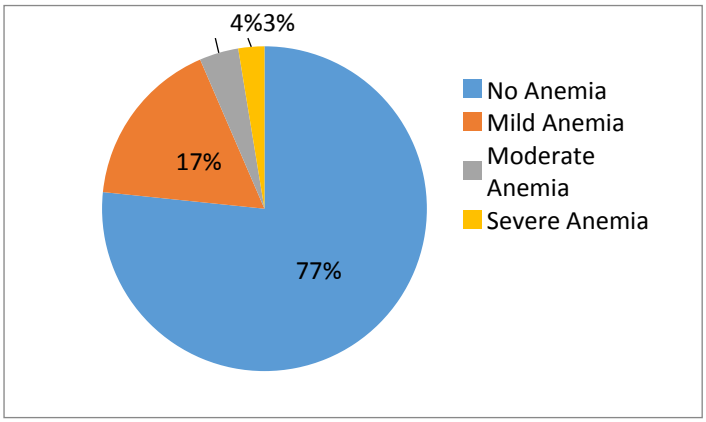
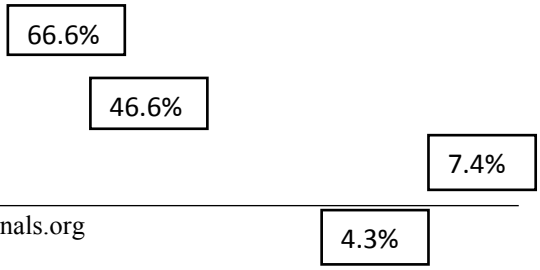


Table 3 : Development of fetal anemia according to maternal Anti-D Antibody prophylaxis(N=77)

Maternal Anti-D Antibody prophylaxis	**No. of mothers received prophylaxis**	**No. OF fetus devloped anemia**	**Percentage(%)**
No Prophylaxis	12	8	66.6%
Antenatal Prophylaxis	15	7	46.6%
Postpartum Prophylaxis	27	2	7.4%
Both Prophylaxis	23	1	4.3%

Fig. VII: Bar diagram showing development of fetal anemia according to maternal Anti-D Antibody prophylaxis.



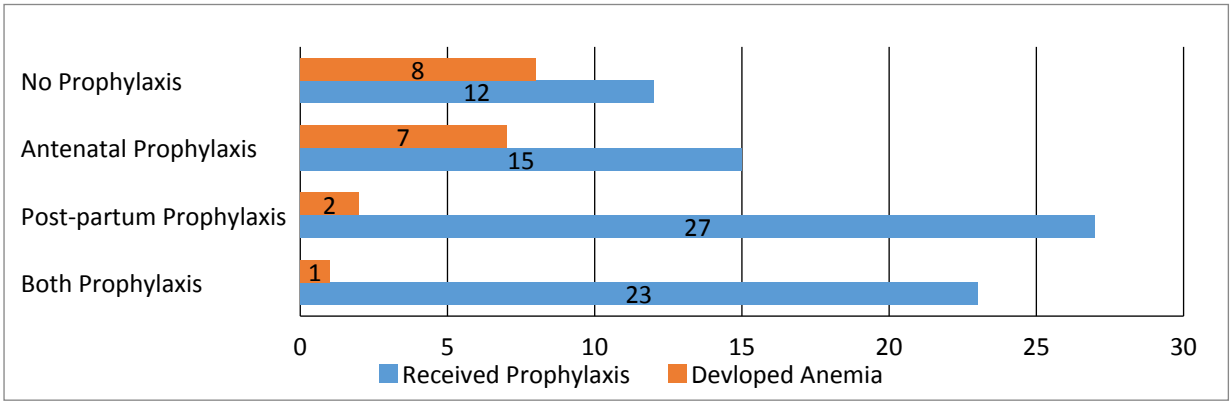


Table 4: Statistical parameters for threshold value of MCA PSV MoM ≥1.50 & ≥1.29

Parameter	**Values for MoM ≥1.50**	**Values for MoM ≥1.29**
Sensitivity	66.6%	94.4%
Specificity	98.3%	88.1%
Positive Predictive Value(PPV)	92.3%	70.8%
Negative Predictive Value(NPV)	90.6%	98.1%
False Positive (FP) Rate	7.6%	29.1%
False Negative (FN) Rate	9.3%	1.8%
P Value	<0.001	<0.001

Fig. VIII: Comparison of statistical parameters for threshold value of MCA PSV MoM ≥1.50 & ≥1.29

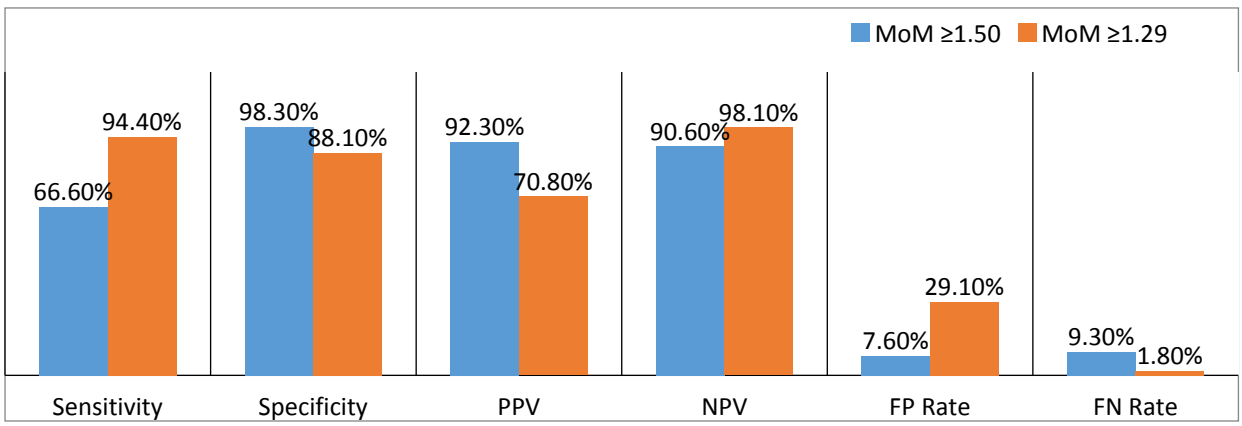
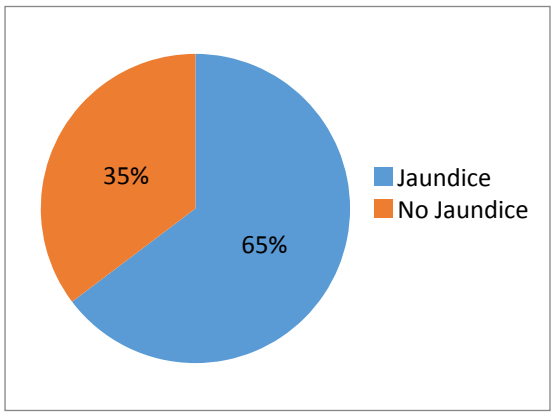
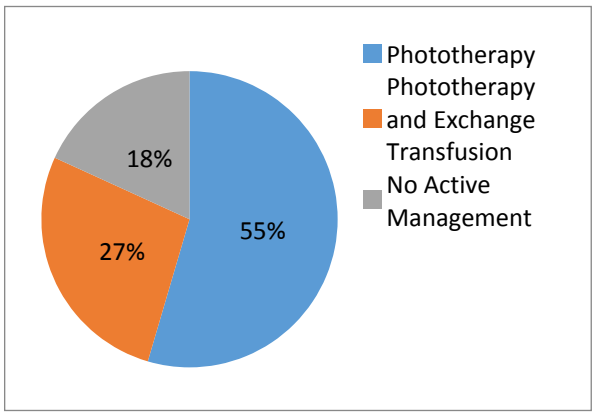


Fig. IX: Distributions of fetuses with anemia according to development of jaundice.

Fig. X: Distributions of fetuses with jaundice according to management given.





IV. Discussion

The goal of our study was to evaluate the reliability of MCA doppler and To determine the threshold value of MoM in the diagnosis of foetal anaemia in pregnancies complicated by Rh iso-immunisation We demonstrated the reliability of this non-invasive sonographic method in a sample of alloimmunized foetuses for early detection of foetal anaemia. The most probable explanation for the observed increase in MCA PSV is that foetal anaemia is associated with decreased blood viscosity, leading to increased venous return and preload with a consequent increase in cardiac output. The faster the velocity, the higher the risk of foetal nemia. A threshold of 1.29 MoM for MCA PSV in detecting any degree of anaemia provided good sensitivity (94.4%) and specificity (88.1%). These results are similar to those found by Teixeira et al. [8] and Cristian et al. [9]. All cases of mild, moderate, and severe anaemia, except one case of mild anaemia, could be diagnosed by this method. While cordocentesis can precisely determine the foetal haemoglobin status, it is an invasive procedure that carries risks, such as increasing maternal alloimmunization and intrauterine foetal death. Though amniocentesis is less invasive than cordocentesis but only useful in situations of foetal anaemia caused by maternal immunity, the validity of repeated measurements of the optical density of the amniotic fluid at 450 nm before 27 weeks of gestation is in doubt. In addition to the present tactics of assessing maternal history, antibody levels, and bilirubin levels in amniotic fluid, the ability to predict foetal haemoglobin levels by Doppler sonography provides a non-invasive, dependable, and repeatable tool in the treatment of alloimmunized foetuses with a focus on optimising the frequency of recurrent blood sampling.

Anti-D prophylaxis has an important role in the prevention of hemolytic disease in newborns. Giving anti-D immunoglobulin to Rh-negative mothers can prevent their bodies from developing anti-D antibodies, which are responsible for hemolysis and the development of foetal nemia. There are both antenatal (at 28–32 weeks of POG) and postpartum (within 72 hours of termination of pregnancy) prophylaxis. Receiving both prophylaxis reduced the risk of developing foetal anaemia markably. However, post-partum prophylaxis reduces the risk of developing foetal anaemia significantly as compared to antenatal prophylaxis (46.6% to 7.4%).

V. Conclusion

The MCA-PSV has been shown to be an excellent tool for the diagnosis of foetal nemia. We calculated the sensitivity and specificity of the MCA PSV of ≥1.29 MoM, the threshold proposed by Mari [2] for detecting any degree of anaemia (haemoglobin ≤0.84 MoM) in foetuses at risk of developing foetal ia. Using a threshold of 1.29 for MCA PSV MoM provides much better sensitivity (94.4%, compared to 66.6% for the threshold of >1.5 MoM) and also good specificity (88.1%) in predicting any degree of foetal nemia. It also has a very low FN rate. Though it has a high FP rate, in our country, it is more important to diagnose all cases of foetal anaemia as early as possible. Anti-D antibody prophylaxis, especially post-partum prophylaxis, reduces the risk of developing foetal anaemia significantly.

There was neither any conflict of interest nor financial support from any agency in this study

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