SOCIETY OF FETAL MEDICINE

Society of Fetal Medicine

SFM Bengal Chronicles

"The Rhesus Recital"

From The President's Desk

March 2024

Dear Friends,

As my term as the President for Bengal Chapter of the Society of Fetal Medicine comes to a close, I want to take a moment to reflect on the incredible journey we've enjoyed together over the past couple of years. It has been a great honour for me to serve for our beloved society. I am extremely grateful for the opportunity to work alongside the dedicated and passionate individuals like you all.

I was fortunate to have inherited a rich legacy from my predecessors Dr Kamal Oswal and Dr Kushagradhi Ghosh and I believe we have gone from strength to strength. This was never going to be possible without a dynamic honorary secretary like Dr Prasanna Roy and the most vibrant team around him. Together we have made significant strides in advancing the allied fields of interest, promoting excellence in education and clinical practice. We have organised successful conferences, workshops, webinars and created invaluable learning opportunities for ourselves. The Bengal Chapter takes pride in publishing the first ever quarterly newsletter "The SFM Bengal Chronicles" in the country. The flagship publication will remain as a glowing testimonial for successful teamworking. We also have the most interactive WhatsApp group to share our experiences whenever we like, at whatever time of the day to get an answer!

I am proud of the collaborative spirit that underpins our society. It will be an incomplete address if I don't mention about the unconditional support we have received from Dr Bimal Sahani, our "always-willing-to help" national president and Dr Ashok Khurana, our beloved mentor emeritus, the unequivocal "go-to-person" for all. It is the central team who made our life easy both for academics and for the administrative purposes. Our members come from diverse backgrounds and specialties, yet we are united by the shared commitment of improving the fetal health. It is your willingness to share knowledge, expertise and best practices that has been instrumental in driving this progress and innovation.

As I pass the baton on to Dr Seetha Ramamurthy Pal, the incoming president, I feel assured that we are in the best hands. I have every reason to believe that under her leadership, we will continue to grow further and build upon the foundation we have already established.

I extend my heartfelt gratitude to each and every one of you for your valuable contribution, dedication and unwavering support throughout my journey. Being the founder secretary I have had the special prerogative of witnessing the growth of our state chapter from a single-digit member strength to wherever we are today. I also tender my deepest apologies for any distress I may have caused to any of you. The intention has always been to safeguard the collective interest.

We have certainly achieved a lot for our professional development and I can safely claim that it is our patients who are getting the maximum benefits out of this exercise. We are providing better care for the unborns but we have a lot more to do and I am excited to see what the future holds for us.

Sincerely yours

A proud SFMian.
A proud member of the Bengal Chapter.

Long live SFM.
Long live multidisciplinary teamworking.

Love you all.

Dr Kanchan Mukherjee
The Outgoing President
Society of Fetal Medicine,
Bengal Chapter

Secretary's Report

Dr. Prasanna Roy

How fast time flies !!!
April 2022-March 2024. I will miss these 2 years.
Finally my term as the secretary of SFM Bengal comes to an end, and I will not disagree to the fact that this makes me a bit sad.

I joined SFM 7 years back, as a junior who wanted to learn the art of fetal ultrasound. I started learning, made mistakes, and again learned from my mistakes. This process was made easy by my seniors in SFM. They embraced me and welcomed me with all their warmth and love. I certainly believe that they favoured me a lot and gave me responsibilities which I did not deserve at that moment of time.

One fine day , I got a call from Dr. Kanchan Mukherjee, that all the seniors of SFM wanted me as the Secretary of Bengal chapter. Initially I was hesitant and scared to accept this responsibility. I did not know how to handle this “new job” in my life. “Don't worry brother, everything will be fine and you will do great”. I still remember these words told to me by my respected President, Dr. Kanchan Mukherjee. He is more of a friend and elder brother, rather than my senior. Whatever I learned in these 2 years regarding how to fulfil this “job”, I have learned from him. Without him, I was nothing.

In this process of learning, Kolkata chapter got renamed as Bengal chapter. We organised 3 outreach programmes at Durgapur, Purulia and Siliguri. We also held our Annual conference in Kolkata. Bengal chapter became the 1st chapter of SFM, to publish a newsletter. We kept on releasing quarterly editions of the newsletter. We also increased our membership strength, but I will admit that this is one area where I did not do very good.

In spite of all difficulties, I managed to somehow complete the job, with the help and inspiration of seniors like Dr. Bimal Sahani, Dr. Kamal Oswal, Dr. Kusagradhi Ghosh, Dr. Seetha Ramamurthy Pal and Dr. Shankar Dey. We have a great team in Bengal and I am sure that Bengal chapter will be taken to greater heights by the incoming team of 2024-26.
Finally I thank our Mentor Emeritus, Dr. Ashok Khurana for trusting me and supporting me throughout my journey. I thank you on behalf of all the members of Bengal chapter to have given us the opportunity to work for SFM. Keep on loving us as always you have done until now.

SFM has grown and matured to become the biggest academic platform for Fetal medicine in India. It has a very strong presence internationally also, with all the international faculties being regular visitors to our country. It will continue to grow at a very rapid pace under the present leadership. It is the best platform for juniors to showcase their work in this particular field. Therefore , I urge everyone to join SFM and be a part of this elite and incredible group.

Thank you,
Prasanna Roy

IMMUNE HYDROPS FETALIS- A BEGINNERS GUIDE

DR GIRIJA R VARIER
MBBS, DMRD, MD (OBS&GYN)

INTRODUCTION

Hydrops fetalis is a condition in the fetus characterized by an abnormal accumulation of fluid in two or more fetal compartments resulting in generalized oedema and fluid build-up in extravascular compartments and body cavities.It is divided into Immune Hydrops Fetalis(IHF) and Non Immune Hydrops Fetalis(NIHF). Immune hydrops accounts for a minority of cases in developing countries and occurs due to feto-maternal blood group incompatibility (rhesus incompatibility))

PATHOPHYSIOLOGY OF HEMOLYSIS IN RHESUS ISOIMMUNIZATION

In red cell isoimmunized pregnancies, maternal haemolytic IgG antibodies cross placenta

↓

Attach to the fetal RBC and damage them

↓

Fetal reticuloendothelial system destroys the damaged RBC

↙ Mild to moderate affection

↓

Intramedullary erythropoiesis as compensation

↓

Mild anemia and icterus in fetus

↘ Severe affection

↓

Recruitment of extramedullary erythropoetic sites (liver & spleen)

PATHOPHYSIOLOGY OF IMMUNE HYDROPS FETALIS

When fetal Hb concentration deficit exceeds 6g/dl

↓

Fetal oxygen falls below the critical level of 2 mmol/l

↙ Infiltration of liver by erythropoetic tissue

↓

Compression of portal vessels that leads to portal hypertension

↓

Impaired protein synthesis and hypoproteinemia

↓

Decreased oncotic pressure

↘

↘ Also hypoxia induced vascular endothelial damage

↓

Increased vascular permeability

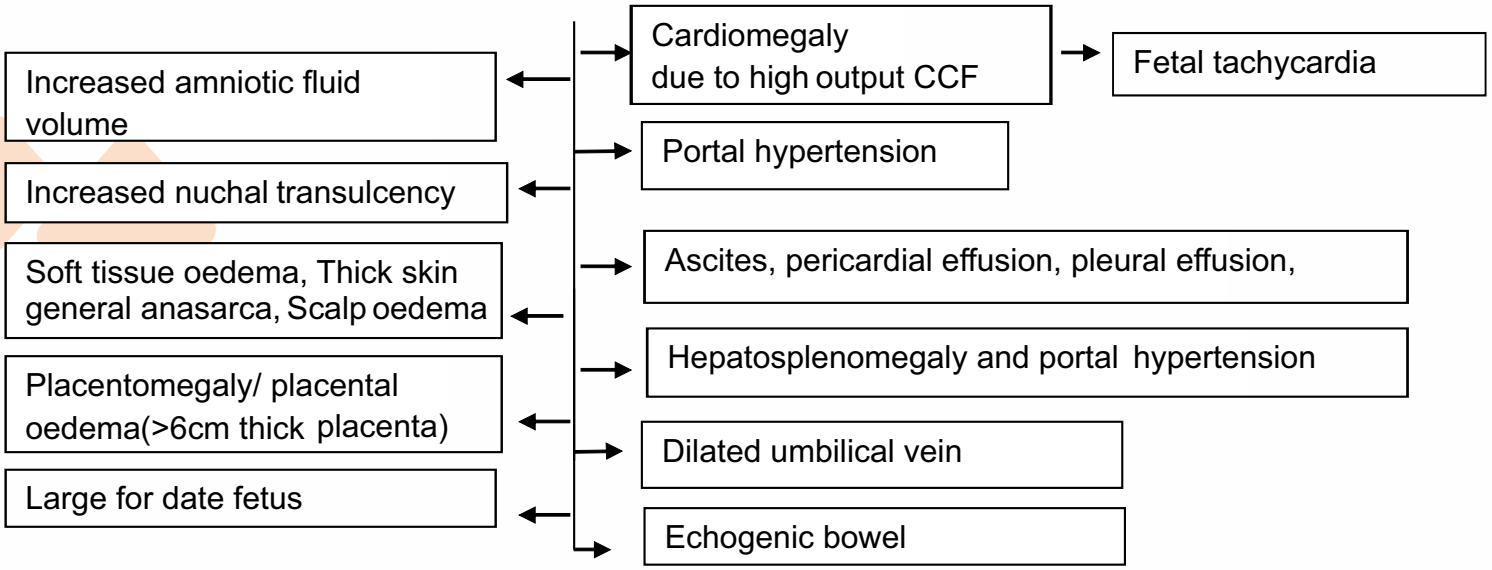
↓

Fluid extravasation

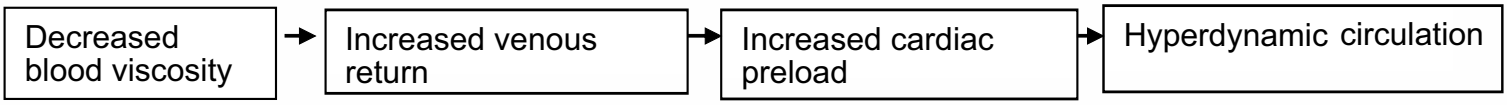
↙

Hydrops fetalis

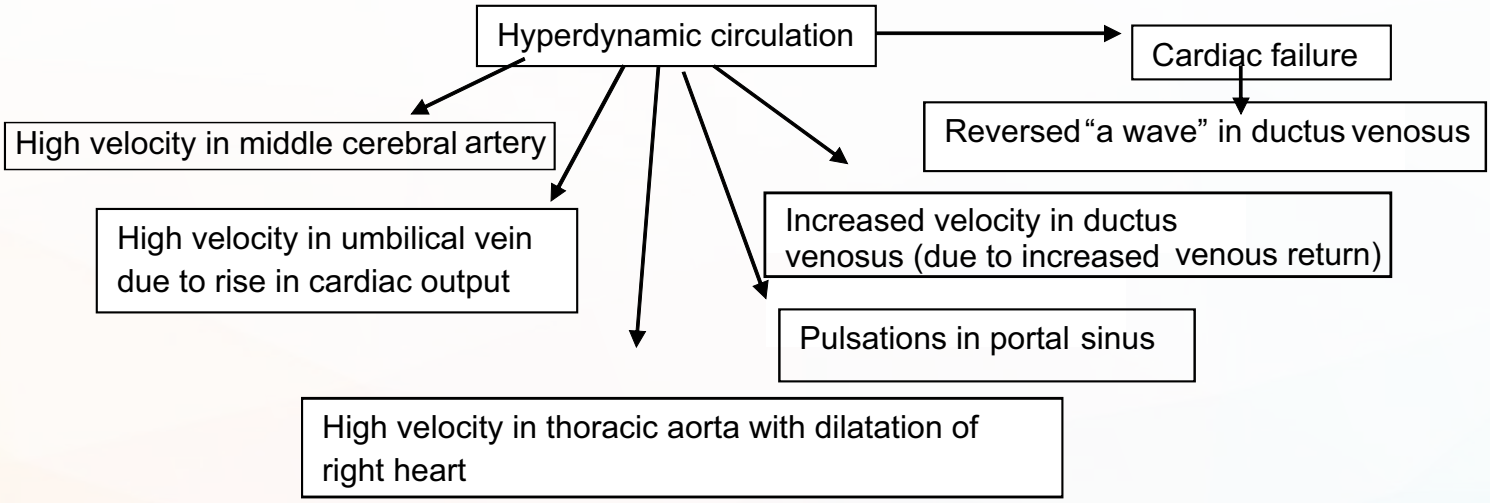
HYDROPS FETALIS AS SEEN ON ULTRA SONOGRAPHY



CAUSE OF HYPERDYNAMIC CIRCULATION



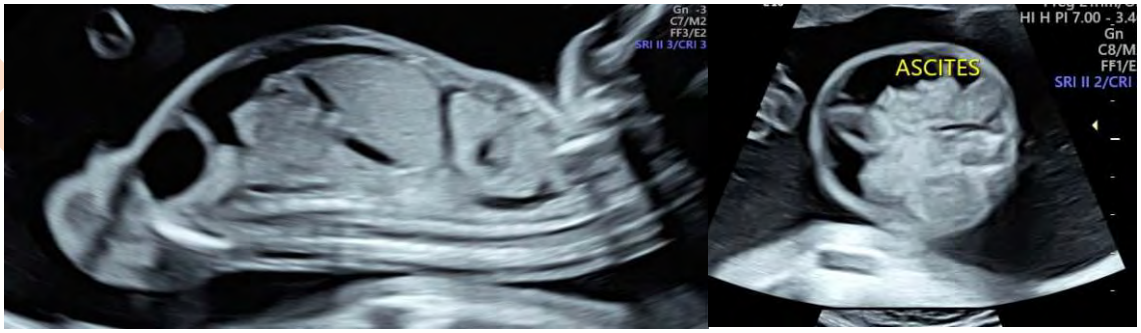
DOPPLER EFFECTS OF HYPERDYNAMIC CIRCULATION



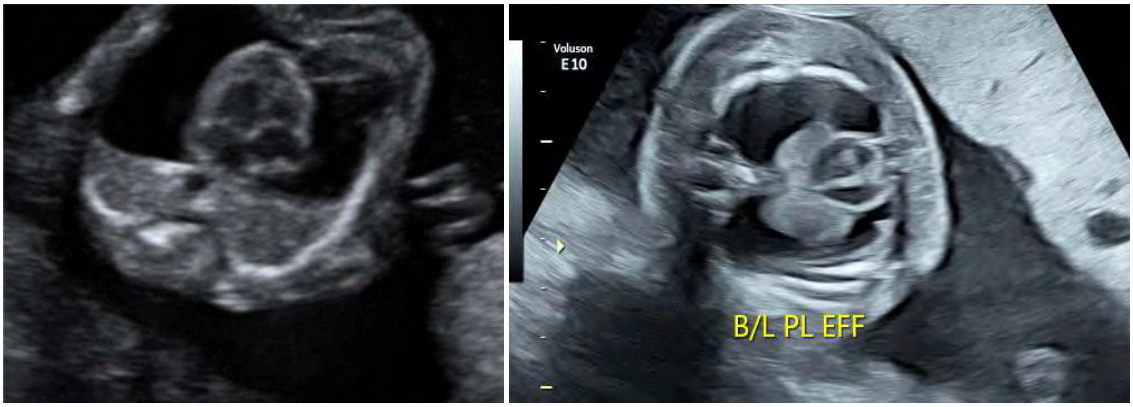
Since placentation is normal, the indices of impedance to flow (PI and RI) in uterine and umbilical arteries are normal, irrespective of severity of fetal anemia

MANIFESTATIONS OF HYDROPS FETALIS ON ULTRASONOGRAPHY

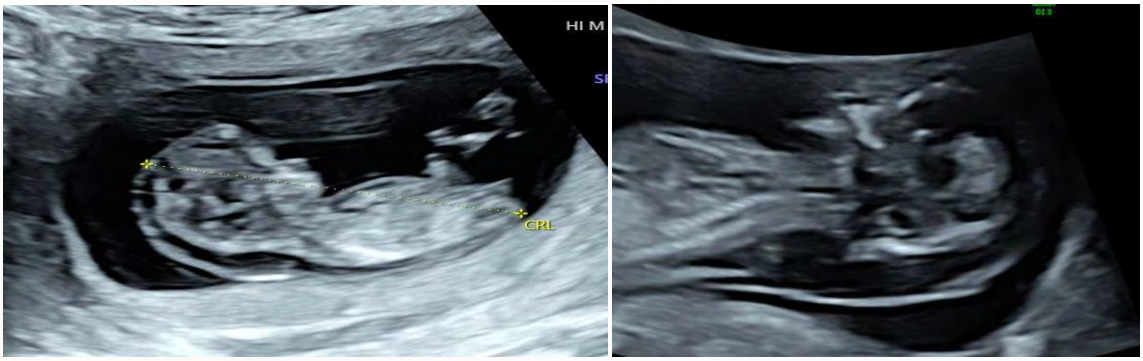
Hydrops is defined as the accumulation of fluid +/- edema involving at least two fetal components, which may manifest as the following



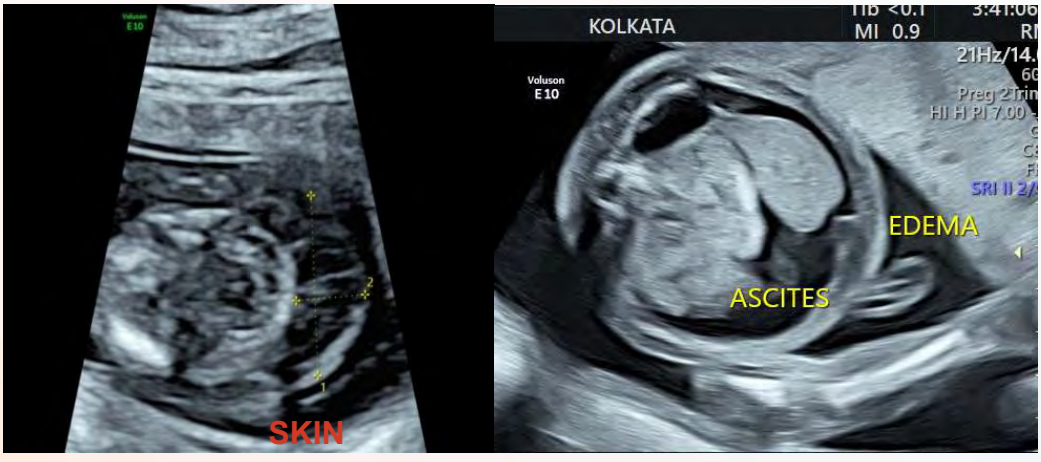
FETAL ASCITES



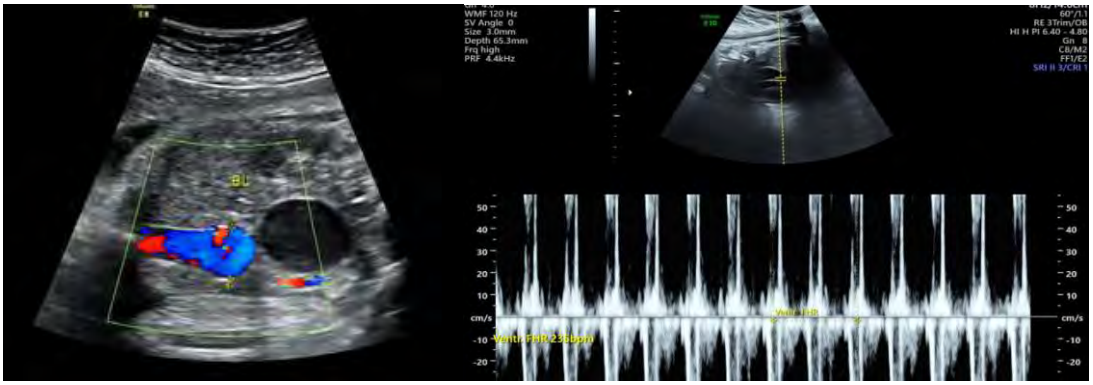
FETAL PLEURAL / PERICARDIAL EFFUSION



INCREASED NUCHAL TRANSLUCENCY IN FIRST TRIMESTER

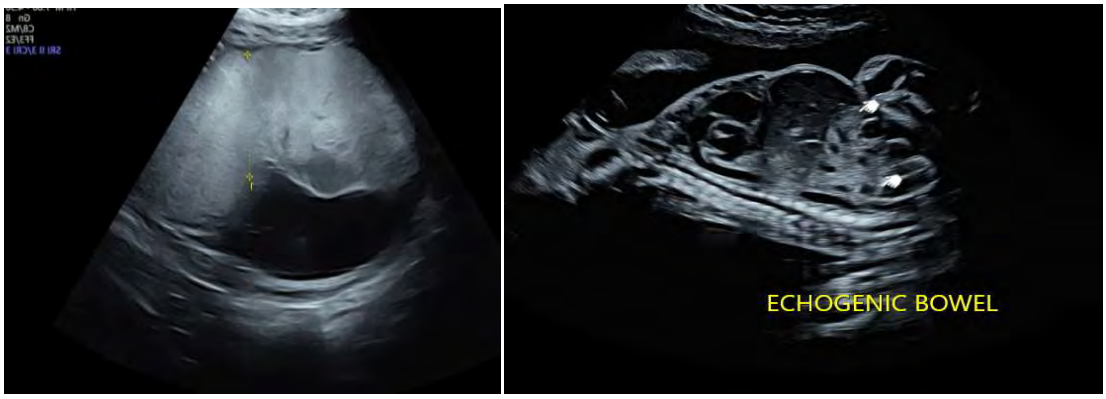


FETAL ANASARCA/ THICK



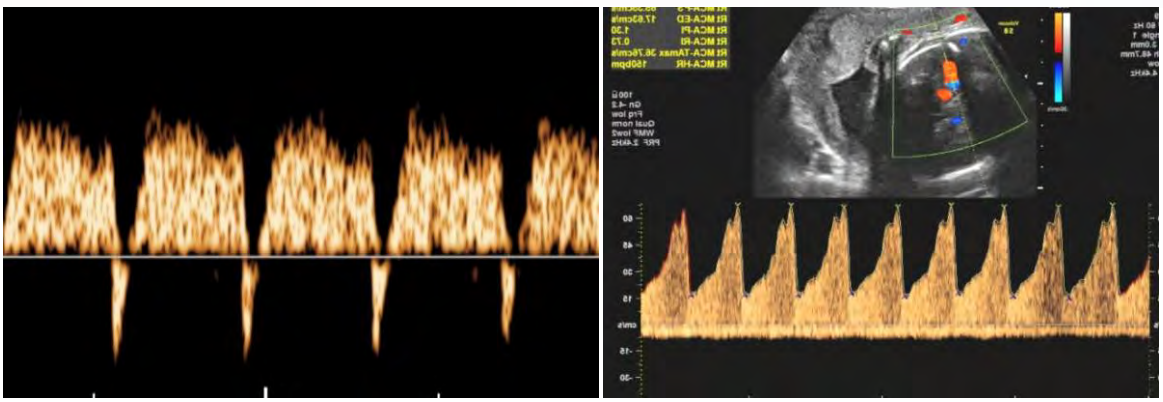
UMBILICAL VEIN DILATATION

FETAL TACHYCARDIA



PLACENTOMEGALY

ECHOGENIC BOWEL



REVERSED “A WAVE” IN DUCTUS VENOSUS

HIGH PEAK SYSTOLIC VELOCITY IN MIDDLE CEREBRAL ARTERY

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https://www.perinatology.com/conditions/Hydrops.htm

The Crucial Role of Father's Genotype in Rh Incompatibility: Understanding the Mechanisms and Implications

Upasana Mukherjee,
BGCI Level II certified Genetic Counselor,
Apollo Multi Specialty Hospitals, Kolkata

Introduction:

Rh incompatibility, also known as Rh disease or hemolytic disease of the newborn (HDN), is a condition that occurs when the Rh factor in the blood of an expectant mother is incompatible with that of her fetus. While much attention is given to the mother's Rh status, the role of the father's genotype in Rh incompatibility is equally significant and often overlooked. This essay delves into the mechanisms and implications of the father's genotype in Rh incompatibility, shedding light on its crucial role in the condition.

Understanding Rh Incompatibility:

The Rh factor, or Rh antigen, is a protein present on the surface of red blood cells. Individuals who have this protein are Rh-positive (Rh+), while those who lack it are Rh-negative (Rh-). Rh incompatibility arises when an Rh-negative mother carries an Rh-positive fetus. During pregnancy and childbirth, the mother's immune system may perceive the Rh-positive fetal blood as a foreign invader, leading to the production of antibodies against it.

The Role of Father's Genotype:

While the mother's Rh status primarily determines the risk of Rh incompatibility, the father's genotype plays a crucial role in transmitting the Rh factor to the fetus. If the father is Rh-positive, there's a chance that the fetus will inherit the Rh-positive allele from him, increasing the likelihood of Rh incompatibility if the mother is Rh-negative.

Mechanisms of Inheritance:

The inheritance of the Rh factor follows Mendelian genetics. Each individual inherits one Rh allele from each parent, resulting in three possible genotypes: Rh-positive homozygous (++) if both alleles are Rh-positive, Rh-negative homozygous (--) if both alleles are Rh-negative, and Rh-positive heterozygous (+-) if one allele is Rh-positive and the other is Rh-negative.

Implications for Rh Incompatibility:

1. Risk Assessment: Understanding the father's Rh genotype is crucial for assessing the risk of Rh incompatibility in pregnancies involving an Rh-negative mother. If the father is Rh-negative, the fetus will inherit an Rh-negative allele from him, eliminating the risk of Rh incompatibility.
2. Management and Prevention: Knowledge of the father's Rh genotype allows healthcare providers to tailor appropriate management and preventive measures. In cases where the father is Rh-positive, interventions such as Rh immunoglobulin (RhIg) administration to the mother can help prevent the development of Rh antibodies and protect future pregnancies.
3. Genetic Counseling: Genetic counseling plays a pivotal role in informing couples about the implications of Rh incompatibility based on their genotypes. Couples with an Rh-negative mother and an Rh-positive father require thorough counseling regarding the potential risks and preventive measures to ensure optimal pregnancy outcomes.
4. Future Pregnancy Planning: The father's Rh genotype influences the likelihood of Rh incompatibility in future pregnancies. Couples with an Rh-negative mother and an Rh-positive father need to consider their options carefully and plan pregnancies under the guidance of healthcare professionals to minimize the risk of Rh-related complications.

Conclusion:

In conclusion, the father's genotype significantly influences the risk of Rh incompatibility in pregnancies involving an Rh-negative mother. Understanding the mechanisms of inheritance and implications of the father's Rh status is essential for risk assessment, management, and genetic counseling. By recognizing the importance of the father's genotype in Rh incompatibility, healthcare providers can offer personalized care and support to couples, ultimately ensuring better pregnancy outcomes and the health of newborns.

Non-Invasive Prenatal Testing for Foetal Rh-D Status

Yashodhara Bhattacharya
Level-II Genetic Counselor (BGC-I)
Sr. Field Genetic Counselor and Product Manager
(Unipath Specialty Laboratory Ltd.)

Rh Hemolytic Disease or Hemolytic Disease of the Newborn (HDN) is a disorder affecting a developing foetus or a newborn when there is an incompatibility in the RhD blood group amongst the mother and the foetus. Due to an increase in prenatal screening and prophylaxis, there has been a decline in the incidence of the disorder, however RhD-incompatibility related foetal mortality rate of 296 among 100,000 neonates has been reported in developing countries [1]. In India, the incidence of RhD negative pregnancies is approximately 3-5.7% [2] which may lead to a potential risk of Hemolytic Disease. The Non-invasive prenatal test (NIPT) was developed to help determine the RhD status in the foetus of an RhD negative mother, to help with the management of the pregnancy and prevention of HDN.

Background: Rh Blood Type and Rh Incompatibility

Blood typing is based on the different antigens present on the red blood cells (RBCs) of an individual. Blood groups are classified based on the antigens, A, B, or RhD present on the surface of the blood cells. In individuals where the RhD antigen is present are classified as RhD positive and those without the antigen are classified as RhD negative.

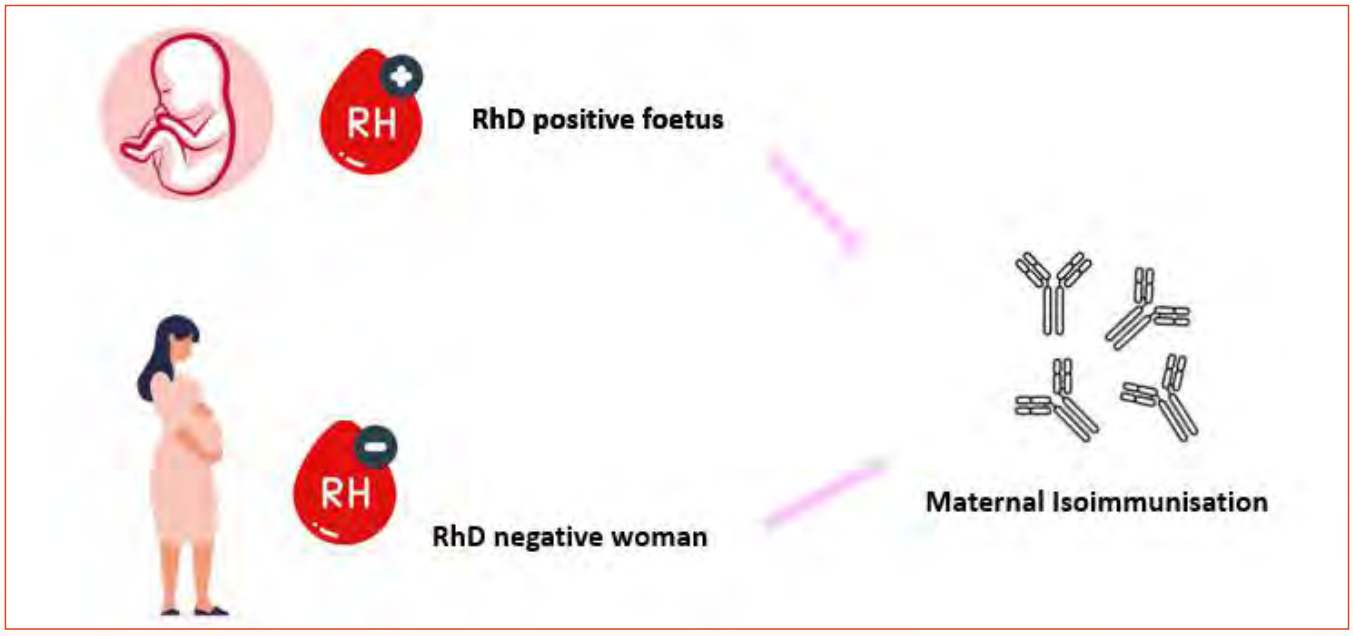

Figure 1: Maternal Isoimmunisation

Rh incompatibility is caused when there is a mismatch between maternal and foetal Rh blood types. This is clinically significant in cases wherein the mother is RhD negative and is pregnant with a RhD positive foetus. The maternal reticuloendothelial system of a RhD negative mother recognises the RhD antigen on the foetal cells which circulate in the maternal blood. The RES responds by forming IgM antibodies against the RhD antigen in small quantities due to the initial response and are stored as memory B- cells. During a second pregnancy wherein the foetus is RhD positive exhibiting the Rh-D antigen, the memory B-cell primed previously get activated and respond more strongly by forming IgG antibodies against the foreign antigen. These antibodies can cross the placental barrier and cause a potentially fatal disease in the RhD positive foetus or newborn known as the Hemolytic Disease or Erythoblastosis fetalis which may result in a spectrum ranging from self-limiting haemolytic anemia to hydrops fetalis.

Clinical features of Hemolytic Disease of the Newborn due to Rh incompatibility:

1. Lethargy
2. Pallor
3. Jaundice/ Kernicterus
4. Scleral icterus
5. Tachycardia
6. Tachypnea and hypotension
7. Hydrops fetalis a severe, life-threatening hemolytic anemia and is associated with a significant mortality rate estimated to be more than 50%.

Prophylaxis and prevention of Hemolytic Disease

In India, to avoid such alloimmunization of the RhD negative mother against RhD antigen, antenatal screening guidelines recommend the blood grouping of the pregnant lady to be carried out at the earliest antenatal visit. In case the lady is RhD negative, the husband is recommended for blood typing. If the husband is identified as an RhD positive individual, then there may be risk of subsequent pregnancies with an RhD positive foetus. To determine the RhD isoimmunisation in the mother, anti- D antibodies are tested periodically by Indirect Coombs Test (ICT).

In RhD negative women who are not isoimmunised, prevention of the sensitization is mandatory. This is achieved by administering a prophylactic dose of anti-D immunoglobulins to counter spontaneous feto-maternal hemorrhages antepartum and postpartum.

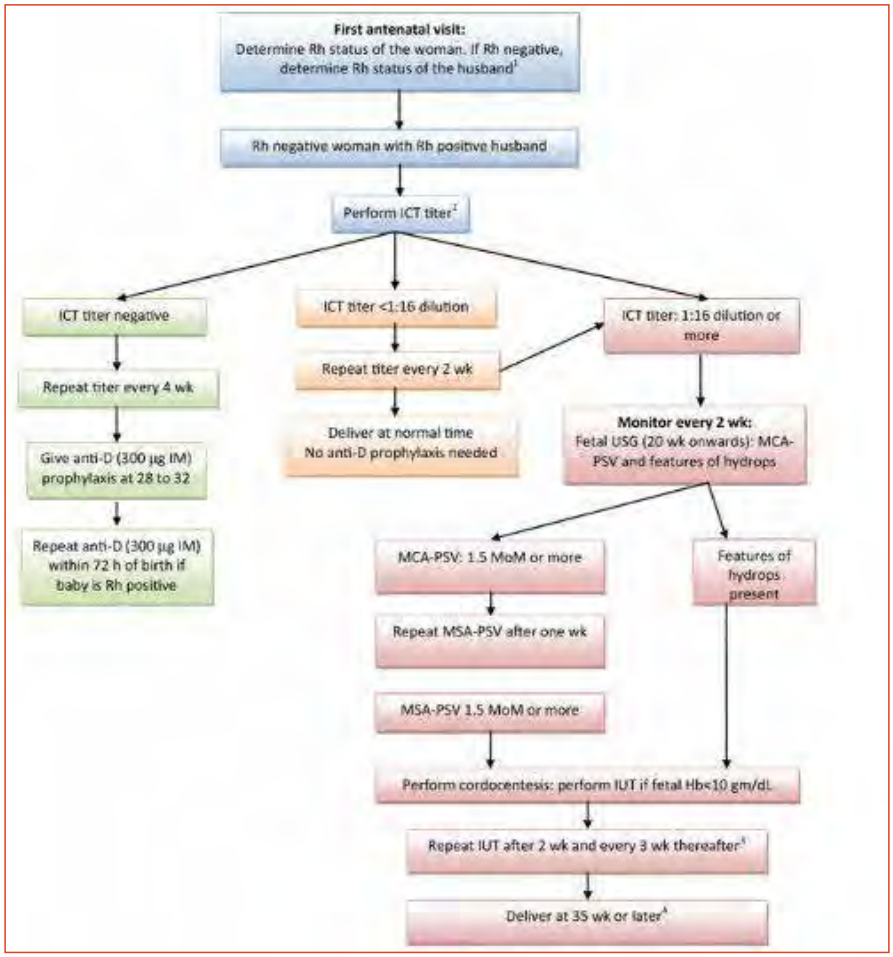

Figure 2: Treatment and Prevention of RhD Isoimmunisation
Image taken from DOI 10.1007/s40556-014-0013-z

The treatment and prevention of the isoimmunisation involves multiple testing and anti-D immunoglobulin injections of the RhD negative mother, as the RhD blood type of the foetus can usually be determined only post birth of the baby. In certain cases, wherein the foetus may exhibit features of hydrops fetalis, cordocentesis and intrauterine transfusion may be required. The prophylaxis and management of RhD isoimmunisation may incur high costs of testing, invasive procedures, lifesaving intrauterine transfusions and administration of anti-D immunoglobulins to the mother. This may cause anxiety in a pregnant mother. Further, anti-D immunoglobulins may carry risk of viral or prion disease which may be transferred to the mother. However, when the conceived foetus has an RhD negative status, there is low risk of RhD isoimmunisation and thus the recommended prophylaxis is not required.

Non-Invasive Prenatal Testing (NIPT) for foetal Rhesus-D status in RhD negative women

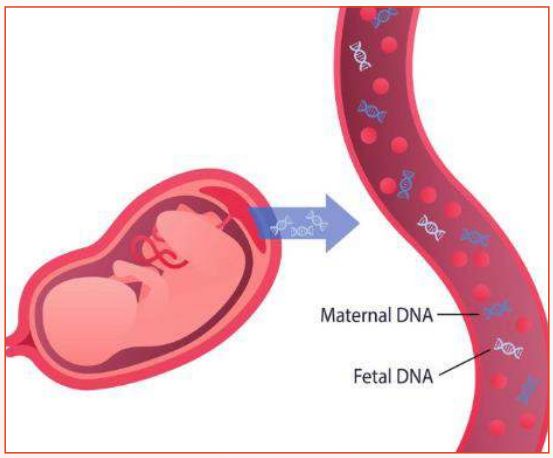

Figure 3: Prenatal cCell free fetal DNA (cff-DNA) testing using maternal blood

How does the NIPT test determine foetal RhD status?

NIPT of foetal RhD status uses a real-time quantitative polymerase chain reaction (PCR) method for predicting the foetal RhD genotype from foetal DNA in the plasma of RhD-negative mother. The test analyses the cell-free foetal DNA, which are small fragments of foetal extracellular DNA shed from the placenta and circulate freely in the maternal plasma. The level of cell-free foetal DNA in maternal blood increases throughout the pregnancy. A woman who is RhD negative does not have a copy of the RhD gene; therefore, the presence of a RhD gene in a RhD-negative pregnant woman suggests a RhD- positive foetus.

Who should be recommended for the RhD NIPT?

The NICE and RCOG guidelines recommend the RhD NIPT test for all RhD negative pregnant women to detect the foetal RhD status, which is essential in planning the prophylaxis against RhD isoimmunisation to prevent haemolytic disease. It may be beneficial for RhD negative women:

1. Who have to undergo an invasive procedure
2. Undergoing miscarriage or abortion
3. Detected with ectopic pregnancies
4. With other RhD sensitizing events during a pregnancy

At what gestational age can the RhD NIPT be recommended?

The RhD NIPT may be recommended as early as 11 weeks of gestation with a sensitivity of 99.93% and specificity of 99.61%.

Challenges of the RhD NIPT

There are a number of genetic causes leading to the RhD negative phenotype and may vary according to ethnic origin. The predominant cause of the RhD negative phenotype is the homozygous deletion of the RhD gene. In certain cases, there is a non-functional copy of the RhD gene, known as the RhD pseudogene (RhD-psi). This gene includes a 37 bp insertion in the exon 4 and a nonsense mutation/ variant in the exons 5 and 6 of the RhD gene, rendering it non-functional. In the presence of the RhD pseudogene, prenatal testing of foetal Rh type from maternal blood would reveal a RhD-positive type, but this would be confirmed as RhD negative by serology because of the abundant maternal D gene sequences that are not expressed but are amplified. Most RhD NIPT target exons 5, 7 and 10 of the RhD gene to help distinguish between RhD negative, RhD positive and RhD psi genotypes. However, in certain cases, the presence of the pseudogene may lead to false-positive results when performing NIPT.

Summary

The RhD NIPT when recommended for all RhD negative pregnant women may help determine the pregnancies with an RhD positive foetus. This can help in planning of the prophylactic measures to avoid Rh Immunization. Further, early identification of an RhD negative foetus can help avoid the unnecessary cost of titre testing and anti-D immunoglobulin injections which may also be a source of blood borne infections, as the risk of RhD isoimmunisation is low in such cases. This may help foetal medicine specialists and obstetricians to counsel the patient families and provide the best management options for high-risk pregnancies.

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RAADP and prophylactic Anti-D - When and How much?

Dr Manjir Mitra
MS, DNB, MRCOG
Associate Consultant, Apollo Multi Specialty Hospitals

They say having a routine today, is the secret of success in the future. Well, if that's a message for life in general, adding Routine Anti-D Antenatal Prophylaxis (RAADP) to your antenatal care plan is the mandate now for a successful outcome in a Rh-negative pregnancy. With recommendations coming straight from the FIGO, ICM, RCOG guidelines, high income countries have almost eradicated the Rh disease. To what extent we can implement in India remains to be seen as because even postnatal/abortal prophylaxis coverage is such a challenge and is far from a cent percent scenario!

Rh alloimmunization can creep in either following a sensitizing event or an incompatible blood transfusion. The antenatal period the risk is still at 10% but during delivery it jumps to a 90% risk making allo-immunisation an almost impossible event to bypass. So herein comes in the importance of Routine Antenatal Anti-D Prophylaxis- a stitch well in time to prevent nine.

Now let's take up the sensitizing events list antenatally and counter them one by one.
Ectopic pregnancy has the consensus divided between NICE guidelines and BCSH. The Greentop Guideline on management of ectopic pregnancy 2016 suggests to give a prophylactic dose if and when there is a surgical management done, or if there is a complaint heavy bleeding or repeated bleeding or associated pain. However BCSH is of the opinion to give anti-D irrespective of management plan.

For spontaneous abortion less than 12 weeks without severe bleeding or pain, no Anti-D immunoglobulin is required. But in case of medical or surgical management of pregnancy it is recommended.

In case of such unfortunate events as an intrauterine fetal death, it is considered prudent to give anti-D at diagnosis only and, also assess for feto-maternal haemorrhage quantification. This quantification of bleed can be assessed by flowcytometry or as the old school of teaching was, by Kleihauer-Betke test. 500IU of Anti-D covers for 4 ml of fetal blood, and additive dose should be considered at 125IU per ml of blood.

We should bear it in mind that Anti-D is best given within 72 hours and can be given upto 10 days of sensitizing event.
But apart from the most obvious bleedings, there are silent events in the late pregnancy which leads to iso-immunization in the first pregnancy itself by 18-27%. Herein, lies the importance of Routine Antenatal Anti-D Prophylaxis- an additional needle prick antenatally. While routine postnatal prophylaxis reduces the risk of iso-immunization by 1.6% and routine antenatal prophylaxis reduces the risk of iso-immunization by 0.16%. the ideal candidate for receiving RAADP is a lady with Rh negative blood group with her partner having a Rh positive group, like the saying goes: opposites attract!

A single dose of 1500 IU Anti-D at 28 weeks or a double dose of 500 IU at 28 and 34 weeks are advisable for RAADP. The single dose is preferrable as it is more patient-friendly from all aspects considered.
But RAADP comes with a disclaimer: it does not rule out the need for an Anti-D immunoglobulin in case a sensitizing event follows its administration. So it does seem like an uphill task to implement this at the moment in India. The country is still struggling to provide postnatal immunoglobulin following abortions and ectopics in as much as 80-90% of the cases. Hopefully with more awareness a better day will dawn for the Rh Negative mothers of India.

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FIGO/ICM guidelines for preventing Rhesus disease: A call to action

‘Other’ red cell antibodies-routine testing or not?

Dr Arkajyoti Mukherjee, MS,DNB(O&G)
Fellowship in Fetal Medicine
Fetal Medicine Consultant
Apollo Multispeciality Hospital,Kolkata

Red cell antibodies and their clinical importance

Since Landsteiner’s discovery in 1901,a total of 30 blood group systems have been described.Each of them is a series of red cell antigens.The main clinical importance of a blood group system depends on the capacity of producing alloantibodies(against antigens not possessed by the individual) to cause destruction of transfused red cells or to cross placenta and give rise to haemolytic disease of foetus or newborn(HFDN).

Present status and importance of screening
There are more than 50 red cell antibodies which are of clinical importance to some extent. Apart from ABO system antigens Rhesus antigens have most immunogenicity.Among the 6 Rhesus antigens (D,c,E,e,C,G), D is the most immunogenic as well as most commonly associated with

Appendix I: Red cell antibodies showing published clinical significance

HDFN. So,testing for Anti-D antibodies in D negative or commonly known as Rh negative pregnant women is of utmost importance.With routine practice of postpartum prophylaxis, estimated incidence of Anti-D alloimmunisation has come down from 15% to 2%.With use of routine antenatal Anti-D prophylaxis (RAADP) it has gone down further to 0.1%(FOGSI key practice points on Anti-D for Rh prophylaxis).Though the actual scenario may be different depending upon the awareness and availability.

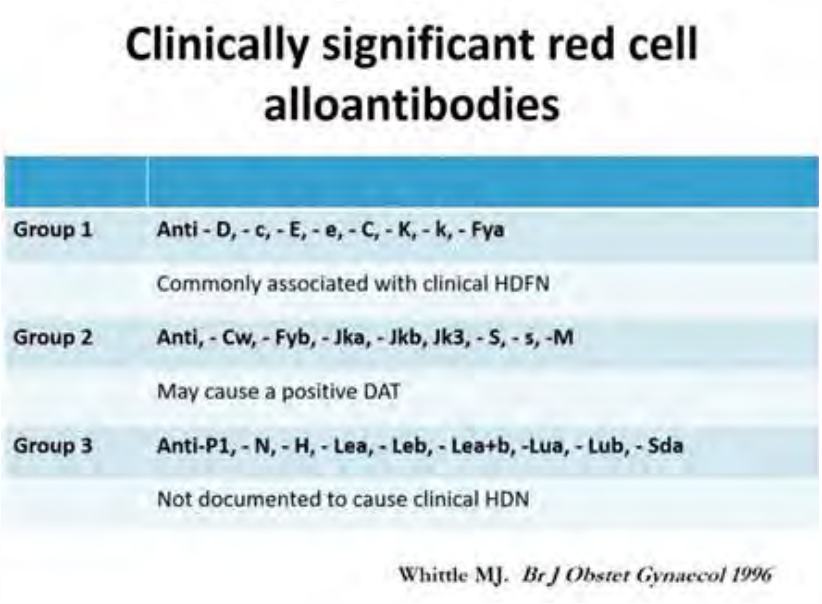
Prevalence of Red cell antibodies

	Varghese etal, Indian J Med Res 138, July 2013	Pahuja etal, Blood Transfus 2011	Veena etal 2017
Total study subjects	5347	3577	370
Prevalence of alloimmunisation	1.48% (n=79/5347)	1.25%(45/3577)	2.9%
Prevalence in Rh negative females	9.43%	11%(41/353)	7%(12/170)
Anti D antibodies	8.85%	9.9%	5.3%
Prevalence in Rh Positive females	0.08%(4/5347)	0.125%(4/3179)	0.5 (1/200)
Non Rh antibodies	Anti- Jka, Jkb, M and S.	K,M,S,Fya	C,c,Jka,Leb

Antibodies apart from the most common Anti-D are referred as 'Other' red cell antibodies here and obviously the most pertinent comes along-should we go for routine testing for these or not? When we go through the available literature, the overall prevalence of 'other' antibodies among Rhesus positive mothers 0.1%-0.5% and it increases as the gravida status increases.So,antibody screening or ICT can be positive irrespective of the Rhesus status.Sensitisation can happen whenever any foreign antigen enter into the circulation or even autoantigens can produce antibodies. Most common sensitising event is previous pregnancy but it is not the only cause.So,ICT can be positive even in primigravida.By routine screening we can identify the foetuses who are at high risk for HDFN which in turn help us to intervene at right moment.

Antibody identification

Among these 'other' antibodies some cause HDFN and it's important to identify them.It help us to utilise the resources in a correct way and reduce anxiety of both parents and physician. The antigen causing sensitisation can be non D even in Rhesus negative pregnancy. Anti D prophylaxis can be given to ICT positive pregnancies in such situations. But,antibody identification is not widely available and in such situations assume it to be the commonest i.e. Anti D.



Antibody quantification

After the antibody being identified it is important to know how much harm they can cause.HDFN ranges from mild anemia to hydrops. It depends on the type of antibody as well as amount of antibodies present in circulation.So,next step is antibody quantification or know the titre.All red cell antibody titre usually correlates with fetal affection except Anti-Kell. Anti-Kell usually cause severe hemolysis irrespective of titre('Kell kills').The minimum titre which is clinically significant or critical titre can only be dictated by the respective laboratory.Mostly it is 1:16 or 1:32.

In a nutshell

Screening for 'other' antibodies or as such antibody screening should be universal and part of routine antenatal investigations irrespective of Rhesus and gravida status.Once it is positive, next step should be antibody identification if available followed by titre measurement.Use of such protocol helps to use our resources in a judicious way and intervene in right cases at right time to reduce both perinatal morbidity and mortality.

RH negative mother, ICT positive – What to do next ?

Dr. Khurshid Alam,
DNB (RD), PDFFM (Mediscan, Chennai),
Consultant Fetal Medicine
Fetomat Wellness, Kolkata
Institute of Fetal Medicine Kolkata

Dr.Tanaya Mukherjee,
MS Obs and Gynae.
Fellow, Fetomat Wellness

Rhesus (Rh) isoimmunisation is an important clinical entity in the field of maternal fetal medicine due to its impact in both prenatal period (fetal anaemia and fetal hydrops, and if not treated can result in intrauterine fetal demise) and postnatal period (severe neonatal jaundice and late anemia needing intensive phototherapy and exchange transfusion respectively).

Pathophysiology behind Rh-isoimmunisation

Isoimmunisation is defined as development of antibodies against antigens of another individual of the same species. The antigens which are present on human Red Blood Cells are mainly ABO antigens (A , B , AB) , Rhesus D antigen (RhD) and infrequently other atypical Rhesus (Rh) antigens like Cc, Ee, Kell(K), Duffy (Fy), Kidd (JK, jk), and M.

Rh-isoimmunisation is the development of antibodies against the Rh antigens present on the surface of RBCs. The important Rh antigen responsible for majority of cases of severe Rh isoimmunisation are c, E and Kell antigens. Rest of the Rh antigens (Duffy, Kidd, M and S) rarely cause significant problems.

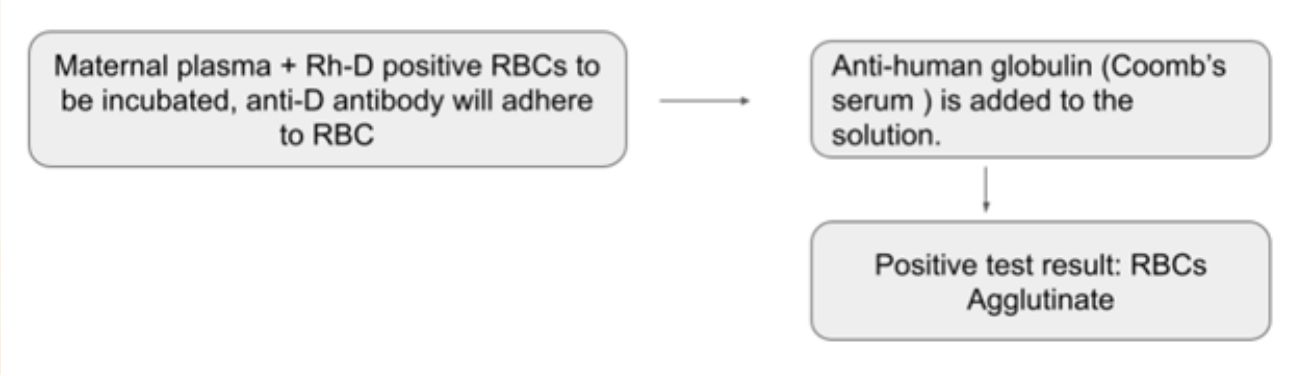
The Rh positive RBCs of the fetus gain entry into the Rh-negative maternal circulation via fetomaternal haemorrhage(FMH) resulting into formation of anti-D antibodies (IgG) by stimulating reticuloendothelial system, which in turn pass to the fetus through placental circulation and destroys fetal RBCs to produce fetal anaemia. FMH occurs throughout pregnancy and the amount of this haemorrhage increases with increasing gestation.

Quantification method to predict affection

To detect sensitisation of mother, presence of anti-D antibodies in maternal circulation is usually detected by **INDIRECT COOMB'S TEST (ICT).**

ICT is basically semiquantitative titration method to determine strength of antibody and risk of hemolytic disease of newborn.The serial dilutions of maternal serum are mixed with the RBCs carrying D antigen and clumping of RBCs at maximum dilution is known as **titre**. Critical titre is associated with risk of development of severe anaemia and hydrops fetalis. Critical titres during pregnancy are key to medical decision making but vary between laboratories. This necessitates patients to undergo follow-up titres in the same laboratory for serial monitoring. Mostly 1:16 or 1:32 is considered as critical titre.The denominator in the ratio is directly proportional to the antibody load (severity of fetal affection). The critical titre value varies with methodology (tube vs gel).

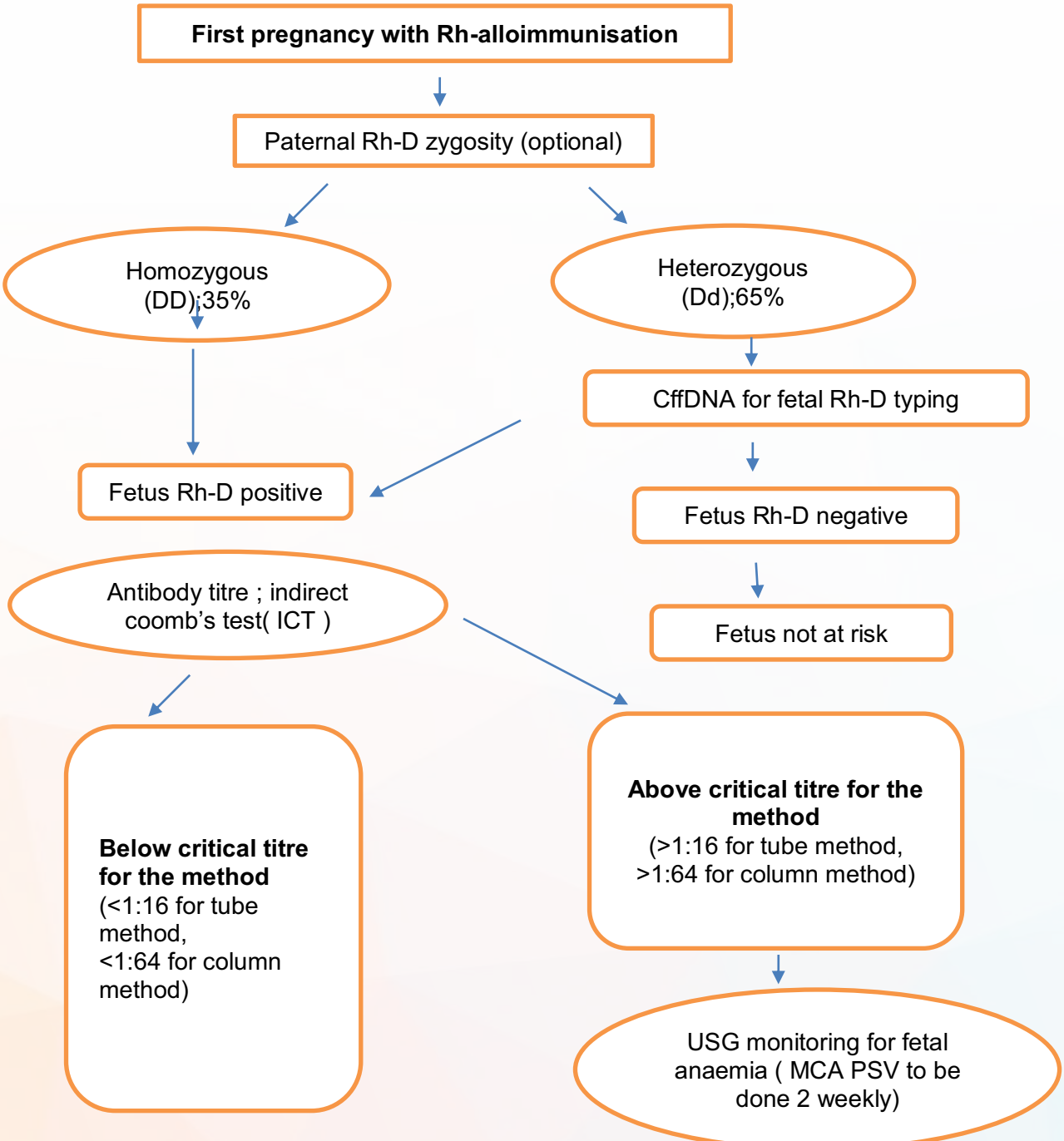
Principle of indirect coomb's test

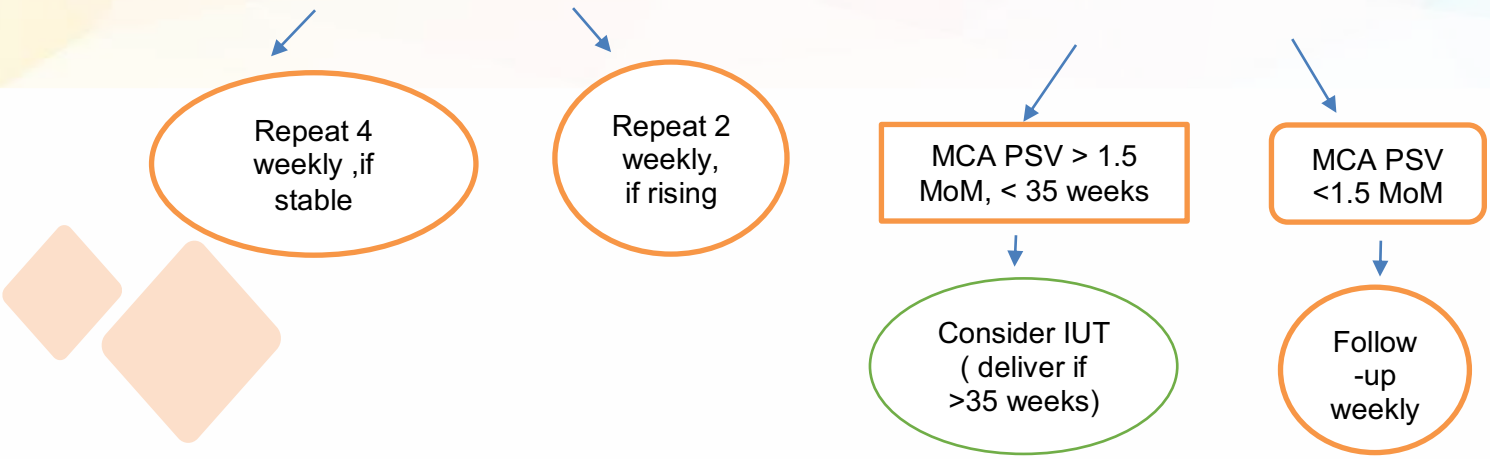


Two different ICT testing methods are described below:

Tube testing method or saline based anti-globulin testing	Gel based testing or gel microcolumn assay (GMA)
1.Traditional method, 2.Manual testing 3. Interobserver variability. 4.Threshold titre used for the result is 1:16. 5.High false positives.	1. Increased sensitivity. 2.Compatible with automation. 3. Less time consuming. 4. Less susceptibility to intralab and interlab variation. 5. A cut-off titre of 1:64 by column method can predict fetal anaemia and hence optimise management.

An algorithm for management of Rh-negative isoimmunisation is depicted below:





Previous pregnancy affected by Rh-D alloimmunisation

Paternal zygosity status (optional)

USG monitoring (MCA-PSV MoM)

To be started from 16-18 weeks gestational age or 10 weeks before the last pregnancy got affected, whichever is earlier.

Fetal anaemia defined as Hb < 2SD below mean for GA ,Hct <30%. In Hemolytic disease of newborn (HDN)- Hb is < 4SD

Appropriate technique for performing fetal middle cerebral artery Doppler study

Dr.Shankar Dey , MS (G&O),
Consultant,UltraClinic ,Asansol (WB)

Foetuses with anaemia exhibit an increase in peak systolic velocity (PSV) of the middle cerebral artery (MCA), which is linked to reduced blood viscosity and elevated cardiac output due to anaemia of any cause of origin.

Singl measurements of MCA PSV have demonstrated predictive capability for moderate to severe fetal anaemia, boasting a sensitivity of 100 percent and a false positive rate of 12 percent. The inter-observer reliability of MCA-PI measurement is reported to be only moderate, with limited agreement between two observers. However, there is an increased incidence of false positives observed after the 35th week of gestation.

Here in the following lines below I've described the correct method of obtaining and measuring the MCA PSV.

Confirm that the foetus is at rest with no movements or breathing

↓

Obtain an axial section of the fetal head including the thalami and the sphenoid bone wings.

↓

Identify the circle of Willis and the proximal MCA, just caudal to the transthalamic plane using colour Doppler.

↓

Visualise the entire length of the MCA and Enlarge the area so that it occupies 50% or more of the screen.

↓

Superimpose the sample volume (The pulsed-wave Doppler gate ,1mm) on the MCA, positioned 2 mm after its origin from the internal carotid artery (proximal one third)

(Because the systolic velocity decreases with increasing distance from the point of origin of this vessel.)

↓

Ensure the ultrasound beam is parallel to the direction of blood flow, with the angle between the ultrasound beam and blood flow direction set at zero degrees.

(This ensures accurate measurement of PSV as per Doppler physics.)

↓

Measure the highest peak systolic velocity. At least three and fewer than 10 consecutive waveforms should be recorded. The highest point of the waveform is considered as the PSV (in cm/s). The PSV can be measured using manual callipers or auto-trace.

↓

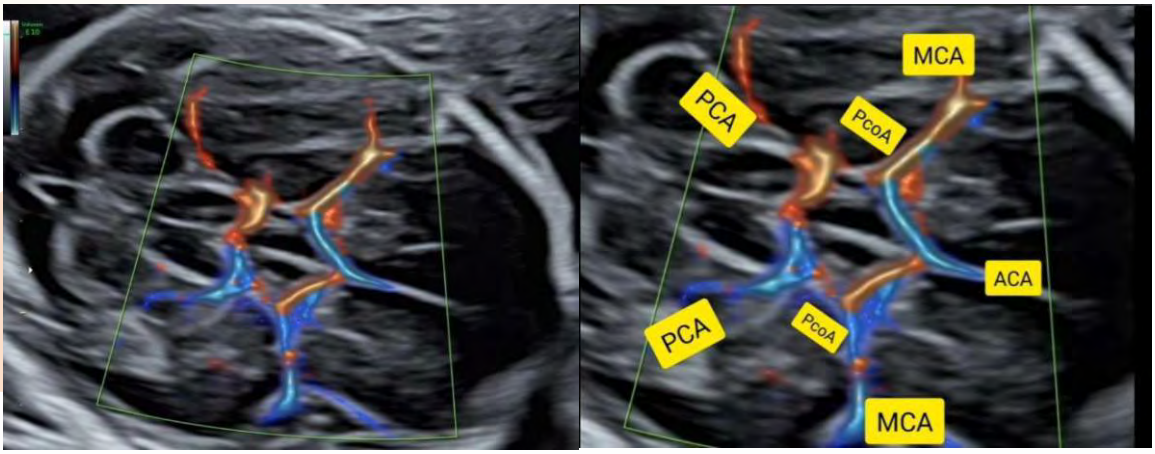
Repeat the measurement at least 3 times for accuracy.

MCA-PSV measurements at the proximal site of the MCA in the near field are comparable to those obtained from the far-field vessel in clinical practice.

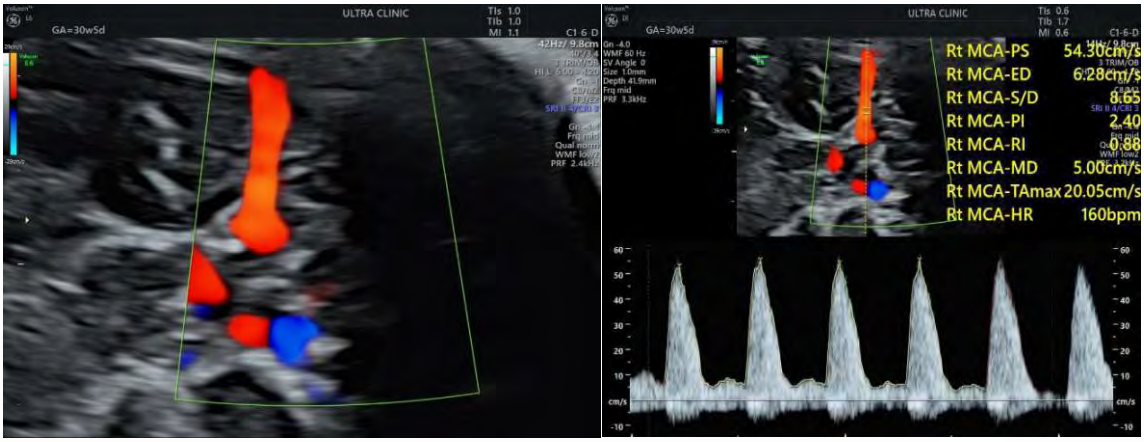
The far-field vessel may be chosen if obtaining an insonation angle of 0◦ is easier for the far-field than for the near-field MCA.

Care should be taken to avoid any unnecessary pressure on the fetal head, as this may lead to increased PSV, decreased EDV (End Diastolic Velocity) and increased PI (Pulsatality Index).

Finally, the rise in MCA PSV serves as an indicator of foetal anaemia and when done appropriately it aids not only in diagnostic assessment but also monitoring of fetal anaemia during prenatal care.



Circle of Willis ,labelled ;ACA-anterior cerebral artery, PCA – posterior cerebral artery,
MCA- middle cerebral artery,PcoA- posterior communicating artery



Appropriate technique of identification and measurement of middle cerebral artery

INTRAUTERINE BLOOD TRANSFUSION
The Grit and Nuances

Dr. Khurshid Alam,
DNB (RD), PDFFM (Mediscan, Chennai),
Consultant Fetal Medicine
Fetomat Wellness, Kolkata
Institute of Fetal Medicine Kolkata

Dr.Shruti Agarwal,
MS Obs and Gynae.
Fellow, Fetomat Wellness

Introduction

One of the most successful in utero therapeutic procedures, in today's era is intrauterine blood transfusion requiring multidisciplinary team (fetal medicine, haematology, transfusion medicine).

It is well established that since the introduction of intravascular intrauterine transfusion in 1981, it has become the treatment of choice in management of fetal anaemia resulting from both RhD and non RhD alloimmunization (Parvovirus B19 infection, chronic fetomaternal haemorrhage, homozygous alpha thalassemia).

Intrauterine blood transfusion is a procedure in which red blood cells from a donor are injected into an anaemic fetus. Aim of Intrauterine transfusion in a fetus with developed anaemia is to prevent or treat, fetal heart failure (hydrops fetalis), and allow pregnancy to continue to a stage where a viable baby can be delivered.

RIGHT TO RIGHT IUT: Includes 4 components

1. Right selection of case
2. Right selection of blood
3. Right technique to perform IUT
4. Right approach for post IUT follow up

Right selection of case

- Pregnancies with severe fetal anaemia at 18 to 35 weeks of gestation are optimal candidates for IUT.
- Severity of fetal anaemia is assessed by measurement of MCA-PSV in middle cerebral artery of fetus. A MCA-PSV of ≥1.50 multiples of the median (MoM) is an indication of moderate to severe fetal anaemia.
- A haematocrit less than 30 percent or a fetal haemoglobin less than 2SD below the mean value for the gestational age can also be used as a threshold for fetal transfusion IUT.

Right selection of blood

- Type O RhD negative, cross matched packed RBC, with donor haematocrit ranging from 75-85%
- The donation should be relatively fresh (<7 days of age) to enhance the level of 2-3- diphosphoglycerate and thus decrease oxyhaemoglobin affinity and to avoid hyperkalaemia.
- Leucocyte depleted.
- Cytomegalovirus (CMV) antibody negative.
- Irradiated by 25 Gy of gamma radiation to prevent graft versus host reaction (shelf life 24 hours).

Right technique to perform IUT

The procedure is performed in a tertiary care centre or a fetal medicine unit and is a day care procedure.

Preprocedural counselling - Survival rate has significantly increased with IUT, to about 85%, ranging from 75% when hydrops is present at the start of intrauterine treatment to over 90% in the absence of hydrops.

Risk of fetal demise 1-3 %.

Pre procedure preparation:

- Selection of right patient is most important decision to be made before deciding IUT.
- A course of antenatal corticosteroids is administered 48 hours before the IUT, where emergency delivery is expected.
- Clear liquids up to 2 hours before the procedure. Avoid meal 4-6 hours prior.
- Prophylactic antibiotic such as a first generation cephalosporin.
- Maternal sedation if needed Midazolam or fentanyl can be used to reduce maternal anxiety.

Choosing fetal access site :

1. Intravascular fetal transfusion (IVT) is preferable to intraperitoneal transfusion (IPT) because of higher survival rates.
2. Umbilical vein at placental insertion site or Intrahepatic umbilical vein — The procedure-related fetal loss rate appears to be similar in both procedures.

Calculation of blood volume transfusion

Volume transfused (ml) = volume of fetoplacental unit (ml) x [final (45-50%) - initial haematocrit] / the haematocrit of the transfused blood (75-85%)

Target HCT > 50% (supraphysiological) is not preferred due to risk of thrombotic events

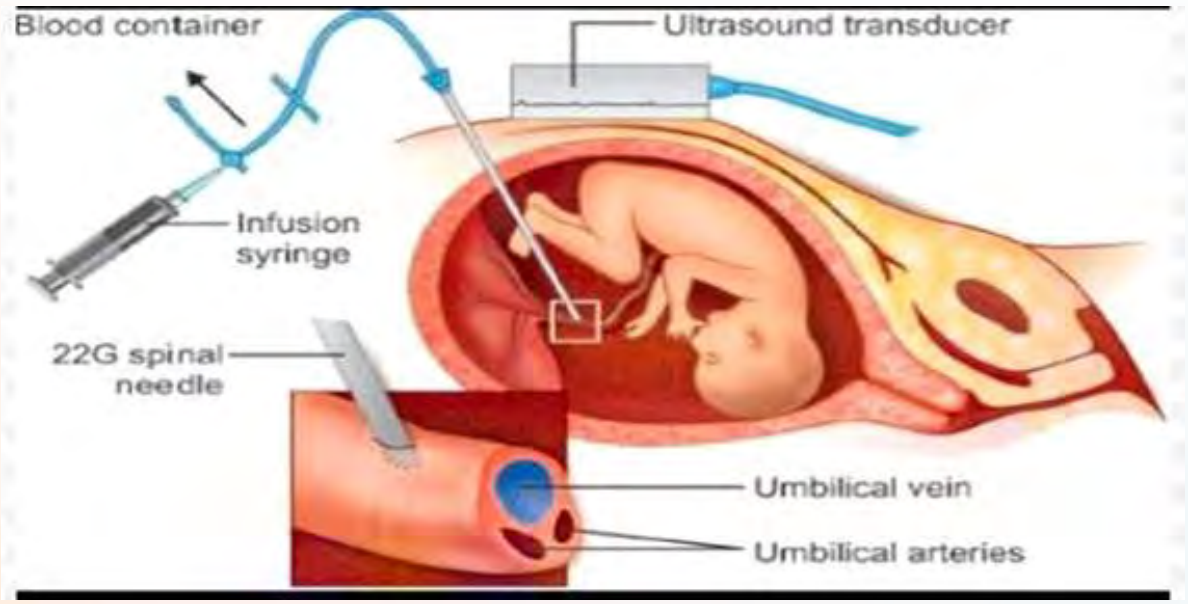
*The fetoplacental volume (ml) = 1.046 + EFW (in gm) x 0.14

Blood transfusion set trolley checklist:

1.	Sterile gloves	7.	10 ml syringe (2-3)
2.	Probe cover	8.	1ml syringes (2-3)
3.	Paint & drape set	9.	Triway stopcock
4.	22 Gauge spinal needle	10.	Paralytic agent
5.	20 G Chiba needle	11.	Gauze pieces
6.	BT set	12.	Kidney tray

Technique

1. Sterile dressing and draping the patient.
2. Tocoprophylaxis (Nifedipine 20 mg 1 hr before followed by 8hr dosing + micronized progesterone 200 mg vaginally morning of procedure or NTG patch 5mg, 2 hr before can be given).
3. A small dose of skeletal muscle relaxant reagent such as Pancuronium / Vecuronium (0.1 mg/kg EFW or Atracurium 0.4 mg/kg) may be used to create fetal paralysis, before IUT.
4. A transfusion line is set using BT set and 3 way stopcock.
5. Identification of the access site and infiltration of the maternal skin with a local anaesthetic.
6. Insertion of needle (20G,chiba) under ultrasound guidance and flush with heparin first.
7. A small blood sample is drawn using 1ml syringe from fetus to check hemoglobin (or hematocrit).
8. The volume of blood to be transfused is calculated and required amount is transfused in fetus by the formula discussed above or using online calculator (eg.perinatology.com).
9. After confirming anemia, a second operator infuses packed RBCs using a 20 mL syringe and a triway stopcock connector.
10. Regular fetal heart rate monitoring during the procedure. Infusion is stopped if any drop in HR noted, until it recovers.
11. Once transfusion is completed, another fetal sample is obtained to check post transfusion haematocrit. Also a MCA-PSV documented.



A pictorial depiction of IUT procedure. Umbilical vein is preferred site for IUT.

Right approach for post IUT follow up

1. Immediate Follow-up - A follow-up ultrasound examination is scheduled for the following day as most cases of fetal loss occur within the first 24 hours post procedure. Immediate blood grouping post transfusion may erroneously report negative blood group.
2. Subsequent transfusions - The goal is to maintain the fetal haematocrit above 25 percent. Generally 1% fall of hematocrit/day or fall of hemoglobin by 0.4g/dl after 1st transfusion (0.3g/dl and 0.2 g/dl after 2nd and 3rd transfusion respectively).
3. MCA- PSV is not used for predicting anaemia for timing of second and third transfusion as rheological property gets altered as fetal RBCs are replaced by adult RBCs.
4. Delivery timing- Best to plan last IUT at 34-35 weeks and plan delivery 3 weeks after

last IUT (preferably 37-38 weeks).

Complications:

Fetal complications can be categorized as procedure-related or not procedure-related. Most frequently occurring complications are:

1. Premature rupture of membranes and preterm delivery
2. Infection
3. Emergency caesarean section
4. Fetal death
5. Neonatal death

Management of neonate

With use of IUTs, overall perinatal mortality in severe anemia has dropped to 10-15%. The primary goal should be to treat hyperbilirubinemia (especially bilirubin induced neurological damage or BIND) and prevention of kernicterus rather than anemia alone. So, focus more on intense phototherapy rather than exchange transfusion.
Late anemia may be encountered as RhD antibody persists for upto 3 months, hence exchange transfusion is needed with only partial correction of anemia to drive active erythropoiesis.
End point to stop exchange transfusion is reticulocytosis.

Conclusion:

The infusion of red blood cells (RBCs) into the fetus is one of the most successful in utero therapeutic procedures. Although never studied in randomized trials, various observational studies across the world have clearly demonstrated that intrauterine transfusion (IUT) of the severely anaemic fetus improves survival. [1]

A compromised fetal condition is assumed to be the main cause of the lower survival in case of hydrops. The outcome of severely hydropic fetuses is poor in cases of persisting hydrops despite adequate correction of fetal anaemia. Therefore, fetal demise after intrauterine treatment may be the result of not only the invasive procedure itself but also of an already compromised fetal state. Because intrauterine transfusion, contrary to diagnostic cordocentesis, is performed only in the anaemic fetus, it is difficult to determine the true complication risk of this procedure. [5]

To prevent procedure-related adverse outcome, technically difficult procedures must be avoided. Fetal condition must be surveyed closely as preterm delivery and its subsequent extrauterine treatment of the potentially viable fetus are reasonable alternatives to an intrauterine transfusion. [4]

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IMMUNOMODULATION IN SEVERE HDFN WITH INTRAVENOUS IMMUNOGLOBULINS- IS IT A GAME- CHANGER?

Dr. Ananya Basu
MS, DNB, MRCOG
Fellowship in Maternal-Fetal Medicine (Apollo, Indraprastha)
Consultant, Fetal Medicine, Fetomat Wellness, Suraksha Diagnostics

My learned colleagues have already given you a nice overview of antenatal prophylaxis and management of Rh-iso-immunization in the preceding articles, but despite all the revolutionary achievements consolidated so far with anti-D, introduction of MCA Dopplers and intrauterine transfusions, the outcomes of severe cases of HDFN are still far from optimal, especially when the catastrophic consequences of kernicterus like permanent brain damage are taken into account.

The mainstay of management of such sick neonates, as we all know, are phototherapy and exchange transfusion. The latter has the distinct advantage of removing maternal antibodies, thereby preventing further hemolysis and correcting anemia. But it still remains a high-risk invasive procedure needing the use of central lines and is associated with a high chance of adverse reactions, with mortality less than 2% but morbidity rates as high as 74% (Smits-Wintjen VE et al) like cardio-respiratory complications, Graft-versus-host reactions, infections, catheter-related complications etc. Herein lies the need of considering treatment options like Intravenous immunoglobulins to replace or at least reduce the need of exchange transfusions.

So, what does the existing evidence say?

A review of literature shows that there is conflicting data about the effectiveness of IV Immunoglobulins in the Rh-isoimmunized babies, though it is a known fact that IVIg blocks Fc receptors on macrophages which reduces destruction of antibody-coated RBCs, enhancing the clearance of maternal antibodies. An RCT conducted by Smits-Wintjen VE et al in 2011 concluded that there was no difference in needs of exchange transfusion and adverse neonatal outcomes in between the IVIg and placebo groups. A 2014 systematic review and meta-analysis by Deepak Louis et al inferred that efficacy of IVIg is not conclusive in studies with low risk of bias indicating no benefit and studies with high risk of bias suggesting benefit. Again, a retrospective cohort study by Preeti Sharma et al (2015-2020) showed that targeted use of IVIg with serum bilirubin rising despite intensive phototherapy or within 2-3 mg/dl of the exchange level is more likely to benefit than harm. Also, a study by Josep Figueras-Aloy et al has revealed an association between use of IVIg and necrotizing enterocolitis in term and late preterm neonates.

So, now that my (I am sure yours too) head is stuffed with a lot of contradictory information, let us just conclude with what the American Academy of Paediatrics says!

- The effectiveness of IVIg to prevent the need for an exchange transfusion is unclear.
- IVIg (0.5 to 1g/Kg) over 2 hours may be provided to the infants whose TSB levels reach or exceed escalation of care threshold (means, 2mg/dl below the exchange transfusion threshold)- Grade C recommendation.
- Dose can be repeated in 12 hours.

The role of preimplantation genetic diagnosis in the management of severe rhesus alloimmunization

***Dr. Dipanjana Datta**, PhD , PDF (USA) , BGCI- Level II Certified Consultant , Genetic Counselor*
Institute of Child Health , Kolkata, Renew Healthcare , Kolkata,
Institute of fetal medicine , Kolkata, Apollo Multispeciallty Hospitals, Kolkata ,
Organization of Rare Disease IndiA, Bangalore

Introduction :

Rhesus (Rh) D alloimmunization manifesting in haemolytic disease of the fetus and newborn has the potential to cause perinatal morbidity, mortality and long-term disability. An RhD-negative woman may develop anti-D antibodies when exposed to an RhD-positive fetus during or after pregnancy. Although various red cell antigens have been implicated in haemolytic disease of the newborn, RhD antigen is the most common and immunogenic . As a result of red blood cell destruction, the fetus develops haemolytic anaemia, which, when severe, leads to hydrops fetalis, intrauterine fetal demise or both.

The Rh blood group system is highly polymorphic, consisting of ≥45 independent antigens. D antigen expression is by the RhD protein while the RhCE protein expresses either C or c antigens together with E or e antigens on the same protein . Although the RhD and RhCE proteins have a high degree of homology, the RhD protein does not express C/c or E/e antigens and the RhCE protein does not express the D antigen.

The RhD and RhCE proteins are encoded by two highly homologous genes, RHD and RHCE respectively, which have been mapped to chromosomal position 1p34.3–1p36.13 . The two genes are each composed of 10 exons that in tandem encompass 69 kilobases of DNA . The gene that encodes the D polypeptide is present in Rh-positive persons and is absent in Rh-negative subjects.

Should a woman become sensitized in her first pregnancy, all subsequent RhD-positive babies will be at risk of haemolytic disease of the fetus and newborn. A fetus has a 50% chance of being heterozygous Rh positive and a 50% chance of being Rh negative if an Rh-negative woman becomes pregnant to a heterozygous Rh-positive father. In the latter case the fetus will avoid any potential adverse sequelae from maternal RhD alloimmunization.

Severe RhD alloimmunization is uncommonly encountered today largely due to the development of anti-D immunoglobulin and its utilization in clinical practice. Antepartum and postpartum prophylaxis with anti-D immunoglobulin are recommended . In spite of the clear reduction in affected women with anti-D's availability and utilization, RhD alloimmunization still occurs. In these sensitized women, Rh haemolytic disease will continue to be a significant problem and for their babies who are affected.

In women who have suffered repeated pregnancy losses, invasive interventions such as serial intrauterine blood transfusions or an affected fetus or neonate, the prospect of having another affected pregnancy with all its complications may seem too great. In such women, rather than risk having another baby with haemolytic disease of the newborn, they may opt to avoid further pregnancies. Even with close monitoring of sensitized pregnant women for the early detection of fetal anaemia and the instituting of intrauterine transfusion at the appropriate time, there is a significant degree of fetal mortality . Although the risk of fetal death from cordocentesis is relatively low, procedure-related fetal loss has been documented . The procedures are also associated with the risk of potentially increasing maternal RhD antibody production through secondary feto-maternal haemorrhage.

Prevention of an affected fetus in future pregnancies : Indications for PGT for management of severe RH alloimmunization :

Each subsequent pregnancy after the first affected pregnancy is likely to manifest more severe hemolytic disease of the fetus and newborn, and at an earlier gestational age. Hemolytic disease of the fetus and newborn can be prevented by avoiding conception of a Rh(D)-positive fetus. Prevention is rarely attempted because of the costs and complexities involved and because hemolytic disease of the fetus and newborn can be treated successfully in most cases. An Rh(D)-positive fetus can be avoided in the following ways:

- In vitro fertilization (IVF) with preimplantation genetic diagnosis – If the potential biologic father is heterozygous for RHD, IVF with preimplantation genetic diagnosis can be used to identify RHD-negative embryos and only these embryos are considered for embryo transfer
- Use of a gestational surrogate – If the potential biologic father is homozygous for RHD, the intended parents can conceive by IVF and the embryo can be carried by a gestational surrogate who is not alloimmunized.
- Use of donor sperm – Sperm from a Rh(D)-negative donor can be used for intrauterine insemination of the alloimmunized mother

PGT was designed for the prevention of genetic disorders in the offspring of couples at increased risk. Since its introduction in 1990, PGT has been mainly used for detection of single-gene disorders such as cystic fibrosis or for screening of chromosomal disorders . More recently, use of PGT for social sexing and HLA matching has been reported in foreign countries. The ethics of such use is beyond the scope of this paper and will not be discussed.

Case Study : Methodology

PGT necessarily involves IVF. After IVF, the early embryo is screened for the disorder before the corresponding embryo is transferred into the uterus of the mother. In Rh disease this allows the transfer of Rh-negative embryos back into the RhD-alloimmunized mother, avoiding the potential complications and morbidity of haemolytic disease of the fetus and newborn.

Though theoretically this is possible, ethically or practically this is not common. Until date, there is only a few case reports for such a procedure have been published

In the case study published by Seeho et al , a couple with a history of severe rhesus alloimmunization underwent preimplantation genetic diagnosis (PGD) during in vitro fertilization (IVF) to prevent hemolytic disease of the fetus and newborn (HDFN) in future pregnancies. PGD involved the selection of RhD-negative embryos using multiplex PCR and STR loci to distinguish between RhD-positive and RhD-negative embryos. Multiplex PCR, using oligonucleotide primers targeting the RHD and RHCE genes, was utilized to distinguish between RhD-positive and RhD-negative embryos. Out of 12 fertilized embryos, two RhD-negative embryos were transferred, resulting in a successful pregnancy without complications. Regular monitoring ensured the fetus remained healthy, and the baby was born RhD negative, affirming the effectiveness of PGD in preventing HDFN. (Human Reproduction, Volume 20, Issue 3, 1 March 2005, Pages 697–701,)

In another case series published in November 2003, in Fertility and Sterility by Yury Velinsky et al , two couples with a history of neonatal death due to hemolytic disease of the newborn (HDN) caused by the K1/K2 genotype in the male partner. Preimplantation genetic diagnosis (PGD) was utilized to identify embryos without the K1 allele for transfer, aiming to prevent HDN in subsequent pregnancies. Single blastomere biopsy and testing were performed after standard in vitro fertilization (IVF). Of the 36 embryos tested across five cycles, 18 were predicted to be K1 allele-free. Nine of these embryos were transferred, resulting in a twin pregnancy, and the birth of two healthy children without the K1 allele. This successful outcome demonstrates that PGD offers a viable option for couples with a heterozygous K1/K2 male partner to avoid HDN in sensitized mothers. (November 2003, Fertility and Sterility 80(4):1047-51)

Conclusion

PGD necessarily involves assisted reproductive techniques where ovarian stimulation and IVF are required to produce in vitro several embryos in order to select unaffected ones for transfer. This means that even couples that are fertile must undergo the processes of assisted reproduction. There are also the financial costs associated with IVF and PGD to consider. However, the economic cost for follow-up and treatment of a typical pregnancy and newborn affected by severe RhD is not inconsiderable together with the psychological and physical burden.

This case demonstrates that PGD can be used to determine the RhD status of early cleavage-stage embryos by single cell analysis. This permits selective transfer of only RhD-negative embryos, avoiding the development of haemolytic disease in the fetus. Although at-risk pregnancies detected by prenatal diagnosis may be treated by intrauterine transfusion, potential complications including fetal death cannot always be completely prevented even after this procedure. Pregnancy termination may also be unacceptable to the couple. In fact, genetic risk and objection to termination of pregnancy are still the most important reasons for couples seeking PGD, with about one-quarter of couples having one or more affected children . PGD may be seen as a preventative treatment measure in couples affected by RhD alloimmunization and a male Rh-positive heterozygote.

Reference :

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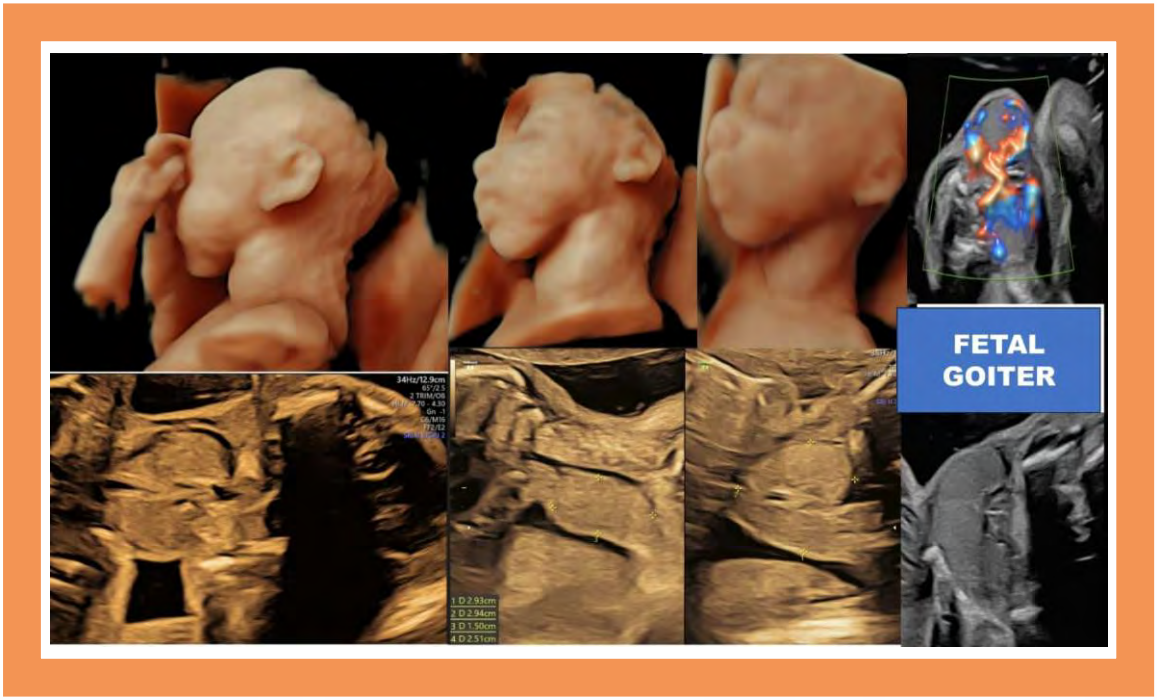
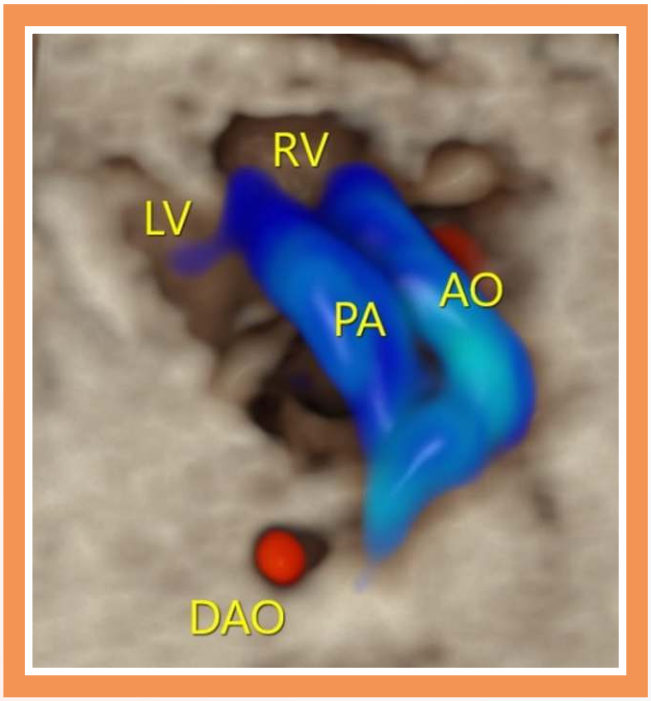
Judges- Dr. Shankar Dey & Dr. Prasanna Roy

Fetal Goitre



1st Prize Image
Dr. Dhaval Patel

Double outlet right ventricle shown on colour STIC in a 22 weeks fetus



2nd Prize Image
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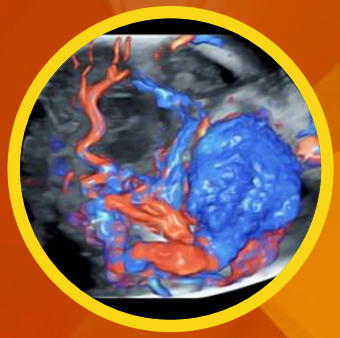

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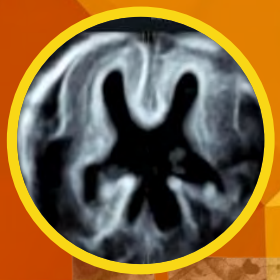

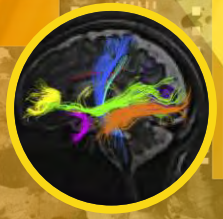

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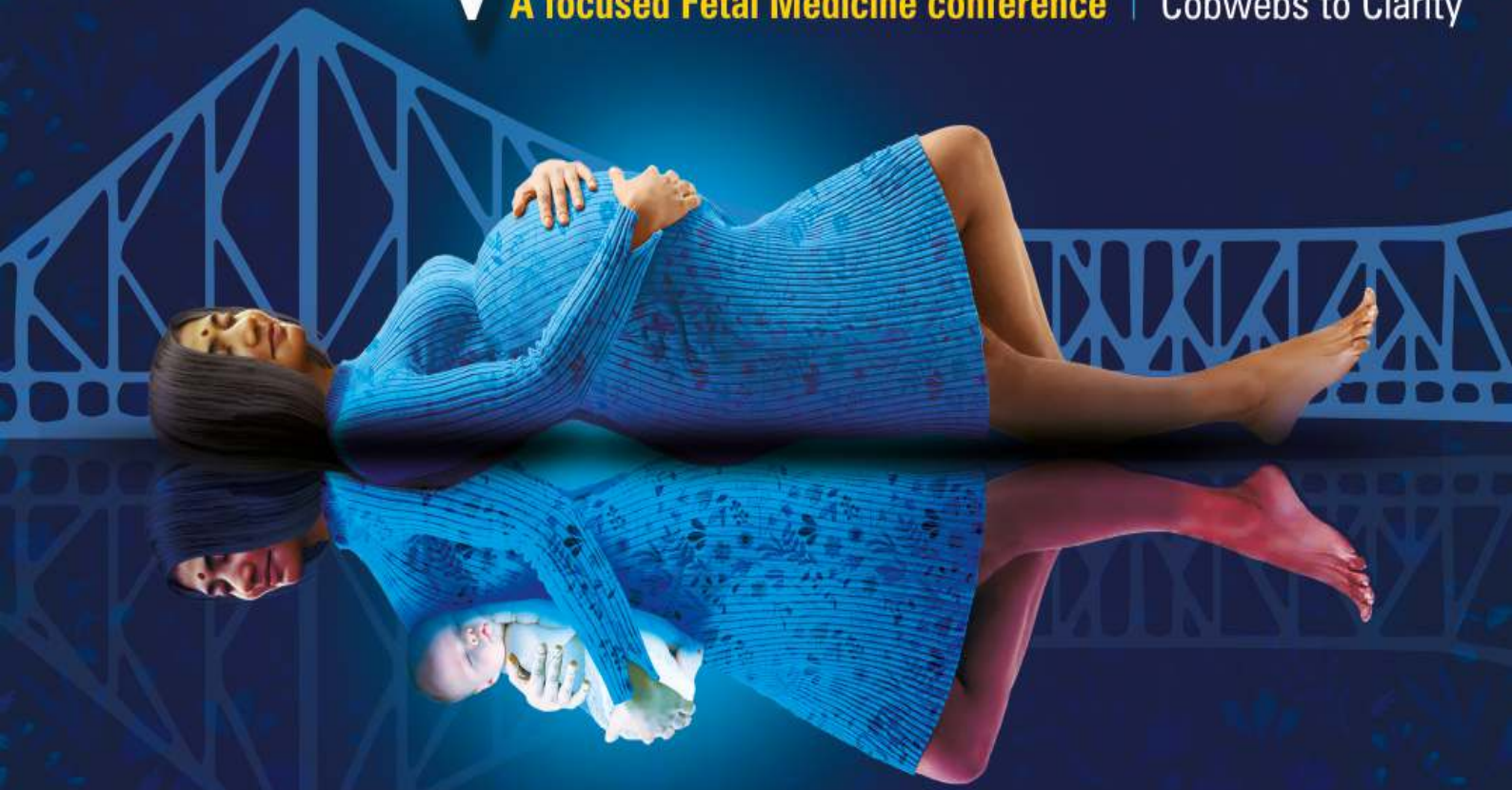

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