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REVIEW ARTICLE

MANAGEMENT OF FETAL ANEMIA AND THROMBOCYTOPENIA WITH INTRAUTERINE BLOOD TRANSFUSION

Mr. Rohan Pal[1], Ms. Nidhi Shree[2], Mr. Snehasis Jana[2], Mr. Arunava Mishra[2], Ms. Alka Kumari[2] and Dr. Arin Bhattacharjee[3]

1. Assistant Professor, Department of Pharmacology, Global College of Pharmaceutical Technology, Krishnanagar, West Bengal.
2. Under Graduate Student, Global College of Pharmaceutical Technology, Krishnanagar, West Bengal.
3. Principal, Global College of Pharmaceutical Technology, Krishnanagar, West Bengal.

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Abstract

Fetal anemia and fetal thrombocytopenia are two of the most unsmiling complications in pregnant women, and they can lead to perinatal mortality and morbidity. After long years of study with intravascular intrauterine blood transfusion, a number of varieties of implications have been described. Intrauterine Blood Transfusion (IUBT) is considered the best method in the case of fetal anemia because it is caused by red cell alloimmunization. Not only for red blood cell transfusion, this method can also be used for the transfusion of platelets to thrombocytopenic fetuses in pregnant women. It is generally detected after a child is born who is symptomatic and shows signs of bleeding in the brain and skin. The biggest milestone for the clinician is to give preventive treatment in next pregnancy. Pregnancies at risk require serial monitoring, and Fetal Middle Cerebral arterial (MCA) Doppler is the non-invasive test that is now proving to be the choice for monitoring. IVIG (Intravenous immunoglobulin) is used to manage severe Rh-immunization and is now showing promising effects. Indications like Parvovirus B19, Fetomaternal hemorrhage (FMH), Fetal SacrococcygealTeratoma (SCT), Twin-twin transfusion syndrome, placental chorioangioma diseases, or other infections can be treated with this method. This review covers fetal transfusion techniques and explores current management of fetal anemia and thrombocytopenia.

Introduction:-

Fetal anemia

Fetal anemia is additionally referred to as fetal red cell hemolysis, which happens when placental diffusion of maternal immunoglobulin G, i.e., (IgG) is increased against a given fetal red cell antigen. Rhesus (Rh) alloimmunization, kellalloimmunization, and parvovirus infections are the major causes of this condition[1].

Corresponding Author:- Mr. Rohan Pal
Address:- Assistant Professor, Department of Pharmacology, Global College of Pharmaceutical Technology, Krishnanagar, West Bengal.

Fetal thrombocytopenia

Fetal thrombocytopenia is a condition in which the platelet count of fetuses gets low because the mother produces an antibody-mediated response against a platelet specific antigen present in the fetus and can cause bleeding leading to intracranial hemorrhage in the fetuses, i.e., a rare but life-threatening state. Conditions like viral infections, immunological disorders, and rare genetic syndromes can be the causes of this disease, which leads to unbidden intrauterine bleeding in fetuses with low platelet counts[2].

Intrauterine Fetal Blood Transfusion: a success

Anemia in fetuses is one the common reason of perinatal mortality in western world. Before the technique like amniocentesis and ultrasonography introduced, the diagnosis on suspected women depended on various non-specific signs like slow movement of fetus in the womb and large for-date uterus with antecedent contrived child. In 1960s, William lily introduced a percutaneous intraperitoneal transfusion with the guidance of x-ray. This method, when paired with amniotic fluid examination for bilirubin levels and the Lileys chart, has saved many lives. However, Hydropic fetuses did not efficiently absorb the transfused blood from the peritoneal cavity[3]. In 1980s, a great scientist named Rodeck et al. described a new technique called intrauterine blood transfusion into the umbilical cord using fetoscopy[4]. Jens Bang et al. in Denmark and FernandDaffos et al. in France were the first to use ultrasound guidance to collect fetal blood. Ultrasound-guided needle insertion in the umbilical vein has been the conventional approach for fetal transfusion since the mid-1980s, and it has yet to be improved[5, 6]. This procedure has been researched in many pregnant women and the efficacy and success rate were very high; the data given by the terribly biggest Single-Centre Cohort study by Van Kamp et al.[7]. Because fetal anemia is induced by red cell alloimmunization, intrauterine blood transfusion (IUBT) is regarded the best treatment option. This procedure can be used to donate platelets to thrombocytopenic fetuses in pregnant women, in addition to red blood cell transfusion.

Pathophysiology:-

Red Blood Cell Alloimmunization

When there is exposure between maternal and foreign RBC surface antigens, an antibody is made referred to as IgM and IgG. Because of lower molecular weight of IgG antibody i.e, (160,000) it crosses the placenta and cause damage to fetal RBCs leading to fetal anemia[8]. Further medullary biological process leads to hepatosplenomegaly, malignant hypertension, tissue hypoxia, hypoproteinemia, and erythroblastosis fetalis[9]. In Rh system, RBC antigen comprises of three pairs of antigen i.e., Cc, Dd and Ee. Attributable to no proof of D antigen, individual with D antigen are diagrammatic as Rh (D) negative. In Paternal Rh genotype (homozygous-DD and heterozygous- Dd), the haplotype combination is feasible and thus the possiblility of fetal phenotype. The antigens aside from D are referred as atypical antigens that are presently inflicting only (10-15) % of cases of alloimmunization. Blood transfusion cross-matched with ABO and D are the main reason behind it. Antigens D, c Kell, and E induce more serious fetal anemia[10].

Fetal Thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is meant to the platelet equivalent of anemic disease of newborn. Yet, in compare to red blood cell alloimmunization, FNAIT happens in first pregnancy in almost 50% of cases[11]. In first trimester of pregnancy, Human Platelet Antigen (HPA) are expressed on fetal platelets. And when mother produces HPA antibodies, the IgG antibodies crosses the placenta and causes platelet destruction. Clinical symptoms are seen when platelet count drop to 50 or even below of it i.e, 30 x109/L. The major complication in fetuses having low platelet count is intracranial hemorrhage (ICH) and can further lead to severe neurologic impairment.

Aims of intrauterine transfusion:-

The main aims of intrauterine transfusion are as follows:

1. To improve fetal tissue oxygenation by restoring traditional hemoprotein, thereby preventing fetal edema.
2. To suppress fetal erythropoiesis through the infusion of fresh, densely packed, infection screened, O negative adult donor red cells.
3. To permit delivery of a healthy child at a mature gestation period, i.e., > 36 weeks.

Methods of intrauterine blood transfusion:-

The supervisors

A senior specialist in fetal medicine with experience in the processes of amniocentesis and chorionic villus biopsy uses an ultrasound-guided needle in the amniotic cavity, umbilical cord, or fetal part for the procedure. Operators

attach a needle guide, interpreting smaller gauge-needle, less time of process, and a lower likelihood of fetomaternal hemorrhage[12].

In several different centers, a single operator operates with the assistance of another sonographer. Before any surgical procedure, the area of operation must be cleaned. Equipment like surgical gloves, gowns, and drapes is needed to prevent the cause of unnecessary contamination. Oral sedatives like anxiolytics or parenteral/anti-emetic mixtures for mothers are advantageous if given an hour earlier. Local anaesthetics are infused into the skin to make it more endurable and help the operator align the needle[13].

Healer of fetal pain and fetal paralysis

To circumvent fetal pain and fetal stress, fentanyl is administered to the fetus through the intrahepatic vein[14]. Throughout the method, fetal movements can give rise to needle displacement and hematomas, leading to the consequences of bleeding. For example, with Vecuronium (0.1 mg/kg) or Pancuronium (0.1-0.3 mg/kg), a fetal neuromuscular blocker is given, which shows its action for about 40–50 minutes to achieve fetal paralysis[15, 16].

Intrahepatic vein is more preferred than umbilical cord transfusion

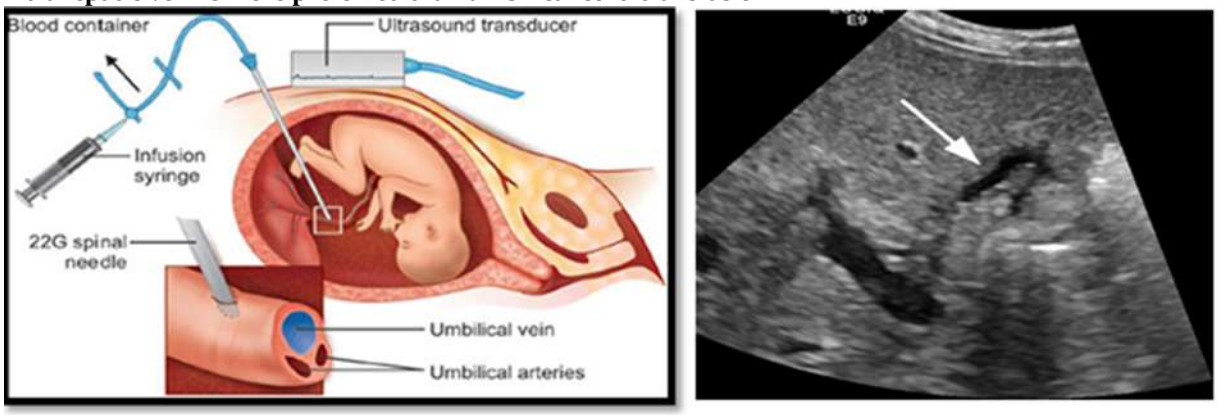


Figure 1: Process of umbilical transfusion and ultrasound of intrahepatic transfusion

There are many possible ways and location through which transfusion can occur, because of its stability, umbilical cord is area of choice for transfusion (Fig. 1) but when root is not clearly seen other technique is utilized. This situation arises when there is an overlying fetus barricades a lack of amniotic fluid, or posterior cord insertion, or if the mother is obese, or there is oligohydramnios. Transfusion through the intrahepatic vein (IHV) is preferable to cord insertion[17].

Visibility of IHV is less difficult in sampling situations, and it provides an alternative to several attempts at cord root, and it does not allow cord tamponade. The intrahepatic vein is used for more than half of all intravascular transfusions[18].

Fetal bradycardia can cause a higher complication risk in umbilical artery transfusion because the artery is much smaller in diameter than the vein, which leads to the spasm and hence is dangerous to incorporate[19]. Hemopericardium, cardiac tamponade, and cardiac arrhythmia, including asystole, can occur due to cardiac puncture, and it can be used as the "last resort" in early gestation[20].

Intravascular or Intraperitoneal transfusion approach

Intravascular transfusion (IVT) is nowadays more applicable than intraperitoneal transfusion (IPT) because the results of IVT are preferable in all regards[21]. All decisions regarding transfusion and delivery can be taken on the premise of the blood type of the fetus, hemoglobin-hematocrit ratio (Hb/Hct), and different RBC parameters. Results of IVT are better in hydropic fetus, because of less fetal breathing movement than in those who cannot take blood from their peritoneal cavity[22]. But in some cases, like in the very early gestation period or in non-hydropic fetuses, intraperitoneal transfusion is still required where intravascular transfusion is very difficult10. Especially in hydropic fetuses, to avoid fluid overload; IVT was initiated as an exchange transfusion process. But as we know, if something

has some benefits, then it definitely has some kind of drawback also. The drawback of exchange transfusion is that it takes more hours of time to complete, hence leading to greater risks in the procedure[23].

Selection of donor's blood

O negative blood from an unrelated donor is primarily needed for the intrauterine transfusion. Before transfusing, it is cross-matched with the mother's blood, and looked for any symptoms of hepatitis B and C, cytomegalovirus, and HIV. The WBCs are removed to neglect the risk of graft versus host like complications and are loaded to a hematocrit of 75–85%. To donate the blood, many parents put their preferences in order to use the maternal self-blood because, theoretically, it is proven that the mother's blood is a good source for donation as it lowers the risk of sensitization to new red cell antigen. Until 33 weeks of gestation, this study does not show any difference in the decline rate of RBCs[24].

Exchange and top-up transfusion

Transfusion of blood straight to the fetus without removing blood (top-up process) from it has been a larger concern because it can lead to volume overload and cardiac problems. Blood is collected from the fetus at regular intervals to prevent hypervolemia[25] (exchange transfusion). Monitoring of umbilical venous pressure is required continuously because if the pressure level rises by 10 mmHg, then blood must be removed and exchanged with the same volume of saline. For more than 20 years, top-up transfusion has been in practice now, having the least chance of any adverse effect[26].

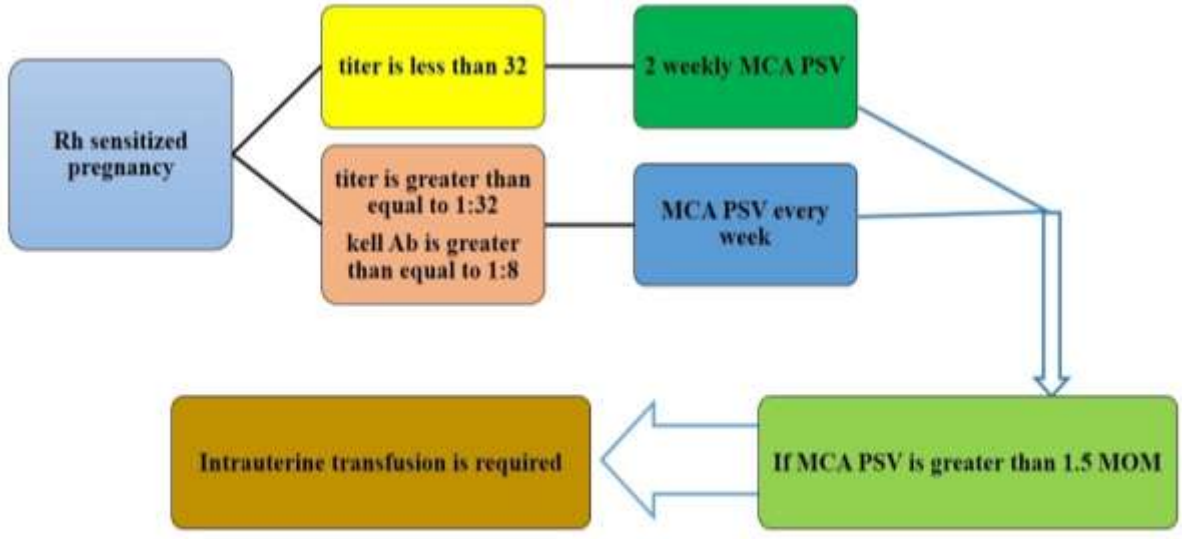
When to transfuse:-

Matter of time

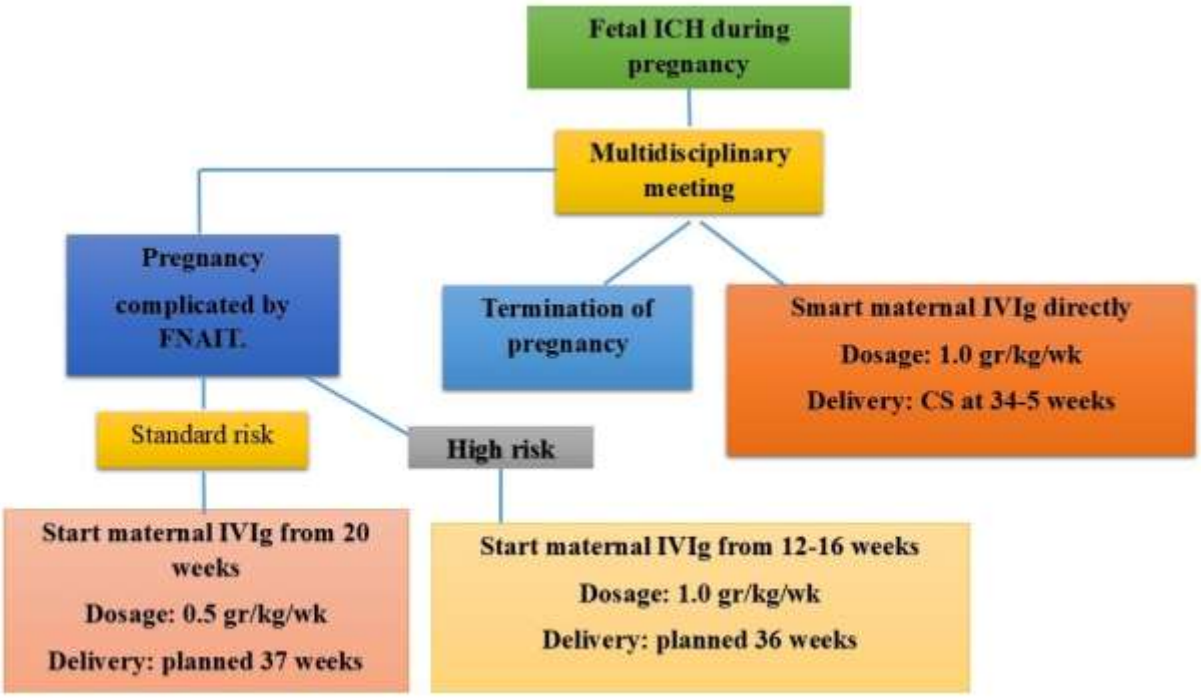
The main aim is to transfuse only when there is a chance of moderate to severe anemia, before the fetus is caught in hydrops. Hence, the chances of survival after intrauterine transfusion in hydropicfoetuses are generally lower than in non-hydropic fetuses[27].

Use of ultrasound and Doppler in Antenatal management of fetal anemia

During the process of transfusion, at the tip of the needle, there must be some turbulence within the vessel and it should be visible. The image of the fetus must be seen continuously and should be checked regularly by handling the transducer[28]. Severe anemia can lead to a rise in cardiac output and a fall in blood viscosity. This can increase systolic flow velocity. From approx. 16 weeks onward, there is a sequence analysis of the middle cerebral artery peak systolic velocity (MCA-PSV) of the Rh-sensitized mother or the anemic fetus[29]. Therefore, for the identification of fetal anemia, in the present scenario, non-invasive monitoring with fetal MCA doppler peak systolic velocity is accepted[30]. When the level of antibody goes to 15 IU/ml, then the patient must be referred for regular follow-up with a fetal medicine specialist until the antibody level goes to 10 IU/ml[31, 32, 33.]



Flow chart 1: Antenatal management in fetal anemia



Flow chart 2: Antenatal management in fetal thrombocytopenia

In mothers who are not sensitized, check-ups are done as per general antenatal scans or 4-weekly; but in sensitized mothers the check-ups are done in-depth and are based on a 2-weekly calculation of MCA PSV. To get the gestational age, PSV must be changed to the multiple of the median (MOM). The red alert moment occurs when the fetus reaches 1.5 MOM, and we must transfuse during this time[34, 35] (flow chart 1).

Antenatal management in fetal thrombocytopenia:-

Intrauterine transfusion

The Intracranial Hemorrhage (ICH) in fetal and neonatal alloimmune thrombocytopenia (FNAIT) happens mainly during pregnancy[36]. So, to decrease the chance of ICH and severe thrombocytopenia, intrauterine platelet transfusions and fetal blood sampling (FBS) were the only solutions. In the year 1980, intrauterine intravascular, ultrasound guided RBC transfusion was introduced. Daffos and his team were the first to introduce this approach on FNAIT. There is a distinction between intrauterine RBC transfusion in fetal anemia and platelet transfusion in fetal thrombocytopenia. FNAIT cause bleeding to the fetus so puncture of umbilical cord is very dangerous, and the half-life of platelet to be transfused is terribly short[37].

Administration of maternal Intravenous immunoglobulins (IVIg)

IVIg was employed in the past year for maternal idiopathic thrombocytopenic purpura (ITP). In the year 1988, a scientist named Bussel came up with a positive conclusion for antenatal maternal IVIg treatment in pregnancy with fetal and neonatal alloimmune thrombocytopenia. It is made from human IgG antibodies and is extracted from human donor blood. The mechanisms which are answerable for their impact are summarized by Wabnitza H et al.[38.]

Treatment based on obstetric medical history is more reliable when a clinical or biochemical marker is absent to predict the platelet count. FNAIT is classified into two categories: high risk and standard risk. High risks are considered when a child has been affected by ICH or hemorrhage in previous gestation, while standard risks are considered when a child or siblings have been affected by FNAIT without ICH in gestation. High-risk pregnancy can be treated with maternal IVIg weekly from 12–16 gestational weeks at a dose of 1 g/kg/week[39](flow chart 2).

In conclusion, it is found that invasive interference has additional complications compared to invasive antenatal management. Hence, the first line of treatment, i.e., maternal IVIg administration, is used as antenatal management in FNAIT[40].

Corticosteroids

Corticosteroids are added to maternal IVIg treatment in some centers. However, the evidence of its use is very fragile and its side effects cannot be ignored. Winkelhorst et al. worked on 11 cases in which they compared IVIg transfusion with or without corticosteroids. In this study, positive effects were found in only one case. Hence, corticosteroids should not be the first line of treatment in FNAIT[41].

Timing and mode of delivery

To minimize the risk of bleeding, peripartum management is focused on several factors. Elective cesarean delivery is still a selective mode of delivery in some places. According to the cohort study, there is an interpretation that CS delivery can cause ICH in FNAIT. In that study, it was found that of approximately 200 cases, 17 FNAIT cases were connected with ICH, which occurs within 24 hours after birth. The exact timing of getting ICH was not certain. So, because of a lack of evidence, in FNAIT cases, CS should not be performed routinely[42].

Future prospectives of treatment

In murine models that have been proven to be efficacious, the cure of RhD via immunoprophylaxis, as well as the formation of FNAIT, have been demonstrated[43]. There is no proof of any clinical trials in humans yet confirmed. One of the future prospects must be an FcRn receptor blocker, which inhibits the transfer of alloantibodies across the placenta. Preclinical research yielded promising results[44].

Long term outcome of treatment with intrauterine transfusion:-

Neurodevelopmental outcome

Many teams have done studies in this regard, with follow up ranging from 6 months to 6 years[42]. Hudon et al. conducted a neurodevelopmental outcome study on 33 infants.In this study, one child was found to be affected by right spastic hemiplegia and one child had bilateral deafness. In both cases, the developmental scores were in the average range, i.e., for the Gesell scale (n = 22, 9-18 months) and for the McCarthy Scale (n = 11, 36-62 months) was found and there was no sign of fetal hydrops[44].

Almost in 18 hydropic fetuses Harper et al. done a study on long term outcome treated with IUT. In 4 out of 18 infants' deaths or major NDI (neurodevelopmental impairment) occurred, i.e. 22%, in 2 out of 16 they had neurological sequelae, i.e. 12%, and in 6 out of 16 they had neurological impairment, i.e. 38%[45].

Cardiovascular outcome

Oberhoffer et al. assessed a study in which fetal cardiac changes were linked with alloimmune anemia with the help of echocardiography. 30 anemic fetuses received 76 IUTs. The thickness of the end diastolic myocardial wall and the dimensions of the ventricle with the pattern of Doppler flow were measured before the procedure. Symmetrical myocardial hypertrophy was seen in those anemic fetuses[46].

In 10 newborns, sonograms were performed in the first 48 hours, in which 5 patients were found to be affected by disproportionate septal hypertrophy. Fetuses who did not get IUTs had a greater septal left ventricular free wall ratio than foetuses after treatment. With the help of echocardiography, only one study assessed the cardiac function of patients who received intrauterine transfusion for alloimmune anemia. This roughly calculates the cardiac structure and function, allowing us to know the effects of anemia and hypoxia on the fetal heart[47].

Complication of IUTs:-

Acute Procedure-Related Complications

Fetal distress is a serious complication during or after the procedure, and it can cause fetal death, premature baby delivery, or neonatal asphyxia. It can happen if there is an accident in the local cord, such as a rupture, spasm, excessive bleeding, or obstruction from a hematoma, chorioamnionitis, or another condition. Fetal demise after IUT can also be the consequence of the compromised fetal state[48, 49,50,51,52].

Long term complications

For the first six months after birth, neonates are treated with IUT, which needs more top-up transfusion, and it can explain the superposition of fetal erythropoiesis[53, 54]. Anaphylactic shocks and viral disease transmission can be seen within RBC donor transfusions, which is at a minimum, but it has theoretical complications.

Intrauterine transfusion and transplacental puncture are linked to the development of new red cell antibodies[55]. FMH after IUT can also form additional antibodies. These extra antibodies can complicate the selection of compatible RBC for mother and fetal transfusions. In addition, these antibodies help in delaying hemolytic transfusion shocks[56].

Indications of IUTs:-

Parvovirus B19 infection

Because of the involvement of erythroid lineage cells, Parvovirus B19, which is an inhibitor of hematopoiesis can cause bone marrow damage. Mortality and morbidity of the fetus (1-2%) can happen when vertical transmission takes place in pregnancies (30–50%) infected by Parvovirus B19. In ultrasonography, signs of fetal anemia can be seen in a patient littered by Parvovirus B19. IUT can treat fetal anemia and reduce the risk of fetal mortality if started early enough[57].

Fetal thrombocytopenia can be treated by intrauterine platelet transfusion, although the complication of fluid overload in hydropic fetuses must be weighed against the low incidence of bleeding in fetuses[58]. The survival rate of perinatal ranges from 67–73% after treatment. However, in hydropic fetuses, there is a chance of neurological damage; hence, IUTs are done just before the hydrops develop[59, 60, 61, 62.]

Fetomaternal hemorrhage (FMH)

FMH stands for fetal-maternal blood movement. Fatal FMH can lead to fetal anemia, fetal distress, hydrops, hypovolemic shocks, or death. To detect the volume of hemorrhage, Kleihauer test is done and to evaluate the fetal flow velocity (MCA PSV), the Doppler test is done to find the fetal anemia which can help in disease management[63]. So, IUT can help in extending the gestation period until the perfect gestation period comes around, which helps in correcting fetal anemia. Perinatal death varies between 31 and 50%[63, 64, 65.]

Twin-twin transfusion syndrome

Fetofetal transfusion in monochorionic twin pregnancies because of the transmitting vascular anastomoses, can cause fetal anemia of twin donor and polycythemia in recipient i.e. TAPS[66] (twin anemia polycythemia sequence). In Monochorionic twin pregnancy, TAPS occur in 3-5% and up to 13 cases of twin-twin transfusion syndrome is handled with laser surgery. TAPS can be maintained using a variety of methods, including IUT and elective delivery. IUT treatment can help in rectifying the donor twin's anemia, but it can also worsen the plethoric twin's condition[67, 68].

Placental chorioangioma

Placental chorioangioma means vascular neoplasm of the placenta and happens in approximately 1% of pregnancies. As several tumors are unknown and asymptomatic, large chorioangiomas can cause fetal anemia, hydrops, as well as fetal death. FMH can cause fetal anemia and hemolysis can occur because of destruction of fetal RBCs in the vascular network of a chorioangioma. As a result, using IUT to treat the fetus can help to improve the fetal status and prevent preterm birth[69].

Fetal sacrococcygealteratoma

Fetal sacrococcygealteratoma (SCT) is a congenital tumor in baby's coccyx that can happen in fetal anemia and can cause hemorrhage or hemolysis within the tumor. Wee et al. showed a fetus having fetal anemia associated with sacrococcygealteratoma. The affected fetuses got 3 IUTS, but unfortunately, the death of the neonate after the birth happened[70].

Conclusion:-

Fetal anemia and FNAIT have been a severe burden. IUT is taken into account as a safe methodology to treat its severity. Antenatal and non-invasive management methods of treatment are today proving to be the most effective and well-liked management. MCA Doppler technology has been a great help in treating fetal anemia. Regardless of the aetiology of fetal anemia, surveillance of at-risk pregnancies, the major aim is to predict the anemia before the onset of fetal hydrops. In this respect, knowledgeable and skilled professionals are needed to perform the operation. In FNAIT, which is at high risk. IVIg treatment should be initiated at 12–18 weeks of gestation with a high dose of FNAIT with standard risk, it should be initiated at 20–28 weeks. Further studies are required to deal with the long-term neurodevelopmental outcome and its natural history. Antenatal screening can help in reducing the risk of this severe malady.

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