SFM Fetal Therapy Practice Guidelines: Intrauterine Blood Transfusion

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Abstract

Despite routine antenatal anti-D prophylaxis with immunoglobulin, Rh alloimmunization and hemolytic disease of the fetus and newborn continue to occur due to a myriad of reasons. Intrauterine intravascular transfusion (IUT) or fetal blood transfusion is a therapeutic prenatal procedure in which specifically prepared and treated unit of donor red blood cells is injected intravascularly into the umbilical vein under ultrasound guidance. Originally introduced in the year 1963, it continues to be the standard treatment for severe fetal anemia. The objective of this guideline is to provide an evidence-based update of IUT for the perinatal healthcare providers.

Keywords
- ICT
- intrauterine transfusion
- MCA PSV
- Rh D alloimmunization

Introduction

Intrauterine intravascular transfusion (IUT) or fetal blood transfusion is a therapeutic prenatal procedure in which a specifically prepared and treated donor red blood cells (RBC) are injected intravascularly into the umbilical vein under ultrasound guidance.[1] Originally introduced in the year 1963, it continues to be the standard treatment for severe fetal anemia.[2] With a better understanding of the immune and nonimmune mechanisms of fetal anemia and the advent of high-resolution ultrasound, there has been a profound change in the technique and protocol of IUT.

Despite routine antenatal anti-D prophylaxis with immunoglobulin, Rh alloimmunization and hemolytic disease of the fetus and newborn (HDFN) continue to occur due to a myriad of reasons outlined below.

Reasons for RBC alloimmunization in the current obstetric practice
- § Unrecognized fetomaternal hemorrhage events
- § Inadequate dosing, unavailability of Kleihauer Betke test
- § Missed prophylaxis
- § Poor patient compliance
- § Inadequate cold chain maintenance
- § Improper technique of administration of anti-D
- § Absence of prophylaxis for other RBC antigens
- § Omission of Kell typing for blood transfusion in women of childbearing age

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Indication

IUT is the standard therapeutic procedure for the treatment of fetal anemia.[2] The various clinical definitions of fetal anemia are outlined below.[3]

Definitions of fetal anemia

Type	Severity		
A. Hematological			
1. Hb deviation from GA mean	**Mild**	**Moderate**	**Severe**
	< 2 g/dL	2–7 g/dL	> 7 g/dL
2. Hb values expressed as MoM	0.86–0.65	0.64–0.55	≤ 0.54
3. Hematocrit	< 30 %		
B. Ultrasound			
MCA PSV	1.3–< 1.5 MoM	≥ 1.5 MoM	
	Mild anemia	Moderate-to-severe anemia	

Measurement of MCA PSV

Sonographically, moderate-to-severe fetal anemia is present when the fetal middle cerebral artery (MCA) peak systolic velocity (PSV) exceeds 1.5 multiples of the median (MoM) between 18 and 35 gestational weeks.[4,5] The MCA PSV has a sensitivity of 86% and a specificity of 71% for the diagnosis of fetal anemia. The fetal hemoglobin (Hb) is typically less than 10 g/dL or the hematocrit is less than 30% at this level of the MCA PSV. Fetal hydrops usually set in as the Hb concentration falls below 6 to 7 g/dL below the mean for the gestational age.[6]

►**Fig. 1** outlines the ultrasound technique for the measurement of MCA PSV.

Fetal anemia may be caused by:

A. Immune mechanisms

The most common indication for performing IUT is HDFN. This occurs when the mother lacks specific RBC antigen (s) and therefore mounts an antibody response against such antigens of the fetal RBC when it enters her blood circulation. The maternal red cell immunoglobulin G antibodies cross the placenta causing extravascular hemolysis of the fetal RBCs. More than 50 red cell antigens have been associated with HDFN. The most prevalent red cell antibodies are Rhesus (Rh)

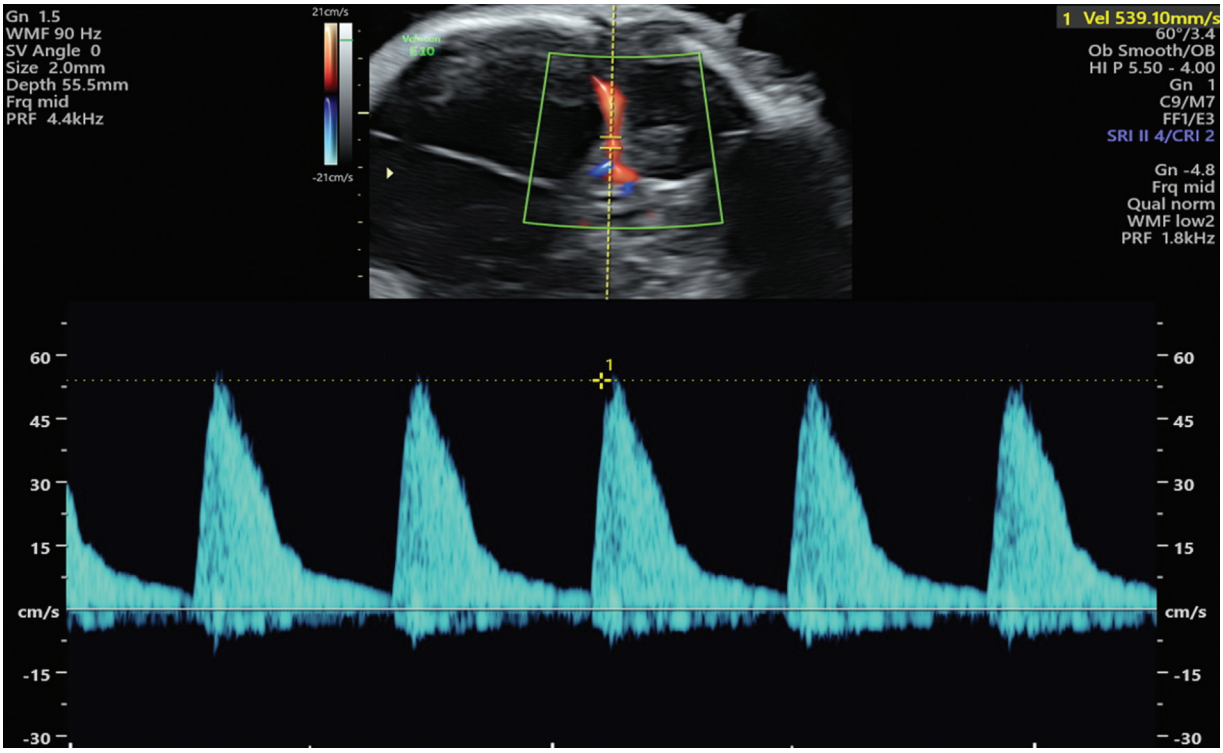

Fig. 1 Spectral Doppler of MCA in a fetus with severe HDFN. This image demonstrates the technique for measuring the MCA PSV. For the objective of assessing fetal anemia, MCA PSV is assessed between 18 and 35 weeks of gestation. The axial image of fetal brain is insonated with color Doppler and the circle of Willis is demonstrated. A pulsed Doppler gate of width 2 mm is placed at the proximal 2 cm of the MCA from its origin. The chief prerequisites to be observed are maternal and fetal quiescence, avoiding undue pressure with transducer and maintaining an insonation angle of 0 degree ideally (always < 20 degree). Three measurements under ideal condition are documented. HDFN, hemolytic disease of newborn; MCA, middle cerebral artery; PSV, peak systolic velocity.

D, Kell, and Rh c.[7] Other antibodies associated with severe HDFN are anti-Rh-e/E (Rhesus), Fy(a)/Fy(b) (Duffy blood group), Kidd (Jka), and anti-M (MNS system).

The commonest scenario of red cell alloimmunization is seen in an Rh D negative mother with a Rh D positive partner.[8] Due to prior sensitization with fetal Rh D positive RBCs, an antibody response ensues. The first pregnancy or the sensitizing pregnancy usually escapes from HDFN. However, future pregnancies are at risk of HDFN. In such a woman, the serum anti-Rh D Ig measured via indirect Coombs test (ICT) is usually above the critical level of 1:16.

The surveillance strategy for Rh D incompatible and sensitized pregnancies is outlined below.

Rh D alloimmunization surveillance protocol

§ All pregnancies with maternal blood group Rh D negative should have partner blood grouping and Rh D testing
§ If partner is Rh D positive, paternal zygosity can be offered (where facility is available)

If father is homozygous for D antigen, fetus will be always Rh D positive. If father is heterozygous for D antigen, fetus will have the antigen in 50 % cases.

§ Fetal genotyping assessed via amniocentesis can be offered (where facility is available).
§ Cell-free fetal DNA or non-invasive prenatal testing (NIPT) is currently available for fetal Rh D determination.
§ In Rh D incompatible pregnancies, an ICT should be offered at the initial visit.
§ ICT is positive when Rh D alloimmunization has occurred (development of antibodies against Rh D antigen).
§ Once alloimmunized, serial titers every 2 to 4 weeks is recommended.
§ Critical titer is usually 1:16 (can vary depending on the laboratory methodology)
§ Serial two-weekly MCA PSV once ICT has crossed critical titers
§ Titers are less reliable in previous HDFN affected pregnancies. MCA PSV should be used in these cases directly.

B. Nonimmune mechanisms

Fetal anemia can also occur from nonimmune mechanisms as listed below.

Parvovirus B19 viral infection in the mother	Xerocytosis
Fetomaternal hemorrhage	Elliptocytosis
Twin-twin transfusion syndrome	Congenital dyserythropoietic anemia
Chorioangioma	Hemochromatosis
Kaposi-like hemangioendothelioma	Mucopolysaccharidosis VII
Fetal sacrococcygeal teratoma	Cytomegalovirus infection
Homozygous α-thalassemia	Congenital syphilis
Black Fan-Diamond anemia	

Objectives of Performing Intrauterine Transfusion

- To treat fetal anemia by improving the oxygen-carrying capacity of the fetal blood by substituting the hemolyzed fetal RBCs with O Rh-negative blood in high concentration thereby preventing hydrops and mortality
- To suppress fetal erythropoiesis
- To reverse already developed hydrops
- To extend the pregnancy to term with the delivery of a healthy nonhydropic neonate
- To minimize the need for exchange transfusion and prolonged phototherapy

Preparation of the Blood Unit for IUT

The donor blood required for IUT is to be obtained from a transfusion medicine unit with expertise in undertaking such preparation. These units are usually located in tertiary care teaching and research centers, oncology hospitals, and specialized blood banks. These institutions usually have a list of prospective donors of O Rh D negative donors.

The prerequisites of the blood unit used for IUT are outlined below.

- Cross matching of the donor blood with the mother's serum. A suitable maternal sample in plain and EDTA vials should be provided to the laboratory.
- Type- O Rh D-negative packed RBCs, if sensitization is to the D antigen, type specific if sensitization is to non-D antigens.
- Infection screening for HIV, hepatitis B surface antigen, hepatitis C virus, and cytomegalovirus (CMV).
- Blood units should be < 7 days old
- Gamma irradiation (25 Gy) to prevent the fatal graft vs host reaction.
- Leucodepletion (to prevent CMV infection)
- Hematocrit of the donor should be 75 to 80%.
- Platelets should be made available if parvovirus B19 or CMV are suspected, or in the presence of hydrops or hepatosplenomegaly.

Specific request forms duly filled with the pertinent details of the pregnancy should be dispatched to the laboratory. Verbal communication regarding any specific requirements can be done with the transfusion specialist in charge. Once the blood unit arrives, it should be verified for all the details prior to performing IUT. If there is a delay in performing the IUT, storage should be continued in the cold box provided by the laboratory. The shelf-life of the blood unit is 24 hours after irradiation and hence transfusion must be completed within this time. Otherwise, a new blood unit must be ordered.

Written and informed consent should be obtained prior to performing the IUT.

Maternal Preparation

The standard protocol for performing any prenatal procedure should be followed.

- Steroid cover for lung maturity in gestational age above 26 weeks, to be administered 48 hours before transfusion.
- Preferable to avoid large meals 4 to 6 hours prior to the transfusion.
- Intravenous (IV) access
- No evidence for routine antibiotic prophylaxis as per the local protocol.
- Maternal sedation is optional, local anesthesia is preferred.
- Aseptic prepping similar to abdominal procedures.

The procedure setting

A standard procedure room with adequate space and ergonomics is generally used to perform the IUT. A double setting either in the labor room or operation theater may also be used especially for IUTs near term.

The following are the essential requirements of the procedure room:

- Patient bed.
- High resolution ultrasound machine
- Procedure tray
- Point of care heemometer or a nearby laboratory
- IV drip stand to hang blood bag
- Operator, assistant, scrub nurse
- Circulating nurse or staff (s) to assist with blood bag, transfusion volume calculation and coordinating with laboratory

The tray for the procedure should have the following contents (►**Fig. 2**).

- Paint set (sponge holder, small bowl for betadine)
- 22G spinal needle
- Blood transfusion set
- 1 mL insulin syringe for fetal anesthesia

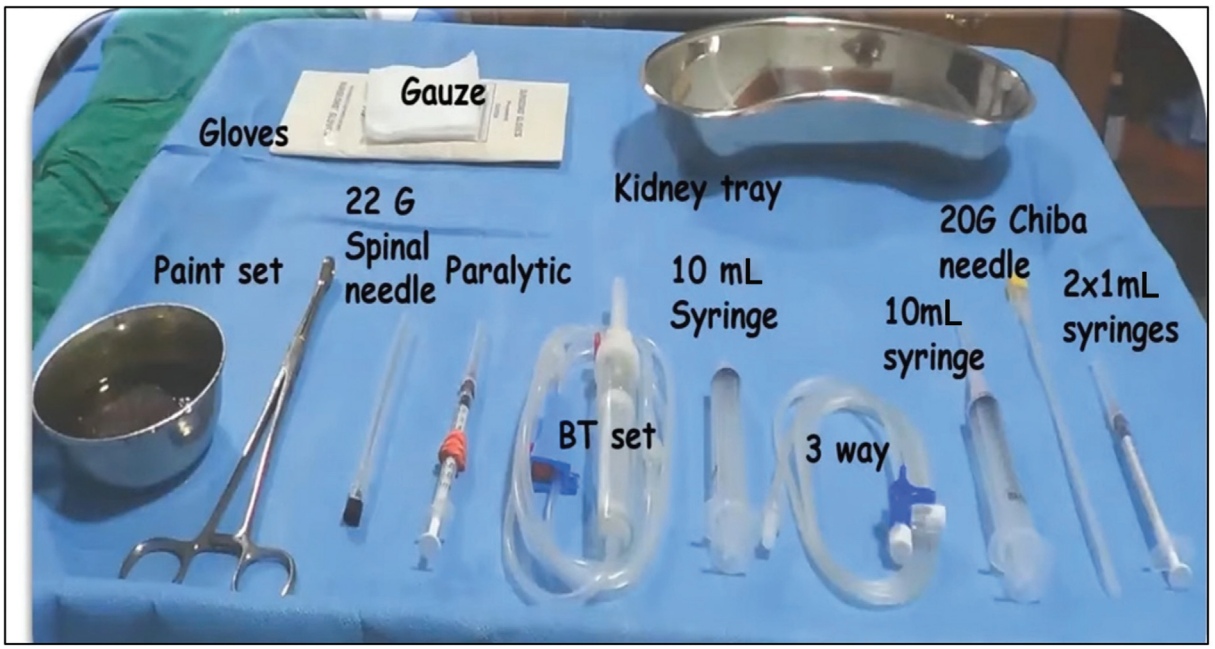

Fig. 2 Contents of the procedure tray prepared for IUT. This image demonstrates the key contents of procedure tray prepared for IUT (image courtesy: Dr. Vivek, AIIMS Kochi). IUT, intrauterine transfusion.

- 10 mL syringe -2 (with Luer lock)
- 3-way with preferably 100 cm long connecting tube
- 20G Chiba needle (15cm long)
- 5 × 1 mL syringes
- Kidney tray
- Gauze pieces
- Gloves
- Normal saline or distilled water to flush the tubing.

Drugs Used in IUT

The following drugs are used in IUT and should be appropriately constituted-

A. **Maternal**

- **Antibiotics**—There is no standard recommendation for antibiotics prior to IUT. However, a dose of IV antibiotic 1 hour before the procedure followed by a repeat dose after 6 hours is offered in most units.
- **Progestogen**—There is no standard recommendation for administering progestogen prior to IUT. However, a course of vaginal micronized progesterone is usually administered prior to the procedure in most units.
- **Maternal sedatives—**Usual combination is intramuscular pentazocine and promethazine. A widely used regime is 1 mg pentazocine and 2 mg promethazine. Alternatively, inj midazolam, 0.5 mg IV over 2 minutes may be given for anxiolysis
- **Local anesthetics—**1% lignocaine should be used for local infiltration whenever using a 20 G or larger needle.
- If the mother is on prophylactic low dose low-molecular weight heparin (LMWH), or unfractionated heparin it is a good practice to stop these 24h prior to IUT and restart 24 hour later. Low-dose aspirin (≤ 150 mg/d) need not be stopped. These are empirical recommendations and physicians are encouraged to follow local protocol as there is no hard evidence in favor of stopping or continuing LMWH or aspirin.
- **Tocolysis prophylaxis:** Consider maternal prophylactic tocolysis for gestational age more than 24 weeks. Options include indomethacin 50 mg orally every 6 hours started from previous evening, 5mg transdermal Nitroglycerine (NTG) patch 2 hours before procedure, nifedipine 20mg every 8 hours started 2 hours before procedure: none of the prophylaxis to extend beyond 48 hours after procedure.

B. Fetal

1. Fetal paralytic agents –
Pancuronium (2 mL ampule with 2 mg/mL of the drug). Dosage—0.1 mg/kg estimated fetal weight (EFW). Dilute 1 mL from the ampoule in 9 mL normal saline or distilled water. Take 1 mL of diluted drug in a 1 mL insulin syringe (0.1 mg/mL).
Alternative—Atracurium 0.4 mg.kg EFW. Atracurium is preferred due to shorter duration of action and lesser side effects.

2. Fentanyl (50 µg/mL) for fetal anesthesia. Dosage: 20 µg/kg EFW. Dilute 1 mL in 9 mL normal saline or distilled water.

Choosing an Access

Currently, IUT is performed via the intravascular approach. The umbilical vein at its placental insertion in an anterior placenta and the intrahepatic portion in a posterior placenta is the most preferred approach. Advantages of the intrahepatic approach include avoidance of arterial puncture and secondary vasospasm and cord tamponade, less Fetomaternal haemorrhage (FMH) and success rates in the region of 90%. Intraperitoneal bleeding is rare, and usually self-limiting and functions as an intraperitoneal transfusion (►**Fig. 3**).

The free loop is usually avoided as it is associated with higher complication rates.

The intraperitoneal approach may be used in selective cases such as an early transfusion (< 22 weeks), in case of failure of the intravascular approach or may be combined with intravascular technique to allow longer interprocedural intervals. Very rarely, direct intracardiac transfusion may be performed as a rescue operation in an actively exsanguinating fetus.

Steps of IUT

Preprocedure checklist—**Annexure I**, Consent form—**Annexure II**.

Actual steps:

Step 1 Set up the transfusion circuit

- Connect the blood transfusion set to the blood bag.
- Hang the blood bag on the IV drip stand.
- Connect the other end of the drip set with the three-way connector.
- The middle outlet of the three-way is connected to a 10 mL Luer lock syringe and the third end to the Chiba needle.
- Fill the circuit with blood ensuring no air is present.
- Take a sample for measuring the donor hematocrit, and enter the value in the calculator.

Step 2 Insert a 22G spinal needle and administer the loaded drugs (paralytic agent + anesthetic) into the fetal thigh/deltoid depending on the ease of access

Step 3 Insert the Chiba needle

- Infiltration of local anesthesia if required.
- Enter the planned intravascular site with the 20 G Chiba needle
- Draw blood for fetal blood hematocrit and complete hemogram (exclude erythrocyte sedimentation

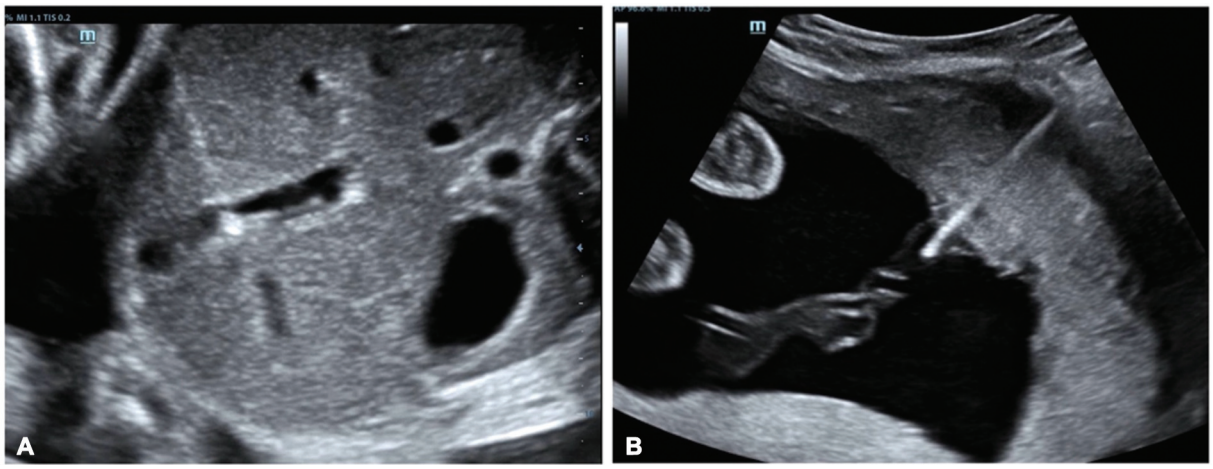

Fig. 3 Two-dimensional grayscale ultrasound images showing the two common intravascular placements of the needle. This image demonstrates the two sites of intravascular placements of the needle for IUT. (**A**) Axial image of fetal liver showing the placement of needle inside the umbilical vein. (**B**) The needle has been guided toward the placental insertion of the umbilical vein. IUT, intrauterine transfusion.

rate), serum bilirubin, blood group, direct Coombs test, reticulocyte count, and fetal karyotype.

Step 4 Calculating the transfusion volume

- The parameters required to calculate the intravascular transfusion volume are
  1. Initial fetal hematocrit
  2. Feto placental blood volume
  3. Donor hematocrit
  4. Target hematocrit 45 to 50%
- The formula most commonly used is
  Fetoplacental vol x (desired hematocrit – fetal hematocrit)
  Donor hematocrit – desired hematocrit
- Feto placental volume = Ultrasound EFW x 0.14
- Fetoplacental blood volume can be calculated based on fetal weight or based on gestational age. The latter is not affected by the presence of fetal hydrops.
- Online calculators are available at the Perinatology.com Web site (http://perinatology.com/protocols/rhc.htm), Fetal Medicine Barcelona (http://medicinafetalbarcelona.org/calc/ and mobile app) and the Fetal Medicine Foundation UK Web site (www.fetalmedicine.org/calculators).

Step 5 Transfusing the calculated volume

- Draw blood from the blood bag into the syringe then close the three-way knob of this side (the side toward the blood bag) and push the blood from the syringe into the needle
- Hold the syringe vertically to avoid air bubble entry.
- Ask the circulating nurse to note the amount transfused.

Step 6 Monitor the fetal activity during the procedure. Be watchful for fetal bradycardia.

Step 7 After the calculated volume has been transfused, inject 2 mL of normal saline via the intravascular needle, wait for a minute, and take a fresh sample of fetal blood for postprocedure hematocrit.

Step 8 Post-transfusion monitoring

- Post-transfusion hematocrit: This is important as it decides as to when and whether a next transfusion may be required.
- Document the fetal heart rate, MCA PSV, and the Myocardial performance index
- Weekly MCA PSV

Planning Subsequent Transfusions

Subsequent transfusions are decided based on the expected fall in the hematocrit. Usually, after the first transfusion the fall in Hb is 0.4 g/dL per day. After the second transfusion, the fall in Hb is 0.3 g/dL per day and 0.2 g/dL per day after the third. The figures of 0.4,0.3,0.2 multiplied by 3 will give the hematocrit (in %). Otherwise, a fall of 1% in hematocrit per day can be used for the sake of convenience. The MCA PSV is not very reliable after transfusions because of the different characteristics of the adult blood and the fetal blood. Some authors have proposed a higher cutoff of 1.7 MoMs instead of 1.5. Another empirical regime is transfusing at 10 days, 2 weeks, and 3 weeks for the second, third, and subsequent IUTs.

Complications[9,10]

Acute	Fetal bradycardia (5–10%)
	Local cord accidents such as rupture, spasm, tamponade from hematoma, excessive bleeding, umbilical artery thrombosis
	Volume overload
	Chorioamnionitis
	Preterm Premature rupture of membranes (PPROM)
	Iatrogenic preterm delivery (prematurity, neonatal asphyxia or death)
	Fetal death (0.9–4.9 %)

Long term	Requirement of top-up transfusions due to suppression of erythropoiesis Transmission of viral diseases Formation of new red cell antibodies Neurological outcome

The procedure-related fetal loss rate in IUT is 0.9 to 4.9%. There is a higher incidence of loss in fetal hydrops, early gestational age, failure of the use of a fetal paralytic agent, use of a free loop of cord for transfusion, arterial puncture, operator expertise, and the severity of anemia. In anatomically normal fetuses, the loss rate is 1%. In those fetuses with structural anomalies and hydrops, the procedure-related loss is 7 and 25%, respectively.

Avoiding a transplacental transfusion, prior cross-match of donor sample with maternal sample and the potential use of a single donor for all transfusions in a particular fetus can prevent the generation of new antibodies. Cord accidents can be avoided by using fetal paralytic agents (preventing needle dislodgement from fetal movement).

The neurodevelopmental outcome following IUT has been observed to be normal in 95% of children assessed at a median age of 8.2 years. Cerebral palsy, severe developmental delay, and bilateral deafness were detected in 2, 3, and 1% of children, respectively. Factors independently associated with neurodevelopmental impairment included severe hydrops, number of IUTs, and severe neonatal morbidity.

Planning Delivery after IUT

A successful IUT regime will result in term delivery more than or equal to 37 weeks of gestation. Generally, if the last transfusion was performed at 34 to 35 weeks, delivery can be planned after 3 to 4 weeks. Induction of labor can be offered if there are no obstetrical contraindications. Delivery should be done at an institution with the availability of neonatologists and level III facilities.

Neonatal hepatic enzyme induction is done prenatally by transplacental therapy: start maternal oral phenobarbital 30 mg three times daily 10 days prior to the planned delivery date. This reduces the need for exchange transfusion by 75%.

Informed Consent

Informed consent was obtained from all women.

Conflict of Interest

None declared.

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Annexure I Preprocedure checklist

Written informed consent
Alert the obstetrician, neonatologist and the anesthetist
Pre-procedure scan and documentation of the EFW, MCA PSV, MPI, cervical length and proposed site of intravascular access
Laboratory staff informed
Minimum three EDTA vials properly labeled (donor, preprocedure and postprocedure fetal samples)
Verification of the blood bag
Procedure tray
Dilution and constituted drugs (pancuronium, fentanyl)
Heparinization of the tubings
Online/offline calculator kept ready to calculate the blood volume
Preprocedure medications: antibiotic, tocolysis, and sedative

Abbreviations: EFW, estimated fetal weight; MCA, fetal middle cerebral artery; MPI, myocardial performance index; PSV, peak systolic velocity.

Annexure II Consent form for IUT

I……., w/o …….. hailing from …….. do hereby give my consent for the procedure "Fetal Blood Transfusion"

I have understood the following information before giving consent, explained to me in my own language by the doctor

1. That the baby inside my womb is affected by severe anemia and continuation of pregnancy without any treatment may result in severe damage or death to the fetus
2. Fetal blood transfusion is the current standard of treatment for fetuses with such conditions
3. The procedure is generally safe for the mother; however, it carries a 1 to 2% chance of procedure-related miscarriage.
4. Depending on the severity of the fetal condition, the survival can be expected to be around 85 to 95% if regular transfusions are undertaken till delivery
5. Post-delivery, the baby may still require transfusion till the baby's blood system is able to compensate adequately
6. That I need to inform immediately to my obstetrician if any symptoms arise such as fever, persistent abdominal cramps, profuse bleeding or leaking fluid per vaginum, or generalized feeling of unwellness following the procedure

Patient Witness
Date:
Counseled by Dr

