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FOGSI Focus on Rh-Negative Pregnancy

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CHAPTER 8

Follow-up Algorithms after Intrauterine Transfusions

Seetha Ramamurthy Pal

INTRODUCTION

Intrauterine transfusion (IUT) also known as fetal blood transfusion is an interventional therapeutic procedure in which specially prepared and treated donor packed red blood cells are injected into the fetal circulation directly or indirectly under continuous ultrasound guidance.[1] It was first introduced in 1963 but now it is the standard of care to treat fetuses with severe fetal anaemia.[2] Since the introduction of IUT, fetal survival has been reported at 85–90% and is approaching 97% for RBC alloimmunization in experienced centers with excellent long-term neuro-developmental outcome even in the context of severe fetal hemolytic disease.[3]

MONITORING OF ANEMIC FETUSES

Anemic fetuses develop a hyperdynamic circulation and this can be detected noninvasively through measurement of the peak systolic velocity of the middle cerebral artery (MCA-PSV).[4] All the professional bodies like Society of Maternal-Fetal Medicine and the Royal College of Obstetricians and Gynaecologists have outlined that patients when detected with maternal antibodies (positive ICT) should be referred to a specialist for MCA-PSV surveillance to monitor the fetus for the development of anemia.[5,6] Historically, these were done by invasive procedures like amniocentesis and cordocentesis, both of which carry a potential risk of fetal loss of about 0.2–1%.[7,8] Advances in Doppler ultrasonography have paved the way for a more safer and effective noninvasive approach.[9] Additionally, cell-free DNA can be used for determination of fetal Rhesus genotype, allowing surveillance to those at risk.[10] However, it must be noted that once the fetus has been transfused, the significance of the maternal antibody decreases, as the IUT procedure itself is a potentially sensitizing event.[11]

THRESHOLD FOR TRANSFUSION

Intrauterine transfusion is basically a procedure to correct the anemia temporarily, but as the pathology remains uncorrected with ongoing hemolysis, serial and multiple transfusions are usually required till delivery in cases of moderate–severe anemia. Hence, your ability to predict the fetal response to each transfusion is critical to optimal care. In the prediction of fetal anemia, the MCA-PSV is usually adjusted through the use of multiples of median as both MCA-PSV and fetal hemoglobin vary with gestational age. Current guidelines recommend fetal blood sampling and IUT when the MCA-PSV reaches 1.5 MoM.[6]

The timing of repeat in utero transfusions is important because each procedure bears a 1.5–3% risk of fetal morbidity and mortality.[12] The overall risk is particularly high in cases of anemia occurring at early gestational ages, for which some five or six serial IUTs may be required during a single pregnancy.[13] While the MCA-PSV has been shown to be very useful for identifying a fetus with "moderate–severe" anemia for the first IUT,[14] evidence is conflicting as to whether measuring the MCA-PSV is as effective in a previously transfused fetus.[15] This is because fetal MCA blood flow is different when replaced by adult RBCs. Adult RBCs are smaller, less rigid, and have different oxygen-carrying capacity and oxygen delivery characteristics. They also have different rheological properties than fetal RBCs. MCA-PSV is not useful in predicting severe anemia in fetuses that already had two previous transfusions. It may aid in the timing of the second transfusion in a series of IUT but published data do not support its use thereafter.[16] In one study, sensitivity of MCA-PSV threshold of 1.5 multiples of the median (MoM) to detect moderate–severe anemia declined from 82% after one transfusion to 75% after two or more previous transfusions.[15]

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FOLLOW-UP

Follow-up after first intrauterine transfusions starts with weekly or twice weekly ultrasound examinations, searching for early symptoms of fetal hydrops (if not present earlier) and measuring MCA-PSV.

Intrauterine transfusion procedures may be required every 2–3 weeks, the frequency minimized by transfusing red cells of high hematocrit and the maximum volume. The aim of each transfusion is to raise the Hct to 0.45. The use of MCA-PSV with a higher cut-off was proposed by Mari et al.,[17] whereas Scheier et al.[18] suggested a decision based on the hemoglobin level reached at the end of the previous IUT and the expected daily decline in hemoglobin.

For subsequent transfusions, if fetal MCA is used, a cut off of 1.69 MoM is better. They can also be decided based on the expected fall in hematocrit. Usually, the rate of fall of hematocrit is 1% per day. The fall in hemoglobin after the first transfusion is usually 0.4 g/dL per day, 0.3 g/dL after second, and 0.2 g/dL after the third transfusion. These figures multiplied by 3 will give the hematocrit (in %). Another empirical regime is timing the subsequent first transfusion at 10 days, next after 2 weeks and then, 3 weeks.

Indications for repeat IUT are usually:

- MCA-PSV >1.5 MoM
- Possible fetal anemia based on the last post-transfusion hemoglobin value and on an expected daily decline of fetal hemoglobin (0.45 g/dL after one IUT and 0.35 g/dL after two or more IUTs)
- Early signs of fetal hydrops

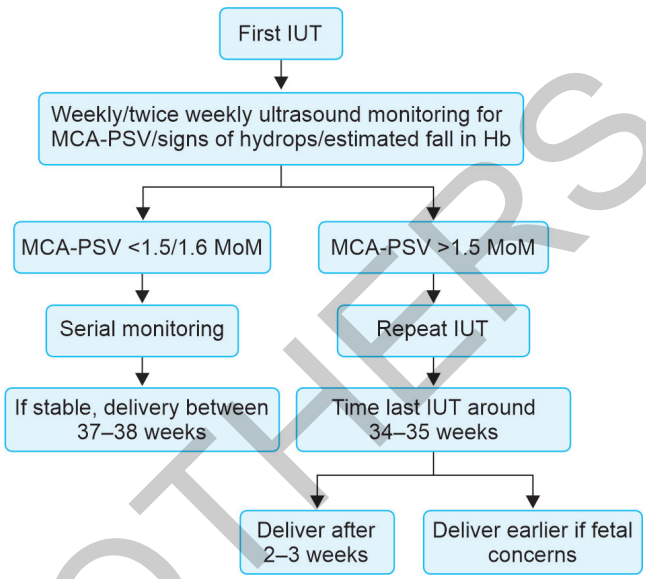
In general, the patient has to be followed up in totality and all the features need to be taken into consideration. It is important to note that hydrops takes a few weeks to settle and hence we have to rely on the fall in hematocrit or MCA-PSV to decide further care.

PLANNING DELIVERY

If an IUT has been required, the timing of delivery will depend on the degree of fetal anemia, time from IUT, rate of fall in fetal Hb/hematocrit and gestation.

If serial transfusions have been successful, pregnancy can be allowed to go to term, ≥37 weeks of gestation. Generally, the last transfusion is timed around 34–35 weeks, so that delivery can be planed after 2–3 weeks. The last transfusion should be done with extra precautions including steroid cover, neonatal and OT back up in case of eventuality.

Flowchart 1: Follow-up algorithm after intrauterine transfusions.



(MCA-PSV: middle cerebral artery peak systolic velocity; IUT: intrauterine transfusion)

Induction of labor can be offered and cesarean section is usually reserved for obstetric indications. However, delivery should be conducted at a tertiary institute with adequate neonatal back up and level III facilities. Once the baby is born, some neonates may experience anemia for a few weeks following birth. However, no long-term consequences have been observed for the mother or the baby **(Flowchart 1)**.

CONCLUSION

In conclusion, severe fetal anemia can be monitored using both MCA-PSV and the mean projected daily decrease in fetal hemoglobin in cases of serial transfusions. However, MCA-PSV should be monitored systematically before cordocentesis and the transfusion can be safely postponed if the value is <1.5 MoM. Indeed, for the many women living in places remote from referral centers, this approach has the pragmatic advantage of allowing subsequent IUTs to be scheduled with the patient's awareness that the procedure may be postponed safely.

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The problem of Rh-isoimmunization dates many years, and we have seen a sea of change in the prevention and management of fetuses affected by this dreaded condition. From effective screening of women who are Rh-negative and their partners to noninvasive screening of fetuses of isoimmunized mothers to intrauterine transfusions which can treat almost 95% of affected fetuses, the entire management has been one of the greatest successes of Fetal Medicine.

This FOGSI Focus aims to focus on all aspects of Rh-isoimmunization starting prenatally to postnatal management. Beginning from the basics of Rh factor and pathophysiology and quantification of fetomaternal hemorrhage, it covers the preventive aspects of Rh-isoimmunization and if fetus affected, the various ultrasound features of Rh-isoimmunized pregnancy. Investigations in cases of Rh-negative pregnancy have been dealt with by algorithms and the original but expanding role of noninvasive prenatal screening (NIPS) has been discussed in detail. Intrauterine transfusions and follow-up cases of intrauterine transfusions with obstetric aspects have been dealt with in detail. Neonatal management and long-term outcomes of these affected fetuses have been covered very well. Finally, less discussed issue of recurrent immune hydrops has been addressed and it ends with a few challenging and interesting cases of Rh-isoimmunization.

We are sure this focus will be a comprehensive read to all who deal with this problem in their daily practice and improve your management of all Rh-negative pregnant mothers.



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