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Original Article

# Short Neonatal Outcomes after Intrauterine Transfusion in Fetal Anemia, the Experience from a Referral Academic Center

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## ABSTRACT

***Background:*** Rhesus D-antibodies and maternal red blood cell alloimmunizations are the major causes of fetal anemia, which can cause hydrops and perinatal death if not treated through intrauterine intravascular blood transfusion (IUT). This paper sought to report the short-term neonatal outcomes after IUT in a referral academic center.

***Methods:*** The population of this retrospective cohort study comprised all pregnancies that underwent IUT between March 2014 and March 2019. The maternal obstetrics characteristics as well as blood group, antibody screen, and titers were reported. Indeed, the fetal and neonatal outcomes and complications were described either.

***Results:*** A total of 141 IUTs were performed in 58 women. Of all, 15 fetuses were hydropic at the first transfusion. The mean±SD (standard deviation) of gestational age and hemoglobin at the first transfusion was 27.06±4.25 weeks and 6.62±2.91 g/dL, respectively. The range of transfusions was 1.8 per woman and the mean±SD amount of blood transfusion in IUT was 84.03±48.79 cc. 7/58 (12%) intrauterine and 6/58 (10%) neonatal death were reported, of which, four cases were hydropic and the others suffered from severe anemia. The mean±SD of gestation age at delivery was 33.6 ± 3.33 weeks. A significant difference was observed between mean fetal hemoglobin levels before and after performing the IUT procedure ($p< 0.01$). Also, middle cerebral artery (MCA) Doppler assessments showed anemia severity decreased following IUT

***Conclusion:*** It seems Intrauterine transfusion is a lifesaving procedure that can boost perinatal survival in fetuses with anemia.

***Keywords:*** Anemia, Hydrops fetalis, Intrauterine blood transfusion

## Introduction

Fetal anemia is one of the most important challenges in perinatal science and mismanagement of this issue may lead to fetal hydrops and death (1). Rhesus D-antibodies, maternal red blood cell alloimmunizations, Parvovirus B19 infections, massive fetomaternal hemorrhage, hemoglobinopathies, and monochorionic twin complications are the dominant cause of fetal anemia (2-4). Untreated, severe fetal anemia leads to hepatosplenomegaly, cardiomegaly, fetal hydrops, and consequent perinatal death (5).

The intrauterine transfusion (IUT) was initially introduced in 1963 by Liley who adopted an intraperitoneal approach, and its indications were

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fetal anemia and thrombocytopenia (1, 6). After 20 years, the procedure developed into a form of transfusion into the umbilical vein (2). Great success has been achieved in the diagnosis and treatment of fetal anemia and this method has been changed by the introduction of the Middle Cerebral Artery Peak Systolic Velocity(MCA PSV)Doppler sonography in 2000 to evaluate fetal anemia (2). The accuracy and non-invasiveness of Doppler sonography make it a standard tool to predict severe severe severe fetal anemia by measurement of MCV-PSV, replacing serial amniocentesis for screening fetal anemia (1, 2, 4). IUT should be done if MCA-PSV Doppler is more than 1.5 multiples of the median (MoM) and/or if signs of fetal hydrops are obvious (5) Hence, frequent doppler measurement for the timing of subsequent IUTs was needed (2).

A fetal hemoglobin level of more than 7 g/dl below the normal or hematocrit of less than 30 percent is defined as the threshold for fetal transfusion (7). In experienced hands, IUT seems a relatively safe treatment. However, there are still complications, even in the fetuses (8). In the previous studies, the rate of pregnancy loss after IUT was 1.2%/ and fetal demise cases were due to hydrops before IUT (9). This study was conducted to describe the perinatal and neonatal outcomes of all IUTs performed from 2014 to 2019 in a tertiary-based university hospital

## Methods

### *Study setting*

This retrospective cohort study was conducted at the Department of Gynecology and Obstetrics of Yas Hospital affiliated to the Tehran University of Medical Sciences. The population consisted of all women undergoing IUT form March 2014 to March 2019. It was scheduled if the MCA-PSV value of the fetus was ≥1.5. MOM and other signs of hydrops fetalis were identified by ultrasonography.

### *Eligibility criteria*

The pregnancies that were complicated by Rh alloimmunization and fetal anemia at 17 to 35 weeks of gestational age were included. RhD-negative allalloimmunization criterion was an abnormality in anomaly scans or incomplete data.

### *Data gathering*

Gestational age was calculated using both the assessment of the last menstrual period (LMP) and sonography by means of the crown-rump length measurement at 11 - 13 weeks of gestation. The patient's obstetric history and past medical history were recorded and fetal middle cerebral artery-peak systolic velocity (MCA-PSV) was evaluated to diagnose fetal anemia.

In addition, CBC (complete blood count), blood group, and indirect coombs were determined, and viral and antibody screening was evaluated.

### *Ethical consideration*

The study was approved by the local ethical committee (IR.TUMS.MEDICINE.REC1398.515). All the patients signed the informed consent before including the study groups.

### *IUT Procedure*

Once the need for IUT was confirmed, antenatal steroids were administered to patients ≥24 gestational weeks 24 hours before the initial IUT in case an emergency delivery was happen. In addition, in patients ≥26 gestational weeks, we administered 4 gr loading magnesium sulfate over 20 minutes and a maintenance dose of 2 gr/hour for 12 hours.

All IUT procedures were performed at a close distance to an operating room. Before the transfusion, maternal sedation (midazolam 1 to 2 mg or fentanyl 25 to 50 mcg intravenously) may be administered to reduce maternal anxiety. All pack cells used units were O blood group, RhD-negative, CMV-negative, and compatible with maternal antibodies.

Before the transfusion, an initial 1cc sample of fetal blood was withdrawn to evaluate complete blood count, bilirubin, direct coombs, and reticulocyte count. If fetal anemia was confirmed (fetal hemoglobin is defined as two standard deviations below the mean value for gestational age or Hematocrit < 30 percent) the transfusion was started using a 20-22 gauge spinal needle.

In our experience the following formula calculates reliable estimates of blood volume for IUT:

Intraperitoneal: (gestational age 20) ×10

Intravenous: 60-90 cc/kg, except in the case of hydrops fetalis.

In hydrops, and fetalis cases, transfusion was conducted for half of the estimated volume to prevent volume overload and the subsequent procedure was scheduled 24-48 h later to reach the target hematocrit (Hct) proportion.

After calculating the blood volume, we paralyzed the fetus using pancuronium to minimize fetal movement. The umbilical vein located at the

cord root into the placenta is the preferred vascular site for IUT because of its safety.

Once the infusion was completed, another fetal blood sample was withdrawn to check the post-transfusion hemoglobin (Hb) and Hct. The target Hct proportion is 45-50%.

The fetal heart rate was monitored periodically during infusion, and in patients > 28 gestational weeks, the monitoring was continued 1 h after the procedure. The interval between the procedures was calculated assuming the post-transfusion Hct fall of 1% per day by weekly MCA-PSV measurements. Thus, we used weekly Doppler measurements for the timing of subsequent IUTs (9).

Further, the IUT procedure was conducted when signs of fetal anemia appeared, especially for fetuses that had hydrops fetalis. The last transfusion procedure was run at 34 gestational weeks and the delivery was scheduled typically at 37 to 38 weeks of gestational age.

### *Outcome*

The main outcome of this study is fetal and neonatal survival. We followed the babies for 6 weeks after their birth to evaluate their hyperbilirubinemia and phototherapy need.

### *Statistical analysis*

All the statistical analyses were carried out by SPSS24.0 (IBM, New York, USA). Quantitative data were expressed as mean ± standard deviation and categorical data were delineated as frequency and percentage. Data distribution as evaluated using the Kolmogorov-Smirnov test . The relationship between variables was assessed using the independent samplesmone-sample t-tests and Crosstabs. P-value<0.05 was considered significant.

## Results

In all, 141 IUTs were performed for 58 fetuses in our center. Table 1.outlines the demographic characteristics of the cases and particulars of the IUT procedures.

More than half of the women (53.44%) had a gestational history of fetal anemia leading to the intrauterine fetal demise (IUFD). All fetuses displayed anemia features at the time of presentation, but hydrops fetalis was observed in 15 fetuses.

The most common cause of fetal anemia was anti-D alloimmunization (n=52) and only 2 patients had multiple antibodies. A case of non-immune hydrops fetalis caused by a parvovirus B19 infection diagnosed by maternal screening was also found.

There was an average of one IUT per fetus, with a range of one to eight. In the majority of the cases, the first IUT was performed at an average age of 27 weeks.

Mean baseline fetal Hb levels ahead of the first IUT procedure were 6.62±2.91 g/dL (range: 1.7-13.5 g/dL). There were 51 (87.9%) Rh immunized pregnancies, of which 20.7% fetuses were hydropic at referral.

The average amount of blood transfusion in IUT was 84.03±48.79 cc. Of the 141 procedures, 49 (84.5%) were through the umbilical vein, 8 (1%) were intraperitoneal IUT and 1 (1.7%) involved both methods.

Severe tachycardia and bradycardia during the procedure occurred in 10 (7%) and 6 (4%) of fetuses, respectively.

Fetal outcomes in 58 fetuses showed that there was 7 (12%) intrauterine death. Of them, four cases were hydropic and cord prolapse occurred during IUT for one of them. The most important cause of death was unfollowing the treatment because of lack of awareness and non-availability in remote parts of the country, The neonatal outcome showed that there were 6 (10%) neonatal death, of them four cases were hydropic and the others suffered from severe anemia (Table 2).

For live fetuses, the mean gestational age at birth was 33.6 weeks (range: 21_37 weeks). The type of delivery was by cesarean section (CS) in 50 cases, of these, a hysterectomy was performed for one patient due to placenta accreta.

Due to a favorable cervix, vaginal delivery with accurate fetal heart rate monitoring was allowed in 8 women who had received an intrauterine fetal blood transfusion. One patient experienced preterm PROM (premature rupture of membrane).

Preterm labor (before 37 weeks) occurred in 53 patients.

Antepartum hemorrhage happened in one patient. The average Apgar score was 7 and the mean of the newborn baby's weight was 2260 gr.

A significant difference was observed between mean fetal Hb levels before and after the IUT procedure (6.6 g/dl vs. 12.6 g/dl respectively; p< 0.01). Also, MCA Doppler assessments showed anemia severity decreased following IUT. In fetuses with moderate and severe anemia, more IUT decreased MCV PSV more.

**Table 1.** Baseline Characteristics of the participants

| Characteristics | Mean±SD/Frequency (%) |
|---|---|
| Maternal history | |
| Mother's age (year) | 31.8 ± 5.3 |
| Gravidity | 4.1 ± 2.1 |
| Previous IUFD | 31 (53.4) |
| Previous IUT | 9 (15.5) |
| Rhogam injection history | 15 (25.8) |
| Maternal blood group | |
| A | 19 (32.7) |
| B | 19 (32.7) |
| O | 15 (25.8) |
| AB | 5 (8.6) |
| $Rh^+$ | 7 (12.0) |
| $Rh^-$ | 51 (87.9) |
| Coombs test | |
| Negative | 9 (15.5) |
| Positive | 49 (84.4) |
| Antibody titer | |
| 1/32 | 5 (8.6) |
| 1/64 | 8 (13.7) |
| 1/128 | 16 (27.5) |
| 1/256 | 8 (13.7) |
| 1/512 | 4 (6.8) |
| 1/1024 | 2 (3.4) |
| missing* | 15 (25.8) |
| Placenta location | |
| Anterior | 32 (55.1) |
| Posterior | 24 (41.3) |
| Anterolateral | 2 (3.4) |

*: In our study, some cases could not follow the treatment and laboratory test regularly, because of the lack of awareness, cost of therapy, and non-availability in remote parts of the country.
IUFD: intrauterine fetal demise
IUT: intrauterine transfusion

All surviving infants were followed up by pediatricians and jaundice was occurred–seen in 74% of babies, phototherapy was required in 72% of them, with 28% requiring a top-up and/or exchange transfusion post-delivery. That means 72 % required only phototherapy, outcome is very good.

A total of 92% of new born babies were anemic and blood transfusion was necessary for 85% of babies. An average of one-time exchange transformed procedure was required per baby, with a range of one to three. Kindly explain the above sentence.

The findings indicated that there was no relationship between the IUT method and pregnancy complications during IUT. There was a significant relationship between pleural effusion, pericardial effusion, hydrops fetalis, and neonatal death (P value<0.05). However, there was no relationship between fetus sex, antibody titer, and IUT outcome.

**Table 2**. Fetal/Neonatal complications

| Fetal/Neonatal complications | n (%) |
|---|---|
| Intrauterine deaths | 7 (12) |
| Neonatal deaths | 6 (10.3) |
| Pleural effusion | 9 (15.5) |
| Pericardial effusion | 8 (13.7) |
| Ascites | 23 (39.6) |
| Edema | 9 (15.5) |
| Hydrops | 15 (25.8) |

## Discussion

This study reports the neonatal outcome after IUT and revealed a statistically significant difference between mean fetal hemoglobin levels before and after the IUT procedure. Also, MCA Doppler assessments showed anemia severity decreased following IUT.

IUT is one of the most important treatments for fetal anemia due to rhesus isoimmunization (10). Intrauterine transfusion is performed in anemia or hydropic fetuses (11). This procedure was reported by Rahimi Sharbaf et al. in Iran in 2007 in which she performed IUT for a severe Rh alloimmunization case with a successful outcome (12).

In Pasman et.al (9) study, 135 IUTs were

conducted for 56 fetuses, in our study 141 IUTs were performed for 58 fetuses. Depka et.al (10) reported mean gestational age of 26.9 ±µ3.3 weeks with median Hct of 17±7.82 at first IUT. In our study, the mean gestational age was 27 weeks with a mean Hb of 6.6 at the first IUT.

In our study mean gestational age at birth was 33.5 weeks, while it was 35.6 weeks in the Pasman study (9).

In our study, preterm birth (birth≤ 36 weeks) occurred in 50% of cases and the general survival rate of fetuses undergoing IUT was 77.5%, which is aligned with that the results reported in recent literature. Van Kamp et.al and Tiblad et.al reported an overall survival of 86%, and 91.8% , respectively. (12).

Thus we reported 7 IUFDs, one death during IUT due to cord prolapse, and 6 baby deaths after birth because of severe anemia. As this study and other literature indicated, in fetuses with severe anemia, the prognosis will be poorer (12).

The most common procedure-related complication in this study was bradycardia; this result was confirmed in a report by Tibald et.al (12). In our study, fetal complications were not associated with catheter place entry.

In our study, hydrops, pleural effusion, and pericardial effusion were linked to an elevatedrisk of adverse events whereas transfusion site and needle entry were not. Also, in Pasman et.al (9) study, hydrops and transfusion in a free loop increased morbidity in babies.

A study by De Boer et all (11) reported that anemic babies who underwent IUT procedures required fewer days of phototherapy and blood transfusion than infants without IUT. In this study, the percentage of babies requiring an exchange transfusion in the IUT group was 71% as opposed to 65% in the no-IUT group (p=0.640).

Exchange transfusion need in infants who underwent IUT was 28% in the present study and the percentage of babies requiring top-up transfusion was 85%. The percentage of infants in need of a top-up transfusion was 77% and 26.5% in the IUT and the no-IUT group respectively (p<0.01). During the neonatal period, phototherapy exchange transfusion and top-up transfusions were needed in most babies (72%).

## Conclusion

It seems Intrauterine transfusion is a lifesaving procedure that can promote perinatal survival in fetuses with anemia.

## Acknowledgments

None

## Conflicts of interest

None

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