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# Intrauterine fetal transfusion in cases with immune hydrops fetalis: when and how effective it is?

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## Abstract

**Objective:** We aimed to assess perinatal and neonatal outcomes in cases who underwent intrauterine fetal transfusion due to immune fetal hydrops, and to determine the factors associated with intrauterine fetal loss.

**Methods:** The cases who underwent intrauterine fetal transfusion due to the diagnosis of immune fetal hydrops within 13 months at Şanlıurfa Training and Research Hospital were retrospectively included in the study. The cases were classified according to the severity of hydrops findings. The cases with intrauterine fetal loss after intrauterine fetal transfusion were examined in terms of hydrops severity, total transfusion number, the week of gestation when transfusion was initiated and other potential associated factors compared to the cases with live fetuses. Other procedure-related complications were evaluated.

**Results:** A total of 11 cases with immune fetal hydrops were found, and 8 cases underwent 19 intrauterine fetal transfusion procedures. Four of 8 cases had intrauterine fetal loss after the procedure, and 4 cases gave live birth. The week of gestation that hydrops developed was determined as the primary factor associated with intrauterine fetal loss. After the procedure, it was seen that one case had spontaneous preterm labor at 31 weeks of gestation.

**Conclusion:** While the primary factor for the success of intrauterine fetal transfusion in cases with immune-related fetal hydrops is the severity of fetal anemia, the success rate of fetal transfusion decreases in fetal hydrops cases with early-onset anemia. The first intrauterine fetal transfusion being successful is a significant prognostic factor in order to achieve live birth.

**Keywords:** Fetal therapy, intrauterine transfusion, hydrops fetalis, erythrocyte alloimmunization.

## *Özet:* İmmün hidrops fetalis olgularında intrauterin fetal transfüzyon: Ne zaman ve ne kadar etkili?

**Amaç:** İmmün fetal hidrops nedenli intrauterin fetal transfüzyon uygulanan olgularda perinatal ve neonatal sonuçları değerlendirmek ve işlem sonrası intrauterin fetal kayıpla ilişkili faktörleri saptamayı amaçladık.

**Yöntem:** Retrospektif olarak Şanlıurfa Eğitim ve Araştırma Hastanesi'nde, 13 ay süre içerisinde immün fetal hidrops tanısı ile intrauterin fetal transfüzyon yapılan olgular çalışmaya dahil edildi. Olgular hidrops bulgularının şiddetine göre sınıflandırıldı. İntrauterin fetal transfüzyon sonrası intrauterin fetal kayıp olan olgular; canlı devam eden olgulara kıyasla hidrops şiddeti, toplam transfüzyon sayısı, transfüzyona başlanılan gebelik haftası ve diğer ilişkili olabilecek faktörler açısından incelendi. İşleme bağlı diğer komplikasyonlar değerlendirildi.

**Bulgular:** Toplam 11 immün fetal hidrops olgusu saptanmış olup, 8 olguya toplam 19 intrauterin fetal transfüzyon işlemi yapılmıştı. Sekiz olgudan 4 tanesinde işlem sonrası intrauterin fetal kayıp gerçekleşmiş olup 4 olguda canlı doğum olmuştu. İntrauterin fetal kayıp ile ilişkili primer faktör hidropsun geliştiği gebelik haftası olarak saptandı. İşlem sonrası bir olguda 31. gebelik haftasında spontan preterm doğum gerçekleşmiş olduğu görüldü.

**Sonuç:** İmmün nedenli fetal hidrops olgularında intrauterin fetal transfüzyonun başarılı olmasındaki ilişkili temel faktör fetal aneminin şiddeti olmakla birlikte, aneminin erken başladığı fetal hidrops olgularında fetal transfüzyonun başarısı düşmektedir. İlk intrauterin fetal transfüzyonun başarılı olması canlı doğuma ulaşabilme açısından en önemli prognostik faktördür.

**Anahtar sözcükler:** Fetal terapi, intrauterin transfüzyon, hidrops fetalis, eritrosit alloimmünizasyonu.

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## Introduction

The primary indication for intrauterine fetal transfusion is the erythrocyte alloimmunization-induced fetal anemia. It is also carried out due to rarer reasons such as Parvovirus B19 infection, fetomaternal hemorrhage, twin-to-twin transfusion syndrome, and fetal/placental tumors.[1] With the addition of Rhesus D (RhD) screening and immunoprophylaxis into the routine practice and being used more frequently, perinatal Rhesus hemolytic disease decreased prominently. Yet, it is still a significant problem due to the reasons such as insufficient practice, unidentified fetomaternal hemorrhage and timing delays. Also, with the decrease of RhD-associated alloimmunization, fetal erythrocyte alloimmunization associated with non-RhD antigens comes into prominence.[2]

Hydrops fetalis is defined as the abnormal fluid accumulation in fetal soft tissues and serous cavities. Non-immune hydrops fetalis defines the group not associated with erythrocyte alloimmunization, and it may develop due to multiple fetal anatomic and functional reasons, and genetic and metabolic disorders. Fluid accumulation in serous cavities is defined as fetal acid, fetal pericardial effusion and fetal pleural effusion. Skin edema is also a definitive finding which develops late in hydrops cases.[3] The most important matter in the approach towards the cases with hydrops fetalis is to define whether there is a condition that can be treated by intrauterine procedure or not. The most important part of treatable cases is the cases with fetal anemia-induced hydrops. Transfusing erythrocytes into fetus is the most successful practice among intrauterine procedures. As shown in many observational studies, intrauterine fetal transfusion prominently increases the survival rate in severe anemic fetuses. More successful results are obtained with the transfusions performed at an early stage before anemia reaches to a severe level. Therefore, transfusion can be planned in risky patients when hemoglobin level decreases below 30%.[4]

Since the time when fetal anemia was first reported to be identifiable as non-invasive in 2000, middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurement has been used in the follow-up of the fetuses under risk.[5] The preferred method today is to collect cord blood sample when MCA-PSV is 1.50 MOM and higher in the follow-up of the patient group under risk and to initiate first transfusion when fetal hemoglobin is below two standard deviations.

Intrauterine fetal transfusion is the standard management method in the treatment of fetal hemolytic disease, and it may be required to repeat many times during the pregnancy. Preterm labor, early rupture of membrane, chorioamnionitis, emergency cesarean section, and fetal and neonatal deaths are among the major complications associated with the procedure. Procedure-related fetal loss risk is 1–3%, and complication risk per procedure is 9%.[6,7]

## Methods

This retrospective study was conducted at the Perinatology Clinic of Şanlıurfa Training and Research Hospital, and the cases with fetal hydrops developed due to erythrocyte alloimmunization between June 2017 and July 2018 were included in the study group. As a tertiary center in the southeastern region of Turkey, our clinic is a busy center which accepts patients referred from nearby cities and carries out 35,000–40,000 deliveries annually. The approval of ethics committee was not obtained since the retrospective method of the study and patient management did not make any change, and the approvals for the use of patient data were taken when collecting the informed consents. The approval for using medical data in scientific studies was obtained from the hospital management. Fetal hydrops was defined according to the ultrasonographic findings. The presence of at least two findings among the following findings was defined as hydrops: Fetal acid, fetal pericardial effusion, fetal pleural effusion and fetal skin edema.

The severity of the hydrops was defined according to the ultrasonographic fetal findings. When free fluid accumulation was observed in only two cavities, it was defined as mild hydrops; with or without subcutaneous edema, fluid accumulation in more than two cavities was defined as severe hydrops. For the definition of erythrocyte alloimmunization as the etiology of hydrops, the presence of increased velocity in MCA and maternal indirect Coombs test positivity were sought. Direct Coombs test was performed on fetal cord blood sample collected before the additional first fetal transfusion, and alloimmunization was confirmed with the positive test result. Fetal karyotypes were examined on cord blood sample of all fetuses included in the study, and the aneu-

ploidies were ruled out. All transfusions were carried out as intravascular transfusion as previously defined in the literature,[8] and transfused erythrocyte volume was calculated by the related formula (http://perinatology.com/protocols/rhc.htm). All intrauterine transfusion procedures were conducted by a single physician (EE). During the repeating transfusions, second transfusion was done ten days later, third and fourth transfusions were done two weeks later, and it was waited for three weeks for the fifth transfusion. Before the repeating transfusions, MCA-PSV being 1.32 MOM and more was considered as a criteria. When it was below that value, the transfusion was not performed. If the pregnancy was not terminated for another reason, it was followed up until 36 weeks and electively terminated at 36 weeks of gestation.

The data of the patients included in the study such as age, gravida, parity, week of gestation when diagnosis was established, initial fetal hemoglobin levels before transfusion, total transfusion numbers and weeks of gestation when transfusions were performed, transfused erythrocyte volumes, RhD or non-RhD alloimmunization data, labor indications and gestational weeks when delivery was carried out were recorded. Neonatal exchange transfusion need was reported.

## Results

During this period, a total of 11 cases with fetal hydrops associated with erythrocyte alloimmunization were identified, and 3 of them were excluded from the follow-up as they refused intrauterine fetal transfusion procedure. One case had twin pregnancy and 10 cases had singleton pregnancy. The mean maternal age was 34±4.2 (range: 24–43) years. A total of 20 intrauterine fetal transfusion procedures were performed for eight cases with singleton pregnancy. Mean week of gestation was 25±2 weeks at the time of diagnosis. While the hydrops was severe in six out of eight cases, fetal free fluid was only limited to abdominal and pericardial areas. Alloimmunization was associated with anti-RhD antibodies in 2 out of 8 patients while it was associated with non-RhD antibodies in 2 cases. Except one case with non-RhD alloimmunization, all cases had the history of fetal hydrops. Fetal loss occurred within the first 24 hours after the procedure in four of eight cases who underwent transfusion. In 3 of 4 ongoing pregnancies, the pregnancy was terminated electively at 36 weeks of gestation. In one case, the pregnancy was terminated due to spontaneous preterm labor at 31 weeks of gestation. Transfused erythrocyte suspension volumes, timings and follow-ups during repeated transfusions of the cases included in the study are given in **Table 1**. Except one pregnancy case terminated at 31 weeks of gestation, other three cases did not have neonatal exchange transfusion need. No neurological morbidity was found in the postnatal examination of the newborns.

## Discussion

Intrauterine fetal transfusion performed in company with ultrasonography is a golden standard treatment method for the intrauterine management of fetal anemia associated with erythrocyte alloimmunization. Although the proper approach is to initiate transfusion before hydrops develops, it is also effective when it is performed after hydrops develops.

In a wide meta-analysis, fetal survival rates were reported 80.5–93.5% for the fetal intrauterine transfusion performed due to erythrocyte alloimmunization.[1] In a review analyzing 19 studies on intrauterine transfusion due to fetal hydrops, mean fetal survival rate was 68% (range: 50–91%).[9] In our study, four of eight cases who underwent intrauterine transfusion due to immune fetal hydrops had fetal loss within first 24 hours after the procedure, and we found fetal survival rate 50%. Although the number of the cases in our study was less than other studies, we found similar survival rates.

All pregnancies continuing after the first transfusion achieved live births. This indicates that the continuation of the live pregnancy after the first intrauterine transfusion is significant in terms of the prognosis of hydropic fetuses. While mean week of gestation is 26.2±2.2 weeks in the ongoing pregnancies, it was 23.75±0.5 weeks in cases with fetal loss after the transfusion. Also, mean initial fetal hemoglobin level was 1.83±0.43 g/dl before the transfusion in cases with fetal loss while it was 5.7±2.5 g/dl in pregnancies which achieved live birth. Many studies reported a negative correlation between the severity of fetal anemia and fetal survival after transfusion.[10]

Considering the severity of fetal hydrops, hydrops was severe in all of the cases with intrauterine fetal loss while it was severe in two of four fetuses which were born alive and mild in two of them. Initial fetal hemo-

**Table 1.** Definitive data, transfused erythrocyte suspension volumes per procedure, and fetal hemoglobin values before and after the procedure for the cases which underwent intrauterine transfusion.

| | Pregnancy | History of hydrops fetalis | Hydrops severity | Total IUT | First IUT (week) | Week of gestation when IUT is performed (week) | Pre-IUT Hgb (g/dl) | Post-IUT Hgb (g/dl) | Transfused erythrocyte suspension (cc) | Result | RhD / non-RhD alloimmunization | Week of gestation at delivery (week) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 | 11 | 0 | Severe | 5 | 28 | 28 | 3.89 | 10.4 | 70 | Live | non-RhD | 36 |
| | | | | | | 29 | 5.94 | 13.6 | 75 | | | |
| | | | | | | 31 | 9.3 | 14.23 | 60 | | | |
| | | | | | | 33 | 9.57 | 12.99 | 80 | | | |
| | | | | | | 35 | 8.62 | 13.1 | 90 | | | |
| Case 2 | 4 | 2 | Mild | 4 | 23 | 23 | 5.07 | 15 | 28 | Live | rhD | 31 |
| | | | | | | 25 | 5.92 | 11.32 | 35 | | | |
| | | | | | | 28 | 4.5 | 12.42 | 58 | | | |
| | | | | | | 31 | 5.03 | 11.93 | 70 | | | |
| Case 3 | 5 | 0 | Severe | 1 | 24 | 24 | 1.44 | 7.2 | 30 | Ex | non-RhD | 24 |
| Case 4 | 4 | 2 | Severe | 5 | 27 | 27 | 4.37 | 11.6 | 50 | Live | rhD | 36 |
| | | | | | | 29 | 5 | 11.36 | 80 | | | |
| | | | | | | 32 | 6.2 | 12.69 | 90 | | | |
| | | | | | | 34 | 8.14 | 14.9 | 100 | | | |
| | | | | | | 36 | 8.03 | 13.98 | 115 | | | |
| Case 5 | 4 | 1 | Severe | 1 | 24 | 24 | 1.5 | 7.3 | 30 | Ex | rhD | 24 |
| Case 6 | 3 | 0 | Severe | 1 | 23 | 23 | 2.1 | 5.4 | 25 | Ex | rhD | 23 |
| Case 7 | 6 | 2 | Severe | 1 | 24 | 24 | 2.3 | 7.8 | 30 | Ex | rhD | 24 |
| Case 8 | 4 | 1 | Mild | 2 | 32 | 27 | 9.5 | 13.5 | 55 | Live | rhD | 35 |
| | | | | | | 34 | 11.2 | 14.1 | 70 | | | |

**Hgb:** hemoglobin; **IUT:** intrauterine fetal transfusion.

globin level was more than 5 g/dl in mild hydrops cases. Van Kamp et al. evaluated the cases, who underwent intrauterine fetal transfusion due to immune fetal hydrops, according to the severity of hydrops. They reported survival rate 55% in severe hydrops cases and 98% in mild hydrops cases.[6] Although there were insufficient data to reach this conclusion in our study, the early-onset of hydrops causes it to be severe and it seems to affect survival rate negatively.

Despite a few reported cases supporting the hypotheses that improving severe anemia and fetal hydrops by intrauterine transfusion may result with neurological sequelae of newborn, this could not be confirmed by further studies. The condition observed in these cases was rather associated with prematurity. Weisz et al. did not observe any neurological morbidity in newborns after the intrauterine transfusion treatment of 40 cases with hydrops.[9] In our four cases, the results of newborn neurological examination were normal.

Spontaneous preterm labor started after the fourth procedure in one of four cases in which fetus was alive after the intrauterine transfusion. Except this case, there was no further complication associated with the procedure in the ongoing pregnancies. In a study where 740 cases underwent intrauterine transfusion, severe fetal bradycardia, fetal death and preterm labor, rupture of membrane and intrauterine infection were reported as the major complications associated with the procedure.[11]

The retrospective design of our study and insufficient number of patients are the major limitations of our study.

## Conclusion

It seems that the week of gestation when hydrops develops is the most significant factor for the success of procedure in cases undergoing intrauterine fetal transfusion due to immune fetal hydrops. Fetal anemia is

more severe in cases with hydrops developing in the early second trimester, and the fetal loss risk after intrauterine fetal transfusion is higher. The first transfusion being successful is considered to be the most important prognostic factor in terms of achieving live birth.

**Conflicts of Interest:** No conflicts declared.

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