ECRONICON OPEN ACCESS

EC GYNAECOLOGY
Literature Review

Intrauterine Transfusion: Indications, Complications and Optimization Techniques

Ayman A Bukhari*

Department of Obstetrics and Gynaecology, King Abdulaziz University, Saudi Arabia

***Corresponding Author**: Ayman A Bukhari, Department of Obstetrics and Gynaecology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Received: October 21, 2018; **Published:** October 31, 2018

Abstract

Intrauterine transfusion has been used for various indications. The use of Rh(D) immune globulin prophylaxis led to the marked decrease in this procedure. This paper is highlighting the known indications for IUT in the era of ultrasound advances and fetal therapy revolution. This method is being done less commonly nowadays as fetal hemolytic anemia with Rh alloimmunization has decreased markedly with Rh alloimmunization prophylaxis. Nonetheless, IUT is still the cornerstone treatment for fetal hemolytic anemia and some other conditions that will be stated in this article. That being said, it is essential to maintain the updated evidence to minimize the complications and associated risks.

Keywords: *IUT; Fetal Transfusion; Fetal Anemia; Rh Disease; Alloimmunisation*

Abbreviations

IUT: Intrauterine Transfusion; MCA: Middle Cerebral Artery; PSV: Peak Systolic Velocity; Rh: Rhesus; FNAIT: Fetal/Neonatal Alloimmune Thrombocytopenia; TTTS: Twin-Twin Transfusion Syndrome; TAPS: Twins Anemia Polycythemia Sequence; IVIG: Intravenous Immunoglobulin

Introduction

Intrauterine transfusion (IUT) was first performed in 1963 by Liley using an intraperitoneal method. In 1982, the technique was upgraded to a transfusion through umbilical vein entry under direct ultrasound vision [1]. Throughout the years, IUT has been used for various indications [2]. Worldwide use of Rh(D) immune globulin prophylaxis decreased the need for IUT vividly [3]. In 1906, hemolytic disease of the newborn was first described by a French midwife in a twin delivery at the royal court of King Henry IV and Queen Marie de Medicis. However, the pathogenesis was not clear and only in 1953, Chown then linked the pathogenesis of Rhesus (Rh) alloimmunization to the cross of Rh-positive fetal red blood cells trans-placentally into maternal Rh-negative blood [4].

This paper is highlighting the known indications for IUT in the era of ultrasound advances and fetal therapy revolution. This method is being done less commonly nowadays as fetal hemolytic anemia with Rh alloimmunization has decreased markedly with Rh alloimmunization prophylaxis. Nonetheless, IUT is still the cornerstone treatment for fetal hemolytic anemia and some other conditions that will be stated in this article. That being said, it is essential to maintain the updated evidence to minimize the complications and associated risks.

Literature Review

Indications

Multiple indications for IUT are mentioned in the literature [2,5,6]. Fetal IUT is considered a pillar aspect in the management of fetal anemia [6]. Fetal hemolytic anemia per se can be seen in red cell alloimmunization complicating the pregnancy in which a progressive type of anemia may occur [7]. The mechanism of the disease was first explained in 1940 with the detection of the Rh grouping system by Landsteiner and Wiener [4,8]. A year later, in 1941, Levine announced the discovery of the Rh(D) antigen which is mentioned later as the responsible cause of the formation of the antibodies in Rh (D) negative mothers [4,9]. When fetal Rh (D) positive antigen is identified by the Rh (D) negative mother, Immunoglobulin type G will be formed, and those antibodies will be able to cross the placenta in further leading to fetal anemia in future pregnancies carrying Rh (D) positive fetuses [4].

With proper diagnosis and with the benefit of fetal IUT, survival rates in those cases generally exceed 90 percent [7,10]. One serious cause of fetal anemia other than alloimmunization includes fetal anemia from erythropoiesis suppression occurring with anti-Kell antibodies [11,12]. Unlike Fetal anemia from red cell isoimmunization with Rh(D) disease, fetal anemia from anti-Kell antibodies cannot be prevented since there is no known prophylaxis for this kind of anemia. For that reason mainly, an increasing incidence of anti-Kell related fetal anemia is being documented the United States of America [13].

Fetal anemia can be diagnosed accurately using a non-invasive method with Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) Doppler Studies [14-16]. After calculating the PSV in the MCA using Doppler Sonography, a cut off in the mean plus 1.5 standard deviations is considered very accurate in identifying fetal anemia with a very low false positive rate [15].

A third well-known indication for IUT includes fetal Parvovirus B19 infection leading to fetal anemia and hydrops [17-20]. In such cases, one study on 2012 suggested an increased risk of long-term neurological complications in children received IUT antenatally for parvovirus infection [21]. With Parvovirus B19 infection before 20 weeks of gestation, the risk of fetal death from hydrops and fetal anemia is increased. This risk can be decreased with proper, timely diagnosis and appropriate management with IUT [22].

Another IUT indication which is considered controversial includes fetal platelet transfusion in cases of Fetal/Neonatal Alloimmune Thrombocytopenia (FNAIT) [23]. Current evidence regarding diagnosed FNAIT is suggesting treatment with IVIG antenatally rather than fetal platelet transfusions with different recommended thresholds for neonatal platelets transfusion postnatally [24].

A well-known specific complication of Monochorionic twins' pregnancies includes Twin-Twin Transfusion Syndrome (TTTS) which is a progressive disease that complicates approximately 15% of Monochorionic twins [25,26]. IUT is considered one of the achievable strategies in managing TTTS complicated pregnancies by which improved survival is assumed. However further studies in this area are recommended [27].

Another less common complication specifically associated with Monochorionic twins' pregnancies is the more recently prescribed disease Twins Anemia Polycythemia Sequence (TAPS) [28]. The incidence of TAPS in Monochorionic pregnancies is calculated to be ranging between 2 - 13% as per different studies including both spontaneous and TAPS post-TTTS laser treatment [28-30]. TAPS management is still controversial in the limited number mentioned in the literature [28]. IUT combined with partial exchange transfusion is thought to be advantageous in managing the anemic twin in cases of TAPS [31].

Alpha Thalassemia Major is one of the differential diagnoses that should be thought about whenever fetal hydrops is diagnosed, and IUT might also be considered in such conditions [32]. Hemoglobin Barts leading to hydrops fetalis is becoming an indication for IUT transfusion which is currently known to improve the survival until late adulthood age [33]. Hemoglobin Barts is a recognized type of alpha Thalassemia (homozygous α0-thalassemia) resulting as a consequence from deletion of entirely 4 α-globin genes which is known to be associated with generally poor outcomes [34].

Fetal anemia seen with fetal masses or placental masses such as chorioangioma that can lead to fetal high cardiac output failure and hydrops with increased circulation and vascularity in those masses are also a causative etiology leading to fetal anemia in which IUT might be considered to improve the outcome [35]

Techniques

In the literature, there are multiple methods and routes mentioned with various indications and clinical scenarios. IL van Kamp., et al. suggested the following Preferred order for IUT aiming to transfuse initially in the umbilical vein at the placental insertion site. If this appeared technically challenging, they were aiming for the second option which was the intrahepatic portion of the umbilical vein. Otherwise, a cord-free loop to chosen for umbilical vein insertion site. The fetal heart being used directly to access the fetal circulation was considered one of the latest or final options available for IUT. If previous routs of IUT were ineffective or undoable, intraperitoneal transfusions were performed [36].

Safety and complications

IUT benefits outweigh the risks when indicated, and the procedure is considered relatively safe [37]. Better outcomes are believed when intervention with IUT for fetal anemia is done before signs of hydrops are seen [36]. Complications of IUT continue to occur, and fetal loss from the procedure is estimated to be about 1.6 - 2% per procedure [37-39]. Some studies in the literature are meant to evaluate options to optimize the settings for IUT to minimize the known associated complications [1,39,40].

Procedure-related complications other than fetal loss with an incidence of approximated to be less than 1% include PPROM, infections, emergency cesarean sections [39].

In terms of optimizing IUT settings, the following might be considered: early gestational age is known to increase almost all known procedure-related complications. Those complications are shown to be more when the procedure is done before 20 weeks gestation, and some may consider although still controversial the use of Intravenous Immunoglobulin (IVIG) to delay IUT [39].

The neurodevelopmental complications in association with IUT treatment were evaluated by the LOTUS study which is the largest cohort established worldwide. The incidence of neurodevelopmental damage in offspring managed with IUT for fetal alloimmune anemia is found in this cohort to be (4.8%). The most solid preoperative predictor for those known neurodevelopment complications such as cerebral palsy or hearing loss is the existence of fetal hydrops in those managed cases [41].

The neurodevelopmental complications in association with IUT treatment were evaluated by the LOTUS study which is the largest cohort established worldwide. The incidence of neurodevelopmental damage in offspring managed with IUT for fetal alloimmune anemia is found in this cohort to be (4.8%). The most solid preoperative predictor for those known neurodevelopment complications such as cerebral palsy or hearing loss is the existence of fetal hydrops in those managed cases [41].

Improving the outcomes

One of the suggested options to decrease the rate of complications is to provide an assigned team with expertise in dealing with IUT cases. With experienced hands, the pregnancy loss rate is thought to as low as 0.6% per procedure [39].

Other considerations include transfusing irradiated blood to prevent Graft versus Host disease and not to transfuse the blood straight from storage at 4°C to avoid the risk of fetal bradycardia. The calculated IUT volume should be carefully calculated depending on the gestational age using the donor, fetal and targeted hematocrits equation (Rodeck and Deans, 2008) to avoid overload and cardiac failure. Including all the previously mentioned points, a clear hospital policy must be written in each unit to provide every possible effort that may be beneficial in minimizing the rate of the associated complications [42].

Conclusions

Incidence of IUT is dramatically decreasing with the prophylactic to administration of anti-D in Rh (D) negative pregnancies. Nevertheless, it is still being done in specialized centers with certain indications. Complications can be reduced with proper preparations and adherence to guidelines from respected organizations as well as specialized centers' policies.

Acknowledgement

The author sincerely acknowledges Walaa Alahmadi for her kind support.

Conflict of Interest

No conflict of interest.

Bibliography

1. Pasman, S., *et al*. "Intrauterine transfusion for fetal anemia due to red blood cell alloimmunization: 14 years experience in Leuven". *Facts, Views and Vision in ObGyn* 7.2 (2015): 129-136.

2. Lindenburg IT., *et al*. "Intrauterine blood transfusion: current indications and associated risks". *Fetal Diagnosis and Therapy* 36.4 (2014): 263-271.

3. Moise K. "Intrauterine fetal transfusion of red cells". UpToDate (2018).

4. Liumbruno GM., *et al*. "The role of antenatal immunoprophylaxis in the prevention of maternal-foetal anti-Rh (D) alloimmunization". *Blood Transfusion* 8.1 (2010): 8-16.

5. Berkowitz RL., *et al*. "Intrauterine intravascular transfusions for severe red blood cell isoimmunization: ultrasound-guided percutaneous approach". *American Journal of Obstetrics and Gynecology* 155.3 (1986): 574-581.

6. van Klink JM., *et al*. "Long-term neurodevelopmental outcome after intrauterine transfusion for fetal anemia". *Early Human Development* 87.9 (2011): 589-593.

7. Oepkes D., *et al*. "Doppler ultrasonography versus amniocentesis to predict fetal anemia". *New England Journal of Medicine* 355.2 (2006): 156-164.

8. Landsteiner K and AS Wiener. "An agglutinable factor in human blood recognized by immune sera for rhesus blood". Rhesus haemolytic disease, Springer (1940): 41-42.

9. Levine P., *et al*. "Isoimmunization in pregnancy: its possible bearing on the etiology of erythroblastosis foetalis". *Journal of the American Medical Association* 116.9 (1941): 825-827.

10. van Kamp IL., *et al*. "The severity of immune fetal hydrops is predictive of fetal outcome after intrauterine treatment". *American Journal of Obstetrics and Gynecology* 185.3 (2001): 668-673.

11. Weiner C and JA Widness. "Decreased fetal erythropoiesis and hemolysis in Kell hemolytic anemia". *American Journal of Obstetrics and Gynecology* 174.2 (1996): 547-551.

12. Vaughan JI., *et al*. "Erythropoietic suppression in fetal anemia because of Kell alloimmunization". *American Journal of Obstetrics and Gynecology* 171.1 (1994): 247-252.

13. Moise KJ. "Fetal anemia due to non-Rhesus-D red-cell alloimmunization". *Seminars in Fetal and Neonatal Medicine* 13.4 (2008): 207-214.

14. Mari G., *et al*. "Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization". *New England Journal of Medicine* 342.1 (2000): 9-14.

15. Scheier M., *et al*. "Prediction of fetal anemia in rhesus disease by measurement of fetal middle cerebral artery peak systolic velocity". *Ultrasound in Obstetrics and Gynecology* 23.5 (2004): 432-436.

16. Mari G., *et al*. "Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline# 8: the fetus at risk for anemia–diagnosis and management". *American Journal of Obstetrics and Gynecology* 212.6 (2015): 697-710.

17. Fairley CK., *et al*. "Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B19 infection". *The Lancet* 346.8986 (1995): 1335-1337.

18. Sahakian V., *et al*. "Intrauterine transfusion treatment of nonimmune hydrops fetalis secondary to human parvovirus B19 infection". *American Journal of Obstetrics and Gynecology* 164.4 (1991): 1090-1091.

19. Schild R., *et al*. "Intrauterine management of fetal parvovirus B19 infection". *Ultrasound in Obstetrics and Gynecology* 13.3 (1999): 161-166.

20. Rodis JF., *et al*. "Management and outcomes of pregnancies complicated by human B19 parvovirus infection: a prospective study". *American Journal of Obstetrics and Gynecology* 163.4 (1990): 1168-1171.

21. De Jong EP., *et al*. "Intrauterine transfusion for parvovirus B19 infection: long-term neurodevelopmental outcome". *American Journal of Obstetrics and Gynecology* 206.3 (2012): 204.e1-204.e5.

22. Enders M., *et al*. "Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases". *Prenatal Diagnosis* 24.7 (2004): 513-518.

23. Overton TG., *et al*. "Serial aggressive platelet transfusion for fetal alloimmune thrombocytopenia: platelet dynamics and perinatal outcome". *American Journal of Obstetrics and Gynecology* 186.4 (2002): 826-831.

24. Winkelhorst D., *et al*. "Treatment and outcomes of fetal/neonatal alloimmune thrombocytopenia: a nationwide cohort study in newly detected cases". *British Journal of Haematology* (2018).

25. Wee LY and NM Fisk. "The twin–twin transfusion syndrome". *Seminars in Neonatology* 7.3 (2002): .

26. Fischbein R., *et al*. "Twin-twin transfusion syndrome screening and diagnosis in the United States: A triangulation design of patient experiences". *PloS one* 13.7 (2018): e0200087.

27. Kanda M., *et al*. "OP26. 06: Outcome of surviving twins underwent intrauterine transfusion for severe anemia subsequent to single fetal death in monochorionic twin gestations". *Ultrasound in Obstetrics and Gynecology* 50 (2017): 133-134.

28. Slaghekke F., *et al*. "Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome". *Fetal Diagnosis and Therapy* 27.4 (2010): 181-190.

29. Robyr R., *et al*. "Prevalence and management of late fetal complications following successful selective laser coagulation of chorionic plate anastomoses in twin-to-twin transfusion syndrome". *American Journal of Obstetrics and Gynecology* 194.3 (2006): 796-803.

30. Habli M., *et al*. "Incidence of complications in twin-twin transfusion syndrome after selective fetoscopic laser photocoagulation: a single-center experience". *American Journal of Obstetrics and Gynecology* 201.4 (2009): 417.e1-417.e7.

31. Slaghekke F., *et al*. "Intrauterine transfusion combined with partial exchange transfusion for twin anemia polycythemia sequence: modeling a novel technique". *Placenta* 36.5 (2015): 599-602.

32. Kreger EM., *et al*. "Favorable outcomes after in utero transfusion in fetuses with alpha thalassemia major: a case series and review of the literature". *Prenatal Diagnosis* 36.13 (2016): 1242-1249.

33. Chui DH and JS Waye. "Hydrops fetalis caused by α-thalassemia: an emerging health care problem". *Blood* 91.7 (1998): 2213-2222.

34. Piel FB and DJ Weatherall. "The α-thalassemias". *New England Journal of Medicine* 371.20 (2014): 1908-1916.

35. Khalek N. "Intrauterine Transfusions". *Neonatal Transfusion Practices*, Springer (2017): 73-79.

36. Kamp ILv., *et al*. "Treatment of fetal anemia due to red-cell alloimmunization with intrauterine transfusions in the Netherlands, 1988-1999". *Acta Obstetricia et Gynecologica Scandinavica* 83.8 (2004): 731-737.

37. van Kamp IL., *et al*. "Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization". *American Journal of Obstetrics and Gynecology* 192.1 (2005): 171-177.

38. Schumacher B and KJ Moise Jr. "Fetal transfusion for red blood cell alloimmunization in pregnancy". *Obstetrics and Gynecology* 88.1 (1996): 137-150.

39. Zwiers C., *et al*. "Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures". *Ultrasound in Obstetrics and Gynecology* 50.2 (2017): 180-186.

40. Tiblad E., *et al*. "Procedure-related complications and perinatal outcome after intrauterine transfusions in red cell alloimmunization in Stockholm". *Fetal Diagnosis and Therapy* 30.4 (2011): 266-273.

41. Lindenburg IT., *et al*. "Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study". *American Journal of Obstetrics and Gynecology* 206.2 (2012): 141.e1-141.e8.

42. New HV., *et al*. "Guidelines on transfusion for fetuses, neonates and older children". *British Journal of Haematology* 175.5 (2016): 784-828.

Volume 7 Issue 11 November 2018