Facts Views Vis Obgyn, 2015, 7 (2): 129-136

Original paper

Intrauterine transfusion for fetal anemia due to red blood cell alloimmunization: 14 years experience in Leuven

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Abstract

Objective: **The purpose of this study is to report on the pregnancy and neonatal outcome of intrauterine transfusion (IUT) for red blood cell (RBC-)alloimmunization.**
Material and Methods: **Retrospective cohort study of all IUT for RBC-alloimmunization in the University Hospital of Leuven, between January 2000 and January 2014. The influence of hydrops, gestational age and technique of transfusion on procedure related adverse events were examined.**
Results: **135 IUTs were performed in 56 fetuses. In none of the cases fetal or neonatal death occurred. Mild adverse events were noted in 10% of IUTs, whereas severe adverse events occurred in 1.5%. Hydrops and transfusion in a free loop were associated with an increased risk of adverse events whereas gestational age (GA) at transfusion after 34 weeks was not. Median GA at birth was 35.6 weeks and 9% was born before 34 weeks. Besides phototherapy 65.4% required additional neonatal treatment for alloimmune anemia. Non-hematologic complications occurred in 23.6% and were mainly related to preterm birth.**
Conclusion: **In experienced hands, IUT for RBC-alloimmunization is a safe procedure in this era. Patients should be referred to specialist centers prior to the development of hydrops. IUT in a free loop of cord and unnecessary preterm birth are best avoided.**

Key words: **Intrauterine blood transfusion, fetal therapy, perinatal survival, procedure related complications, fetal anemia, red blood cell alloimmunization.**

Introduction

Intrauterine transfusion (IUT) was introduced in 1963 by Liley, who used an intraperitoneal approach (Liley, 1963). Almost 20 years later, the procedure was improved to a transfusion into the umbilical vein under constant ultrasonographic guidance (Berkowitz and Hobbins, 1981; Clewell et al., 1981). The intravascular approach compared to the intraperitoneal route turned out to be especially advantageous to the hydropic fetus because the absorption of red blood cells is less effective from a peritoneal cavity filled with ascites.

Indications for IUT are fetal anemia and thrombocytopenia, although the latter has become an increasingly rare indication since the introduction of immunoglobulins for fetal and neonatal alloimmune thrombocytopenia (Bussel et al., 1988; Van Den Akker et al., 2007). The majority of IUTs used to be performed for fetal anemia caused by Rhesus-D antibodies. Nowadays, despite a large decrease because of prophylactic administration of anti-D immune globulins in Rhesus negative patients, maternal red blood cell (RBC)-alloimmunization remains an important cause of fetal anemia (Moise, 2008). However, indications

have shifted to a diversity of other antibodies than those against the Rhesus-D antigen. Timely referral is now ensured since irregular antibodies are routinely checked for in maternal blood in the first trimester and repeated later in gestation for Rhesus negative mothers. This has led to a lower number of hydrops in fetuses requiring IUT.

Risk factors for severe fetal anemia included: relevant obstetric history, presence of maternal red blood cell antibodies, ultrasound markers as cardio-, hepato- and splenomegaly and signs of hydrops and diminished fetal movements. Timing of transfusion used to require amniocentesis for determining delta OD450 indicating levels of bilirubin and thus hemolysis (Pasman et al., 2008). This has changed since the introduction of MCA PSV (middle cerebral artery peak systolic velocity) Doppler measurement to predict severe fetal anemia in 2000 (Mari et al., 2000). Because of the accuracy and non-invasiveness of MCA PSV measurement this new technique quickly became the standard (Oepkes et al., 2006). It can be used weekly or more frequently when required and is a reliable diagnostic tool between 16 and 36 weeks gestation in experienced hands. Furthermore, Doppler measurements can be used for timing of subsequent IUTs (Scheier et al., 2006) instead of planning the subsequent IUTs by a standard schedule. Therefore, although the technique of IUT has not significantly changed, the management of these pregnancies has evolved significantly in the last 14 years.

Few studies have reported on the safety of IUT in large cohorts (Van Kamp et al., 2005; Somerset et al., 2006; Tiblad et al., 2011). We will report on the pregnancy and neonatal outcome of all IUTs performed from 2000 till 2014 for fetal alloimmune anemia in the University Hospital of Leuven and identify risk factors for adverse events.

Materials and Methods

Study subjects

All reports of IUTs, performed between January 2000 and January 2014 were collected from the electronic prenatal (Astraia software gmbh Munich, Germany) and obstetrical (Java-KWS, UZ Leuven, Belgium) databases. To ensure full patient inclusion, a cross-check with the hospitals financial records regarding the billing of IUT procedures and with the distribution of blood products from the blood transfusion center was performed. Intrapartum and postpartum data of the children born in referring hospitals, were collected by contacting the referring obstetrician or neonatologist. Prenatal, peripartal and neonatal data were analyzed retrospectively.

In this study, only IUTs for RBC-alloimmunization were included. Hydrops was defined as mild when there was a distinct rim of ascites, with or without pericardial effusion, and as severe when there was an abundant amount of fluid collection, usually ascites, with skin edema (Van Kamp et al., 2001). Prior to 2002, only amniocentesis was used to predict fetal anemia. From 2002 onwards, anemia was predicted by assessment of the MCA PSV, which was converted to multiple of the median (MoM) (Mari et al., 2000). An MCA PSV above 1.5 MoM was considered an indication for IUT. Sonographic features related to fetal hydrops were also indication for fetal blood sampling. A fetus with a hemoglobin value of at least two standard deviations (SD) below the mean for gestational age at fetal blood sampling was regarded as anemic (Nicolaides et al., 1988).

Intrauterine transfusion technique

During the study period, three operators performed the IUTs. Antenatal corticosteroids were given to women carrying fetuses with at least 26 weeks of gestation age before IUT to anticipate the need for an emergency cesarean section. For the same reason, IUT after 28 weeks of gestation were performed under combined spinal epidural analgesia (CSE). Fetal pain relief and immobilization was achieved by either intravenous or intramuscular injection of a curare derivative (pancuronium or cisatracurium) in combination with atropine and fentanyl. A 20 or 22G spinal needle was used for the IUT. The volume of packed cells to be given (V) was calculated using the formula (Moise et al., 1997):

$$V = \frac{\text{FPV (Ht target – Ht first sample)}}{\text{Ht donor blood}}$$

With

FPV (fetoplacental blood volume) = 1.046 + (0.14x ultrasound estimated fetal weight (g))

The target hematocrit (Ht) was usually 40%. The hematocrit of the fetal blood sample was assessed through a Sysmex pocH-100i (Sysmex NV Belgium). The donor blood was O Rhesus D-negative or compatible with the antibody of the mother. It was leucodepleted and obtained from CMV negative donors, collected within 72 hours before the procedure. The blood was concentrated to a hematocrit between 75 and 80% and underwent gamma irradiation less than six hours before administration.

IUT was performed into the umbilical vein either at the placental cord root, into its intrahepatic course or into a free loop of cord, by choice of the operator. After completion of the IUT, a second blood sample was taken to confirm adequate transfusion. In some cases blood was transfused into the peritoneal cavity as an addition to the IV transfusion. Usually, the aim was to diminish the direct burden on the cardiovascular system, or to prolong the period until the next procedure. Delivery was usually planned 2 weeks after the last IUT. Neonatal follow-up was collected until discharge from the hospital in good condition, including ambulant controls during the first 6 weeks of life.

Mild procedure related adverse events were considered e.g. transient contractions requiring tocolysis and transient bleeding from the puncture site. Severe adverse events were defined as (1) rupture of membranes or preterm birth within seven days after transfusion, (2) intrauterine infection, (3) emergency cesarean section for fetal distress within 24 hours after procedure, (4) fetal death and (5) neonatal death (Van Kamp et al., 2005).

Statistical analysis

Data were stored and analyzed using an Excel database (Microsoft Corp) and analyzed by SPSS for Windows version 20.0.0. Univariate analysis was performed with procedure related adverse events as the independent factor and hydrops, severity of anemia, gestational age prior to 20 weeks or after 34 weeks and puncture technique as dependent factors. Continuous variables were analyzed using parametric independent samples t-test and categorical variables were analyzed using Chi-square test as appropriate. For the multivariate logistic regression analysis, only variables that were significant on univariate analysis were included in the model. A value of $P < 0.05$ was considered to indicate statistical significance.

Results

Population and hematologic parameters

During the study period, 135 IUTs were performed in 56 fetuses. Most were transfused in the last eight years, as such, 89% of IUTs were performed between 2006 and 2014. There was a median of two IUTs per fetus, with a range of one to seven. The median gestational age at the time of procedure was 31+1/7 weeks, ranging from 18+2/7 weeks, to 35+6/7 weeks. Number of IUTs performed before 20 weeks was three (2%) and after 34 weeks it was 20 (15%). The indications for IUT are presented in Table I. The contribution of Rhesus-D alloimmunization did not change over time.

Hematological values before and after IUT are shown in Table II. The hemoglobin level before IUT was found to be between –1.1 and –10.8 SD below the normal mean (Nicolaides et al., 1988). The hemoglobin level was within 2 SD (non anemic) in four of 127 procedures, which were all first transfusions between 29 and 33 weeks. In 5.4%, the achieved Ht was below 35%, mostly because of concern for cardiovascular decompensation. In 6.9% the achieved Ht was above 45%.

There were 48 (86%) nonhydropic, five (9%) mildly hydropic and three (5%) severely hydropic fetuses at first transfusion. At subsequent IUTs, seven fetuses were mildly hydropic and one fetus was still severely hydropic. As expected, the mean hemoglobin level and hematocrit before transfusion were significantly lower in mildly and severely hydropic fetuses than in nonhydropic fetuses, 6.4 g/dL versus 8.5 g/dL ($p < 0.001$) and 22% versus 26% ($p < 0.001$), respectively.

Technique

The puncture was done at the level of the umbilical cord root in 64 cases (47.4%), mostly transplacental (n = 60), occasionally transamniotic (n = 4), or directly into a free loop of the umbilical cord in 26 cases (19.3%). In 39 procedures (28.9%), the intrahepatic portion of the umbilical vein was punctured. In seven of these intrahepatic cases, a combination of IV and IP transfusion was performed. In six cases (4.4%), the puncture site was not recorded.

Procedure related complications and mortality

There were no fetal or neonatal deaths in our study population. One hydropic fetus with Kell antibodies (for which one uneventful transfusion was given) was later diagnosed with cerebellar hypoplasia and the parents opted for termination of pregnancy.

90% (n = 121) of the procedures were uneventful. In 10% (n = 14), mild adverse events occurred. In two (1.5%) of these 14 cases, this led to a severe adverse event, as defined in the method section (Van Kamp et al., 2005): one emergency cesarean section within 24 hours after IUT and one preterm birth within 7 days after IUT, described in more detail below.

The most common mild event was prolonged post-procedure hemorrhage for more than one minute from the puncture site (n = 7, 5.2% of all procedures), which in most cases (n = 6) did not lead to a severe adverse event, although in one case

Table I. — Type of antibody causing the fetal anemia, per fetus and per intrauterine transfusion (IUT).

		Nr of fetuses (%)	Nr of IUTs
Red blood cell-alloimmunization			
Antibodies:	D (alone or with C or E)	45 (80.4%)	110 (81.5%)
	D (with Kell or Jka)	2 (3.6%)	8 (5.9%)
	C (with E or G)	2 (3.6%)	2 (1.5%)
	c (alone or with E)	4 (7.1%)	9 (6.7%)
	Kell	2 (3.6%)	5 (3.7%)
	E	1 (1.7%)	1 (0.7%)
Total		56 (100%)	135 (100%)

after a moderate bleeding from a puncture in a free loop of the cord, a cesarean section was performed within 24 hours after IUT, at 30 weeks. This cesarean section was because of fetal distress of unknown cause (hypothesis of vasoconstriction or thrombosis of the umbilical cord). Prolonged bleeding was noted after five punctures in a free loop of the cord and two at the cord root (one transamniotic and one transplacental approach).

In two cases IUT was accidentally performed partially intraperitonealy because of visual impairment during IUT (5.3% of IUTs in the intrahepatic part of the umbilical vein).

Another frequent mild adverse event was uterine contractions (n = 4, 3% of all procedures), which was treated with tocolysis successfully in three cases but led to the one other serious adverse event of a birth within two days after uneventful IUT at 30 weeks of gestation in a severely hydropic fetus.

Influence of hydrops, gestational age and technique

The number of adverse events (mild and severe) is shown in Table III showing the influence of hydrops, severity of anemia, gestation, and location of IUT.

No adverse events were encountered when IUT was planned to combine IV with IP transfusion (n = 5). There were no reports of abnormalities in the cases the neonates that had received IP transfusion (n = 6).

Multivariate logistic regression analysis showed that hydrops only was independently related to adverse events ($p = 0.02$, pseudo-R^2 Nagelkerke = 0.071).

Pregnancy and neonatal outcome

Outcome of pregnancy is shown in Table IV (one pregnancy terminated at 23 weeks not included). We noted a trend to increased GA at birth during the study period. Most deliveries were induced because of the RBC-alloimmunization. Of the emergency cesarean sections, one case was considered procedure related, one case anemia related (before IUT) and one case not related to anemia or IUT. The lowest recorded pH was 6.80, in the case with severe hydrops that went into preterm labor as mentioned previously.

The majority of the neonates (51/55, 92.7%) were treated for hemolytic disease of the newborn (HDN). All of treated neonates received phototherapy. In 15 (27.3%) cases this was the only additional therapy. Top-up transfusion in 19 (34.5%), exchange transfusion in 2 (3.6%) and both in 15 (27.3%) cases were given as additional treatment for HDN. In addition, IV-immunoglobulins were given to 34/55 (61.8%) neonates and treatment with recombinant erythropoietin was given to 8/55 (14.5%) neonates. A change in bilirubin cut-off values around 2009 is reflected in a decline in exchange transfusions, since then only two have taken place. In 4/17 (23.5%) neonates with exchange transfusion, platelet transfusion was necessary afterwards.

Table II. — Mean, SD and range of hemoglobin (Hb), hematocrit (Ht) and platelets (PLT), before and after intrauterine transfusion (IUT).

	Before IUT			After IUT		
	n	Mean (SD)	range	n	Mean (SD)	range
Hb (g/dL)	127	8.3 (2.1)	1.6-12.7	127	13.6 (1.6)	5.2-17.5
Ht (%)	131	25.2 (6.1)	8.9-40.0	130	40.3 (3.9)	16.1-53.0
PLT (*10^9/L)	95	213 (73)	13-379	99	146 (57)	20-342

Table III. — Relation of percentage adverse events (mild and severe) to hydrops, severity of anemia (Z-Hb), gestational age at IUT and location of transfusion.

	Uneventful IUT	Adverse events (mild and severe)	p-value	Nr severe adverse events
Hydrops non	109 (92%)	10 (8%)	< 0.001	1
Hydrops mild	10 (83%)	2 (17%)		0
Hydrops severe	2 (50%)	2 (50%)		1
Mean Z-Hb	-5.3 SD	-5.9 SD	0.11	
IUT < 20 weeks	3 (100%)	0 (0%)	0.56	0
IUT 20-34 weeks	99 (88%)	13 (12%)		2
IUT > 34 weeks	19 (95%)	1 (5%)		0
Cord root transplacental	56 (93%)	4 (7%)	< 0.001	0
Cord root transamniotic	3 (75%)	1 (25%)		0
Free loop	20 (77%)	6 (23%)		2
Intrahepatic	36 (92%)	3 (8%)		0

Non-hematological neonatal complications can all be considered as prematurity related problems, occurring in 13 of 55 neonates (23.6%). Conventional ventilation or continuous positive airway pressure was needed in eight cases. Gestational age (GA) at date of birth in these cases ranged from 30.7 to 35.9 weeks. In these eight cases ventilation was further complicated by pneumothorax in two cases, persistent hypoglycaemia in one case and IVH gr2 with hydrocephalus in one case. Only short oxygen therapy was needed in two cases with GA at birth of 33.9 and 35.6 weeks. Necrotizing enterocolitis occurred in three cases with GA at birth between 35.1 and 36.3 weeks.

Discussion

In our series of 135 IUTs for alloimmune anemia, there was no fetal, peripartal or neonatal death and neonatal morbidity was mostly related to hematologic complications and the consequences of a late preterm birth. Mild adverse events (prolonged bleeding, accidental intraperitoneal transfusion and uterine contractions) occurred in about 1 in 10 IUTs. Severe adverse events were rare and occurred in only two procedures (1.5% procedure related risk).

Our study is one of the few cohorts of IUTs for alloimmunization described since the large cohort published by Van Kamp et al. (2005). They reported on 254 patients in whom 740 IUTs where performed between 1988 and 2001. They found a severe adverse event rate of 1.6%, which is similar to the result in our study of 1.5%. However, they described a perinatal mortality of 4.7% (12/254), whereas no deaths occurred in our series. This in part can be explained by the fact that in their series the fetus was (still) hydropic in 21% of IUTs, whereas this was 12% in our series. The timing of first IUT by MCA PSV instead of amniocentesis is unlikely to cause this difference. Screening for antibodies have made timely referral possible, decreasing the percentage of hydrops. Noteworthy is that fetal loss in case of severe hydrops after uncomplicated transfusion was not taken into account of the procedure related risk in their study. A different study describes a cohort from 1997 to 2004 (n = 221 IUTs) (Somerset et al., 2006). A perinatal loss rate of 4.7% and a rate of procedure related complications of 7.6% (mostly bradycardia, ruptured membranes and chorioamnionitis) were reported. Another study describes a cohort from 1990 to 2010 (n = 284 IUTs) (Tiblad et al., 2011). A 1.4% perinatal loss rate and a 4.9% rate of procedure related complications are reported (mostly bradycardia and needling problems). Yet another study describes a cohort from 1999 to 2012 (n = 225 IUT's), including procedures for Parvo B19 induced anemia (Garebedian et al., 2014). A perinatal loss rate of 10% in the alloimmunized group is documented. However, in this study they also performed intrauterine exchange transfusions, which had a higher complication rate compared to the usual IUT. The earlier detection as well as the progress in fetal therapy and in neonatal care, may well explain the better survival rates in our series, that report 56 cases treated between 2000 and 2014.

In our study, hydrops was the only risk factor for adverse events in a multivariate analysis. Hydrops was also shown to be an important risk factor for later neurodevelopmental impairment in the long-

Table IV. — Pregnancy en neonatal outcome after intrauterine transfusion (IUT) (GA = gestational age, Hb = hemoglobin, Ht = hematocrit).

Outcome	n = 55
Median GA at birth (range)	35.6 (30.7-37.6)
Nr GA at birth < 34 weeks	5 (9%)
Nr GA at birth ≥ 37 weeks	8 (14.5%)
Median birth weight (range)	2635 (1300-3450)
Nr Spontaneous delivery	4 (7.3%)
Nr Induction of labor	26 (47.3%)
Nr Planned cesarean section	22 (40%)
Nr Emergency cesarean section	3 (5.4%)
Nr Apgar ≥ 7 at 1 minute	45 (81.8%)
Nr Apgar ≥ 7 at 5 minutes	54 (98.2%)
Median cord blood pH (range)	7.32 (6.80-7.43)
Median Hb (g/dL) after birth (range)	12.3 (6.2-17.7)
Median Ht (%) after birth (range)	36.2 (19-56)

term follow-up Lotus study (Lindenburg et al., 2012). As such, we can only advocate early detection of anti-RBC antibodies, as well as swift referral to a specialized fetal therapy center to avoid the onset of hydrops (Van Kamp et al, 2001).

We advocate a onetime referral to a tertiary centre in case of increased red blood cell antibodies for counseling and planning of follow-up and timing of delivery. High risk pregnancies should best be followed in a tertiary centre from 15 to about 20 weeks pregnancy. After 36 weeks the MCA PSV is more often false positive or false negative, thus should not be used as a single crucial diagnostic for clinical management.

In a recent study, a higher perinatal loss rate was shown for fetuses receiving their first IUT before 20 weeks (Lindenburg et al., 2013). We could not confirm this finding, probably due to the small number of cases in our series (n = 3 IUTs). We also did not encounter more adverse events after 34 weeks (n = 20 IUTs). Good experience with IUTs late in pregnancy made us more reluctant for premature delivery and less reluctant for planning one more IUT up to 36 weeks.

The location of the transfusion was related to the risk of adverse events in univariate analysis. A puncture in the free loop of the umbilical cord or transamniotically in the cord root of the placenta had a higher risk compared to transplacental puncture in the cord root or in the hepatic umbilical vein. Prolonged bleeding after puncture in a free loop of cord is a known risk factor (Van Kamp et al, 2005; Tiblad et al., 2011). Thus, IUT performed transamniotically at the cord root or in the free loop should be reserved for otherwise inaccessible transfusion sites.

An important number of neonatal complications in our study is related to prematurity. In the Lotus study both birth before 32 weeks and severe neonatal morbidity were significant risk factors for neurodevelopmental impairment (Lindenburg et al., 2012). Thus, we advocate to prolong the pregnancy and rather plan another transfusion up to 35 weeks or even 36 weeks, to try to plan delivery after 37 weeks. This can also increase the chance of successful induction of labor.

During the study period the practical protocol for IUT in our center has evolved. Nowadays, Nifedipine (Adalat Oros® 30mg) is often given as a tocolyticum before procedure and if necessary repeated the same day. In our case series, the four patients with contractions after IUT had not received Nifedipine. In contrast to fetoscopic procedures, antibiotics are not administered routinely at IUT in our center, since we never encountered post procedure infection. Chorio-amnionitis has been described in other studies though (Van Kamp et al, 2005; Somerset et al. 2006). Fetal paralyticum and analgeticum are used routinely nowadays. Especially in transfusion in the hepatic umbilical vein, it is of benefit to start with a separate injection to administer fetal medication IM. We did not encounter any PPROM within a week after IUT in our study cohort. Thus the risk of an extra puncture, with a fine needle, seems justified. Adding Atropine to the fetal medication seems to be protective for fetal bradycardia since this was reported frequently in earlier cohort studies and was not described during any IUT in our cohort (Somerset et al., 2006; Tiblad et al., 2011). After 26 weeks, routine corticosteroid administration is given to ensure lung maturation in case of preterm birth, which is a

common occurrence. After 28 weeks a CSE is usually given to be prepared for back-up cesarean section. The need for CSE is open for debate, as we did not encounter the need for urgent cesarean section during the procedure in the last 14 years. When prolonged bleeding leads to persistent bradycardia or unreassuring CTG monitoring, urgent cesarean section should be a possibility. Nevertheless, CSE can lead to maternal hypotension, compromising the fetal condition in some cases. We recommend performing the procedure in an operating theatre where cesarean section can be performed swiftly when needed.

The target hematocrit at the end of transfusion was met in most instances in our study. We advocate adjusting the target hematocrit according to gestation. A normal hematocrit at 18 weeks is 33%, at 22 weeks 35%, at 26 weeks 37%, at 30 weeks 39% and at 34 weeks 41% (Weiner et al., 1991). It is to be expected that the hematocrit will increase somewhat in the hours after IUT (Kamping et al., 2014). Thus caution should be taken to transfuse up to polycytemic values. The p95 at 24 weeks is 40% and at 34 weeks in 45% (Weiner et al., 1991).

Neonatal management of hemolytic disease in the newborn due to alloimmunization has also evolved in the past years. Especially the use of curves for bilirubin values with adjusted cut-off points has ensured a decline in exchange transfusions (Smits-Wintjens et al., 2008). Neonatal management consists of intensive phototherapy starting immediately after birth whereas IVIG and EPO are no longer routinely used since 2011 (Smits-Wintjens et al., 2011; Santos et al., 2013; Mainie, 2008). It is noteworthy that three cases of NEC were encountered in neonates born after 35 weeks. All these neonates had received IVIG. It has been suggested that IVIG increase the risk of NEC in neonates with hemolytic disease (Figueras-Aloy et al., 2010). We advocate performing an early neonatal brain scan in all neonates that received an IUT, since we encountered a case of intraventricular hemorrhage grade 2 with sequelae in the neonatal period.

Shortcoming of our study is the retrospective design, which may lead to an underreporting of mild adverse events and lack of long term follow-up of neuro-developmental outcome as is reported in the Lotus study in 291 patients who received IUT (Lindenburg et al, 2012). Neurodevelopmental impairment was shown to be around 5%.

In conclusion, in experienced hands, intrauterine transfusion is a safe and effective procedure to treat RBC-alloimmunization. We did not encounter any perinatal mortality in our center over the last 14 years. Adverse events were mostly related to hydrops, so that timely referral remains mandatory. Since the number of patients with alloimmunization will decline in coming years, it is important to centralize these procedures in centers of excellence to maintain enough needling experience per operator. Also, management in centers of excellence may avoid an unnecessary preterm birth and optimize neonatal management of alloimmune anemia.

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