Fetal fluid and protein dynamics
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Fluid shift out of the fetal circulation during intrauterine red cell transfusion

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Abstract

Introduction
Intrauterine transfusion presents a considerable burden on the fetal circulation by increasing volume and pressure. Already during transfusion, a fluid shift out of the fetal circulation occurs. Aim of the study was to quantify the intraprocedural fluid shift, and the effect of procedural and fetal characteristics on this fluid shift.

Methods
In 95 alloimmunized pregnancies, we calculated fluid shift at first intrauterine transfusions, by determining initial and final blood volumes. We evaluated the association of the fluid shift with speed and volume of transfusion, severity of anemia and presence of hydrops.

Results
Of the included fetuses, 11 were mildly hydropic and 4 were severely hydropic. A mean fluid shift of 36% of transfused volume was found. Fluid shift related positively to transfused volume (p<0.001), and inversely to speed of transfusion (ml/kg/min) (p<0.001). The % fluid shift of transfused volume was not related to severity of anemia (p=0.55) or hydrops (p=0.66). At low gestational age, fetuses had been unintentionally burdened with relative high volume and speed of transfusion.

Discussion
Around one third of transfused volume is lost from the intravascular compartment already during intrauterine transfusion. However, a large variation, only partly explained by volume and speed of transfusion was observed. Severity of anemia or hydrops played no clear-cut role, therefore, other unknown factors that require further studies may explain the variation in fluid shift. The probability that hematocrit will still increase after transfusion, due to a continuing fluid shift, should be considered in transfusion policy.
Introduction

During intrauterine red cell transfusion, a considerable volume of donor blood is administered in a short period of time. The transfused volume is up to 20 to 60% of initial fetoplacental blood volume, while transfusion-times are merely 10 to 30 minutes. It has been shown that both arterial and venous blood pressure significantly increase after intrauterine transfusion [1-4].

Increase in fetoplacental blood volume after transfusion has been shown to be smaller than added donor blood volume [5;6]. Red cells cannot leave the intravascular compartment so this volume loss is believed to be the result of a loss of plasma. This immediate fluid shift can theoretically take place towards the interstitium of the fetus or that of the placenta, the maternal circulation or even towards amniotic fluid, for example through blood vessels on the surface of the placenta.

In animal experiments, Brace et al found that 37% of the transfused volume was shifted out of circulation already during the procedure [5]. One hour after transfusion, another 20% was lost. In a study in human fetuses, Hoogeveen et al found a similar mean fluid shift during transfusion of 31% of transfused volume [6].

Improved insight in pathophysiology and fluid dynamics around transfusion is important to further reduce fetal mortality and morbidity in these high risk pregnancies. Prevention of volume overload and prevention of unphysiological elevation of hematocrit in the period following transfusion, can be important steps in improving safety and decreasing morbidity as a result of intrauterine transfusion [7].

Purpose of this research was to investigate to what extent the fluid shift was influenced by transfusion rate and fetal condition. We hypothesised that the amount of fluid shift would be positively correlated with volume and speed of transfusion, and could be associated with severity of anemia and presence or absence of fetal hydrops.

Methods

Our methods for treatment of severe fetal alloimmune anemia with intrauterine transfusion have been described previously [8]. In short, a pre-transfusion sample is taken to measure the hemoglobin concentration and hematocrit (Ht). The required amount of donor blood \( V_{\text{donor}} \) is determined by the formula proposed by Rodeck et al. [9]:

\[
V_{\text{donor}} = \frac{V_{\text{initial}}}{\text{FP}} \times \frac{\text{desired Ht} - \text{initial Ht}}{\text{Ht donor blood}}
\]
The initial fetoplacental blood volume ($\text{FPV}_{\text{initial}}$) is based on estimated fetal weight and normal values for fetoplacental blood volume as proposed by Nicolaides et al. [10]. Usually, Rodeck’s formula underestimates the required donor volume, to reach desired hematocrit, since the formula does not take an increase in blood volume during transfusion into account. Furthermore, normal values found by Nicolaides were somewhat lower than what we have calculated [6;11]. Packed red cells, with a hematocrit of around 80%, are usually transfused at 5 ml/min, depending on fetal heart rate stability. After the transfusion and a two minute waiting period, to allow even distribution of the donor blood, a post-transfusion sample is taken to check if the desired level of hematocrit (45-50%) is reached. Fetoplacental blood volume is routinely calculated at every transfusion.

During the study period, from January 2002 to September 2006, we included all first intrauterine transfusions for fetal anemia due to red cell alloimmunization. We excluded fetuses with non-immune hydrops, structural or chromosomal anomalies, or congenital infection. Estimated fetal weight was determined with the formula of Hadlock et al. [12], using sonographically measured biparietal diameter, head circumference, abdominal circumference and femur length, within two days before or at the time of transfusion. Hydropic fetuses were classified as mild or severe using criteria described by Van Kamp et al. [13]. Briefly, mild hydrops was defined as the presence of a distinct rim of ascites, with or without pericardial effusion, while severe hydrops was defined as the presence of a more abundant amount of fluid collection, usually ascites, with skin edema. In severely hydropic fetuses, fetal weight was also estimated using the formula of Hadlock, but with a measurement of the abdominal circumference that excluded the abundant amount of ascites. For this purpose, the tracing ellipse, in the usual transverse plane, included all fetal organs, except the intra-abdominal collection of fluid and the anterior abdominal wall. In this way an attempt was made to estimate the nonhydropic size of the fetus.

Initial fetoplacental blood volume ($\text{FPV}_{\text{initial}}$) was calculated as described by our group previously [11]. In short, given the known amount of adult hemoglobin in the donor blood, and the dilution of fetal hemoglobin with adult hemoglobin, the initial red cell volume ($\text{RCV}_{\text{initial}}$) can be calculated. Since the initial hematocrit is known, initial fetoplacental blood volume can then be determined.

The volume ($V$) and hematocrit ($Ht$) of the initial sample and the transfused donor blood, are used for calculation of final red cell volume ($\text{RCV}_{\text{final}}$). The final hematocrit together with calculated final red cell volume determines final fetoplacental blood volume ($\text{FPV}_{\text{final}}$). Next, the difference between initial blood volume with added donor blood volume and the calculated final blood volume, determines the fluid shift. The
volume of atracurium (atr) and saline (NaCl) administered during transfusion are taken into account, to determine the most exact volume of fluid shift.

The following formulae where used to determine the final fetoplacental blood volume and subsequently the volume of fluid shift:

\[
R_{CV_{\text{final}}} = R_{CV_{\text{initial}}} - (V_{\text{sample}} \cdot H_{\text{initial}}) + (V_{\text{donor}} \cdot H_{\text{donor}})
\]

\[
F_{PV_{\text{final}}} = \frac{R_{CV_{\text{final}}}}{H_{\text{final}}}
\]

\[
V_{\text{fluid shift}} = F_{PV_{\text{initial}}} - V_{\text{sample}} + V_{\text{atr}} + V_{\text{donor}} + V_{\text{NaCl}} - F_{PV_{\text{final}}}
\]

To calculate transfusion speed, the time at first sampling and at last sampling was noted. Thus, time during occasional needle dislodgement or complications otherwise delaying the procedure was included.

Linear regression analysis was used to investigate the relations between fluid shift and transfused volume, and speed of transfusion. Quadratic regression analysis was used to investigate the relation between speed of transfusion and gestational age. Severity of anemia was expressed as the standardized hemoglobin deficit (Z-hemoglobin), defined as the number of standard deviations that an actual value deviated from the normal mean for gestational age. Reference values for hemoglobin were derived from the literature [14]. Linear regression analysis was used to investigate the relation between the percentage of fluid shift of transfused volume and severity of anemia (Z-hemoglobin). Oneway anova was used to test the difference between the percentage of fluid shift of transfused volume in nonhydropic, mildly hydropic and severely hydropic fetuses. We considered a p-value of <0.05 to be significant. Statistical software programs SPSS 16.0.2 and Graphpad Prism 5.0 were used.

Results

During the study period, we performed 125 first intrauterine transfusions in red cell alloimmunized anemic fetuses. We included 95 transfusions with complete data. Alloimmunization, was caused by anti-D or anti-D+C (n=74), anti-Kell (n=12), anti-c (n=6), anti-Jka (n=1), anti-Kpa (n=1) and anti-Verdegaal (n=1). Gestational age ranged from 17 to 35 weeks and estimated fetal weight ranged from 167 to 3033 gr. There were 80 nonhydropic fetuses, 11 mildly hydropic and 4 severely hydropic fetuses.
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included. Hemoglobin concentration ranged from 1.8 to 11.8 g/dl. The severity of anemia (Z-hemoglobin) ranged from -2.1 to -11.7 SD and was not related to gestational age (p=0.27).

The mean amount of transfused volume was 52 ml/kg estimated fetal weight. The mean amount of transfused volume was 43% of initial fetoplacental blood volume and this percentage was strongly correlated to gestational age (p<0.001). Notably, fetuses below 20 weeks gestation (with a mean Z-hemoglobin -7.5 SD) received a transfused volume of 48 to 99% of initial fetoplacental blood volume, while this was 11 to 55% in fetuses above 30 weeks gestation (with a mean Z-hemoglobin -6.7 SD).

A fluid shift with a range of 1 to 83 ml was found. The mean fluid shift was 14% of the initial fetoplacental blood volume (SE=0.7%, SD=7%) and 36% of the transfused volume (SE=2.2%, SD=21%). Figure 1 shows that the fluid shift was positively and linearly related to the amount of transfused volume (R²=0.40, p<0.001).

As shown in figure 2, the fluid shift was inversely related to the speed of transfusion, expressed as transfused volume/ estimated fetal weight/ minute (R²=0.18, p<0.001). However, there is no evident relation with amount of fluid shift at low transfusion speed. Surprisingly, as shown in figure 3, we found a strong decrease of relative transfusion speed with gestational age (R² quadratic=0.68, p<0.001).

Figure 4 shows the wide variation in fluid shift, without an evident influence of severity of anemia or the presence of hydrops. The relation between the percentage fluid shift of transfused volume and Z-hemoglobin was not significant (R²=0.01, p=0.55). Finally, there was no significant difference, between the means of the nonhydropic, the mildly hydropic and the severely hydropic fetuses, in the percentage fluid shift of transfused volume (respectively 35%, 41% and 40%, p=0.66).
Figure 1  Correlation between transfused volume and extravascular fluid shift during intrauterine transfusion. Hydropic fetuses are depicted.

![Graph showing correlation between transfused volume and fluid shift](image)

$R^2 = 0.40$

Figure 2  Correlation between transfusion speed and extravascular fluid shift during intrauterine transfusion. Hydropic fetuses are depicted.

![Graph showing correlation between transfusion speed and fluid shift](image)

$R^2 = 0.18$
Figure 3  Relative transfusion speed in our patients as a function of gestational age. Hydropic fetuses are depicted.

Figure 4  Correlation between severity of anemia (Z-hemoglobin) and % fluid shift of transfused volume during intrauterine transfusion. Hydropic fetuses are depicted.
Discussion

In this study, the volume of donor blood given to the fetus was approximately half of the initial fetoplacental blood volume. The mean extravascular fluid shift during intrauterine transfusion was 36% of the transfused volume. As expected, we found a positive linear relation between volume of fluid shift and transfused volume. In contrast to our hypothesis, the fluid shift was decreased at relatively high speed of transfusion. Also, we found no relation between severity of anemia or presence of hydrops, and the relative amount of fluid shift.

Our large human study confirms data from previous animal and human studies, showing that around one third of transfused volume leaves the intravascular space during transfusion [5;6]. A large interindividual variation was observed, though. This may in part be due to measurement error, since some of the measured values (that are expected to contain small errors) appear more than once in our formula, enlarging the over-all error in calculated fluid shift. Furthermore, biological variation in vascular compliance, interstitial compliance and capillary filtration coefficient may explain the variation in fluid movement between vascular and interstitial space. In general, the fetus is able to keep its blood volume closer to normal than adults after reduction or expansion in volume [15;16]. Besides these causes of variation, other factors may influence the amount of fluid shift, some of which were investigated by us.

One of the factors influencing fluid shift was the speed of transfusion. We initially hypothesised that with increasing speed of transfusion, blood pressure is increased accordingly, thus enhancing fluid shift. However, there was a decrease in amount of fluid shift with higher transfusion speed. It is possible that vascular compliance increases with higher infusion pressure, or capillary filtration capacity restricts fluid shift velocity. Apparently fluid shift is a process requiring a certain amount of time. It is therefore likely that this process continues after transfusion.

Other factors, hypothesized to influence the amount of fluid shift, were severity of anemia and presence of hydrops. On average, fetuses with severe anemia have a decreased concentration of plasma albumin [17]. This may be the result of decreased synthesis in the fetal liver [18] or a relative increase in plasma volume [11]. Another possibility is that albumin is lost from the intravascular compartment due to endothelial damage [19;20], which could imply an increase in the capillary filtration coefficient. Furthermore, a smaller difference between the concentration of albumin in the intravascular compartment and the interstitial compartment results in a diminished
capacity to contain water in the vascular compartment. Cardiac backward failure, leading to an increase in central venous pressure, also could promote extravascular fluid shift. Moreover, fetuses are particularly susceptible to interstitial fluid accumulation because of their vulnerability to venous pressure on lymphatic return [21]. On the other hand, cardiac forward failure could result in a failure to increase arterial blood pressure during transfusion, thus relatively reducing fluid shift. Finally, congestion in anemia can also be the effect, not of myocardial failure, but of retention of fluid in the vascular compartment as a result of a kidney mediated neuro-humoral cascade, induced by a low arterial pressure as a consequence of the low hemoglobin level [22-24]. In our study, there was no evident difference in fluid shift between mildly and severely anemic fetuses and nonhydropic or severely hydropic fetuses. Caution in drawing conclusions should be made, since the number of severely hydropic fetuses was limited. Our findings, however, are in accordance with the findings by Brace et al. [5] and Hoogeveen et al. [6]. Both positive and negative influencing factors might be present, thus not resulting in a clear-cut effect on fluid shift.

We found that younger fetuses in our hospital were transfused with significantly higher relative volumes and speeds. In fact, fetuses below 20 weeks’ gestation were transfused with relative speeds up to 5 times higher than fetuses above 32 weeks. This usually was an unintentional effect. With increasing gestational age, fetoplacental blood volume increases exponentially, since it is linearly correlated with fetal weight [11]. A much smaller amount of donor blood is thus required to achieve a desired rise in hematocrit in younger fetuses. Further, administering donor blood at the same speed is thus a much higher burden in younger fetuses. It is possible that this attributed to the fact that low gestational age is a risk factor for complication of intrauterine transfusion, besides the increased procedural difficulty [7]. Perinatal mortality was 5.6% per procedure between 16 and 20 weeks, compared to 0.8% between 32 en 36 weeks. Fetal mortality after intrauterine transfusion has already been shown to be associated with a large increase in venous pressure [2], as well as with a relative large increase in hematocrit [25].

In animal experiments, fetal hematocrit was further increased in 1 hour after transfusion [5]. Although fetoplacental blood volume was not normalized after 24 hours, it was found that human fetuses maintain their total blood volume at different degrees of anemia [11]. Thus, it can be expected that a return to initial fetoplacental blood volume will take place shortly. This has clinical implications, since it may be hazardous to let the hematocrit increase to polycythemic values. In a recent (possibly pre-selected) cohort of neonates that had received an intrauterine transfusion, 24%
showed moderate to severe abnormalities on cranial ultrasound (personal communication G. van Wezel-Meijler), possibly baring clinical consequences. This may be due not only to hypoxic but also to polycythemic mediated damage. The hematocrit in the final sample after transfusion could be considered to be a temporary value. The formula of Rodeck [9], that seems to underestimate the required amount of donor blood, therefore could actually be a correct guideline, assuming that in the hours or days after transfusion fetoplacental blood volume returns to the initial value. Final hematocrit in the Rodeck formula would then become the desired level that is chosen, not directly after transfusion but after a few hours or days.

The decay of donor cells has been calculated to be around 2% per day [26], by comparing the final hemoglobin level after transfusion with the initial hemoglobin level at the subsequent transfusion. This probably is an underestimation of the adult red cell decay, assuming that hematocrit first rises in the period after transfusion, before it declines again. This problem was already addressed by Egberts et al. since they sometimes found a surprisingly low decline and even an increase of adult hemoglobin concentration at the second transfusion. Furthermore, it is likely that the donor red cells do not decline linearly in time [27-29]. The difference between the adult red cell volumes at the end of transfusions, as calculated in this study, and the adult red cell volumes at the beginning of the subsequent transfusions, measured at different time intervals, might learn us about the actual decay of donor red cells in human fetuses.

Future research could resolve what other factors influence the fetal cardiovascular reaction to intrauterine transfusion. Calculations as were performed in this study can be combined with measurements of blood pressure, colloid osmotic pressure or rheological measurements before and after transfusion, difference in placenta size, changes in ANF, angiotensin, AVP and other hormone concentrations and functional echocardiography. From the factors studied in this investigation, volume overload can not be easily predicted. Our advice is to be cautious with amount and speed of transfusion in younger fetuses and to strive for a hematocrit that is not higher than the desired level at the end of transfusion.

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