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Consequences of fetomaternal haemorrhage after intrauterine transfusion

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Abstract

Fetomaternal haemorrhage was studied after 68 consecutive fetal intravascular transfusions performed in 20 patients with Rh isoimmunisation. α Fetoprotein concentration was assayed in maternal blood taken before, and immediately after each transfusion and three and 24 hours later. An increase of 50% or more in the concentration in any of the samples after transfusion was considered to indicate fetomaternal haemorrhage. Fetal α fetoprotein concentration in blood sampled before transfusion was also assayed and the amount of fetomaternal haemorrhage calculated. Fetomaternal haemorrhage occurred in 21 of 32 patients with an anterior placenta and in six of 36 with a posterior or fundal placenta. The mean estimated volume of haemorrhage was 2·4 ml, which was on average equal to 3·1% of the total fetoplacental blood volume. When the volume of fetomaternal haemorrhage at the first transfusion was greater than 1 ml there was a greater increase in maternal Rh (D) antibody titres and a greater fall in fetal packed cell volume.

Sampling of fetal blood should not be routinely done early in patients with Rh isoimmunisation, and intrauterine transfusion should be delayed as long as possible. Sampling sites other than the placental cord insertion reduces the risk of fetomaternal haemorrhage.

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Introduction

Intravascular blood transfusion has been advocated as the best approach to managing fetuses with severe Rh haemolytic disease.[1-5] This procedure allows precise assessment of the degree of fetal anaemia and of the volume of Rh negative donor blood that must be transfused to raise the fetal haemoglobin concentration and packed cell volume to normal values. Two different procedures are commonly used: fetoscopy and ultrasound guided needling of the umbilical cord, the intrahepatic tract of the umbilical vein, or the heart under ultrasonic guidance.

Rodeck *et al* achieved good results with fetoscopy[1] but Mackenzie *et al* did not,[6] and transabdominal needling is now used by most centres as it is easier and safer. A fetal mortality of about 1% was reported by Daffos *et al* in a large series of diagnostic samplings,[7] though the rate is probably higher in fetuses with Rh haemolytic disease as the procedure is usually done several times. Reports of several series have claimed that this technique is the first choice in the management of patients with Rh isoimmunisation. Direct access to the fetal circulation avoids the problems of indirect tests such as spectrophotometry of the amniotic fluid in evaluating the severity of the disease.[8]

Transplacental ultrasound guided needling may result in fetomaternal haemorrhage, which in cases of Rh isoimmunisation may increase the severity of the disease by enhancing the maternal immunological response to fetal antigens. Fetomaternal haemorrhage has been investigated after amniocentesis[9,10] and fetoscopy[11] but not after transabdominal needling. We therefore studied the occurrence of fetomaternal haemorrhage in patients undergoing intrauterine transfusions for Rh haemolytic disease by transabdominal needling. The severity of the haemorrhage was related to the site of sampling and to changes in maternal antibody titres and fetal packed cell volumes after transfusion.

Patients and methods

Fetomaternal haemorrhage was studied after 68 consecutive fetal intravascular transfusions performed from November 1986 to June 1987 in 20 patients with Rh isoimmunisation. Fourteen procedures were the first performed in each patient and 54 were subsequent ones. Gestational ages ranged between 18 and 33 weeks. All the transfusions were performed by transabdominal needling under continuous ultrasonic control with a 20 gauge spinal needle. Fetal blood (2 ml) was taken for immediate estimation of packed cell volume (Coulter Channelyzer) before transfusion of packed erythrocytes from Rh negative donors, which had been cross matched with maternal blood.

The site of sampling and transfusion was the placental cord insertion in 47 procedures and the intrahepatic vein, fetal umbilical cord insertion, or free cord in the remaining 21. The umbilical artery was not sampled. The placenta was mainly anterior in 32 patients and posterior or fundal in 36.

The aim of intravascular transfusion was to raise the fetal packed cell volume to about 0·4. The rate of infusion of donor blood (packed cell volume 0·6-0·8) was 1-7 ml/min. Throughout the procedure the fetal heart rate and the flow of transfused blood in the umbilical vein were monitored continuously by ultrasonography. In 46 procedures an intraperitoneal transfusion was carried out immediately after the intravascular transfusion. In all cases the whole procedure was accomplished within 45 minutes.

Maternal blood (2 ml) was taken before and immediately after the procedure and then three and 24 hours later. Serum from the fetal sample taken before the transfusion and the maternal samples was frozen. Maternal serum samples were assayed subsequently for α fetoprotein. An increase of 50% or more in the α fetoprotein concentration in any of the samples taken after the transfusion was considered to indicate fetomaternal haemorrhage. Fetal serum samples from those patients who showed haemorrhage were also assayed for α fetoprotein. The volume of haemorrhage was estimated by the formula AB/C (1−P), where A=increase in maternal α fetoprotein concentration, B=maternal plasma volume,[12] C=fetal α fetoprotein concentration, and P=fetal packed cell volume. Haemorrhage was also expressed as a percentage of the estimated total fetoplacental blood volume for gestational age.[13]

Rh (D) antibodies were assayed before the first transfusion and then three weeks later. The rate of fall in fetal packed cell volume was also calculated in these patients as the fetal packed cell volume after the first transfusion minus the fetal packed cell volume before the second transfusion divided by the interval (in days).

The data were analysed with the χ^2 test or Fisher's exact test when appropriate and Student's *t* test when the population was normally distributed; when this was not the case data were transformed logarithmically and the Mann-Whitney test used for comparison of two populations.

Results

Fetomaternal haemorrhage occurred after 27 of the 68 intrauterine transfusions. The mean estimated volume of fetomaternal haemorrhage was 2·4 ml (confidence interval 1·5 to 3·7; range 0·3-15·4), which was on average equal to 3·1% of the total volume of fetoplacental blood (2·2 to 4·5; 0·5-14·0). A significant positive correlation (r=0·60, p<0·01) was found between the absolute volume of haemorrhage and gestational age, but no correlation was found between haemorrhage expressed as a percentage of the total volume of fetoplacental blood and gestational age.

An increase in maternal α fetoprotein concentration greater than 50% was found in 21 of the 32 patients with an anterior placenta and in six of the 36 with a posterior placenta; this difference was significant (p<0·001). When the site of sampling and transfusion was the placental cord insertion fetomaternal haemorrhage occurred in 18 patients with an anterior placenta and in five with a posterior placenta, whereas when it was the intrahepatic umbilical vein or free cord the figures were three and one respectively (table I). The difference was significant (p<0·05) for those patients with an anterior placenta but not for those with a posterior placenta.

TABLE I—*Incidence of fetomaternal haemorrhage in relation to site of sampling*

	No with haemorrhage	No without haemorrhage
Anterior placenta	21	11
Placental cord insertion	18	4
Intrahepatic vein, free cord, umbilical cord insertion	3	7
Posterior or fundal placenta	6	30
Placental cord insertion	5	20
Intrahepatic vein, free cord, umbilical cord insertion	1	10

TABLE II—*Changes in maternal Rh (D) antibody concentrations after first intravascular transfusion in relation to volume of fetomaternal haemorrhage*

Case No	Fetomaternal haemorrhage (ml)	Rh D antibody concentrations: At intrauterine transfusion (IU/ml)*	After 3 weeks (IU/ml)*	Change (%)
1		40·2	42·0	+4
2		10·5	15·2	+45
3		117·0	266·0	+127
4		27·1	23·0	−15
5	0·3	48·0	43·0	−12
6	0·7	116·0	111·0	−5
7	0·8	117·0	166·0	+42
8	1·1	412·0	384·0	−7
9	1·1	9·3	307·5	+3206
10	1·5	44·0	2075·0	+4616
11	1·7	12·3	102·0	+729
12	2·7	915·0	420·0	−54
13	4·0	37·9	442·0	+1066
14	7·8	13·1	62·0	+373

*5 IU=1 μg Rh (D) antibodies.

Table II relates the changes in maternal Rh (D) antibody concentrations to the volume of fetomaternal haemorrhage at the first transfusion. In those cases in which haemorrhage did not occur or was less than 1 ml the increase in Rh (D) concentration was always less than 150%, whereas five of the seven patients in whom haemorrhage was more than 1 ml had an increase of over 150%. In the two groups the median increase in antibody titre was 4% (range −15% to 127%) and 729% (−54% to 3206%) respectively; the difference was not significant. The rate of fall in fetal packed cell volume after the first transfusion was higher in those patients with a fetomaternal haemorrhage greater than 1 ml (mean 1·36%/day; confidence interval 0·93 to 1·78; range 0·7-2·0) than in those with haemorrhage of less than 1 ml (0·97%/day; 0·63 to 1·32; 0·5-1·4); the difference, however, was not significant.

The need for a second transabdominal needle puncture for an intraperitoneal transfusion did not increase the risk of haemorrhage, which occurred in 15 of the 46 patients compared with 12 out of 22 who did not have an intraperitoneal transfusion.

Discussion

Transabdominal needling of the umbilical cord, especially if the cord insertion is on an anterior placenta, differs from other procedures as it seems to break the rule that penetration of the placenta should be avoided. Several reports have associated transplacental amniocentesis and fetoscopy with fetomaternal haemorrhage, and in fetoscopy intra-amniotic bleeding from the placenta makes visualisation difficult and may lead to severe fetal anaemia.[14] In contrast a transplacental approach is deliberately chosen to needle the cord insertion of an anterior placenta.

Simpson *et al* emphasised the danger of fetal sensitisation to maternal red cell antigen after fetoscopy. They reported a mean increase in maternal serum α fetoprotein concentration of 212 μg/l after fetoscopic blood sampling.[11] This is approximately equivalent to 0·5 ml of fetomaternal haemorrhage. Haemorrhage can occur spontaneously, but Tabor *et al* did not find an increase in maternal serum α fetoprotein concentration of more tha 50% in any of 268 control patients between 14 and 23 weeks' gestation, while this occurred in 15·6% of patients who underwent amniocentesis at between 14 and 19 weeks.[10] We used the same

threshold and showed a 40% incidence of fetomaternal haemorrhage with a significant difference according to the site of the placenta.

Administration of anti-D immunoglobulin is routine after invasive procedures in Rh negative patients but is not appropriate for those already sensitised, in whom it would be ineffective.[15] In patients undergoing intrauterine transfusions, however, fetomaternal haemorrhage may enhance maternal sensitisation. Not only might the disease be worsened in a subsequent pregnancy but also in the present pregnancy the rate of fall in fetal packed cell volume might be accelerated by an increase in maternal antibody titre, particularly after the first transfusion, when fetal erythropoiesis is generally not yet suppressed.

Precisely estimating the volume of fetomaternal haemorrhage is difficult. In patients undergoing intrauterine transfusions the Kleihauer-Betke test cannot be used because donor red cells cannot be identified in the maternal circulation. The increase in maternal α fetoprotein concentration can give a reliable estimate if fetal α fetoprotein concentration is also assayed. Possible sources of error are the estimated maternal blood volume, which cannot practically be assessed in each patient, and passage of α fetoprotein into the maternal circulation from fluids other than fetal blood, such as the amniotic fluid. This second possibility is unlikely as fetomaternal haemorrhage occurred most commonly when the site of sampling and transfusion was the placental cord insertion with an anterior placenta—that is, when the needle entered directly into the cord without any communication with the amniotic cavity. Moreover, any contribution of α fetoprotein from the amniotic fluid to the rise in maternal α fetoprotein concentration should be irrelevant as the concentration in fetal blood is more than 100 times that in amniotic fluid.[16]

De Silva *et al* reported that 0·28 ml of red cells produced a secondary Rh immune response in all of their 14 volunteers[17]; in our study the increase in maternal Rh (D) antibody concentration was clinically important when the volume of haemorrhage was greater than 1 ml. As the mean fetal packed cell volume at the first transfusion was 0·20 (range 0·08-0·31) the results were comparable. In some instances the rise in antibody titre was dramatic, and although the consequences were not important as far as the rate of fall in fetal packed cell volume was concerned, the course of the disease in a subsequent pregnancy will probably be affected.

These results also suggest that sampling of fetal blood in patients with Rh isoimmunisation should not be routinely done for blood grouping early in pregnancy. It would be without consequence in Rh negative fetuses but might convert a mild case into a severe one if a considerable increase in maternal antibody titres was provoked by the procedure. Because fetomaternal haemorrhage can also occur in patients with posterior placentas, albeit less commonly, the risk of further sensitisation is present in all patients. The optimal time for intrauterine transfusion is the latest possible gestational age before fetal anaemia becomes severe. Other sites of sampling and transfusion can be chosen instead of the placental cord insertion, especially at the first transfusion, when fetomaternal haemorrhage would transfer only fetal cells. This policy would considerably reduce the risk of haemorrhage.

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Sensitivity and specificity of Rinne tuning fork test

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The Rinne tuning fork test is used regularly by specialists and non-specialists in patients with hearing impairments to indicate whether there is a conductive (external or middle ear) component to their deafness. Its ability to do this can be judged only by its sensitivity and specificity in detecting conductive hearing defects of various magnitudes as determined by pure tone audiometry. To our knowledge these have not been previously reported.

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Methods and results

The Rinne test was done in a standard manner[1] with 256 Hz and 512 Hz tuning forks in 132 patients with otological symptoms, before reading the referral letter, taking the history, examining the patient, or carrying out pure tone audiometry. All patients were tested by both loudness and threshold comparison methods. To compare loudness the forks were presented alternately as air and bone conduction, and the patient was asked to report which was louder. In the comparison threshold method patients reported when they no longer heard the sound by bone conduction and were then asked whether they heard it again when it was presented by air. The responses were classified as Rinne positive if the sound by air conduction was louder than that by bone conduction, Rinne negative if bone conduction was louder than air conduction, and equivocal if the bone conduction and air conduction were equally loud. Subsequently, pure tone audiometric thresholds were assessed by standard methods.[2]

We analysed the results from the better hearing ear (defined as better bone conduction at the frequency of the tuning fork used) to eliminate any potential need to