Vox Sang 1990;58:45–49

0042–9007/90/0581–0045 $2.75/0

Management of Fetal Alloimmune Thrombocytopenia by Weekly in utero Platelet Transfusions

M. F. Murphy[a], *H. W. H. Pullon*[b], *P. Metcalfe*[a], *J. F. Chapman*[a], *E. Jenkins*[b], *A. H. Waters*[a], *K. H. Nicolaides*[c], *R. S. Mibashan*[b]

[a]Department of Haematology, St. Bartholomew's Hospital and Medical College; [b]Academic Department of Haematology LIBRA Laboratories, and [c]Harris Birthright Fetal Medicine Research Centre, King's College Hospital, London, UK

Abstract. Alloimmune neonatal thrombocytopenia (ANT) may cause intracranial haemorrhage in utero as well as at delivery. Recent management has concentrated on attempts to minimise fetal thrombocytopenia and prevent its complications. This report describes further experience with the use of repeated intravascular transfusions of compatible platelets in utero. The patient studied had already had one infant with intracranial haemorrhage due to ANT. In her next pregnancy, weekly intra-uterine platelet transfusions were given from 26 weeks, but intra-uterine death occurred at 30 weeks after the mother had a heavy fall. In her most recent pregnancy, weekly intravascular transfusions of platelets were given by cordocentesis from 29 to 34 weeks. The fetal platelet count was maintained above 30×10^9/l for almost all of the last 6 weeks of pregnancy before delivery of a normal infant by Caesarean section at 35 weeks' gestation. This approach is effective in preventing severe fetal thrombocytopenia in the last trimester of pregnancy and is contrasted with alternative treatments of ANT. Further data are required to determine the efficacy and risks of these treatments.

Introduction

Alloimmune neonatal thrombocytopenia (ANT) is due to fetomaternal incompatibility for platelet-specific antigens, most frequently PI^{A1} [1–3]. Its prevalence is reported to be between 1:2,000 and 1:5,000 [1, 4]. The most serious complication of ANT is intracranial haemorrhage, which leads to death or neurological complications in about 15% of affected neonates [5, 6]. The risk of intracranial haemorrhage has been assumed to be greatest at birth, but there are increasing reports of intracranial haemorrhage before delivery [3, 7–19].

The first affected child with ANT is unexpected as PI^{A1} typing of mothers is not part of routine antenatal screening, although a pilot study is being performed in Canada to detect pregnancies at risk [20]. The incidence of ANT in subsequent pregnancies is 97% [21], and the degree of thrombocytopenia is usually as severe as, or worse than in the previous affected sibling [6]. Although a rising titre of maternal anti-PI^{A1} antibodies might be expected to indicate that the fetus is at high risk, monitoring of maternal anti-PI^{A1} antibodies has not proved useful in predicting the severity of fetal thrombocytopenia [6, 22]; in one series, maternal antibodies were not even detectable in 20% of cases [22]. Fetal blood sampling is the best way of establishing the diagnosis and also provides a means for intra-uterine transfusion of PI^{A1}-negative platelets. This has been performed as a single transfusion prior to delivery [18, 22, 23], or as repeated intra-uterine platelet transfusions to prevent intracranial haemorrhage in the last trimester of pregnancy [22, 24, 25].

This paper reports our experience in the management of a case of ANT using ultrasound-guided needle puncture of the umbilical vessels for fetal blood sampling and weekly intra-uterine platelet transfusions in the last trimester of pregnancy.

Methods

Platelet Serology

The lymphocytotoxicity test was used for testing for the presence of HLA antibodies with a comprehensive panel of typed lymphocytes [26].

The platelet immunofluorescence test (PIFT) was used for the detection of platelet-specific antibodies and for platelet antigen typing [27]. PI^{A1}-specificity of platelet-specific antibodies was assigned by test-

Table 1. Fetal response to platelet transfusions

Gestation weeks	Platelet concentrate		Cord platelet count		Recovery factor	Cord haemoglobin	
	concentration $\times 10^9$/l	volume infused, ml	Pre $\times 10^9$/l	Post $\times 10^9$/l		Pre g/dl	Post g/dl
29	2,200	50	17	374	0.43	13.1	10.5
30	1,340	65	75	281	0.43	11.9	9.7
31	2,750	54	31	510	0.54	11.2	9.3
32	2,450	69	80	563	0.55	11.4	9.8
33	1,700	90	69	*	*	10.6	*
34	1,440	72	24	269	0.54	10.2	8.3

* Clotted sample.

ing against platelets from known PI^{A1}-positive and PI^{A1}-negative donors. PI^{A1}-typing was carried out using known anti-PI^{A1} antisera from patients with post-transfusion purpura. PI^{A2}-typing was carried out using serum from patient I. T. (described by Taaning et al. [28]). Serum I. T. also contained HLA antibodies and the platelets were first treated with chloroquine to remove HLA antigens [29]. PI^{A2}-typing was also carried out using immunoblotting. Solubilized platelet proteins were separated by SDS-polyacrylamide gel electrophoresis under non-reduced conditions [30], and transferred to nitrocellulose paper by semi-dry electrophoresis [31]. Strips of nitrocellulose paper were then incubated with serum containing anti-PI^{A2} (serum A.M., reported by Chapman et al [32]), and AB serum (as a negative control). Antibody binding was visualised by subsequent incubation with alkaline phosphatase-conjugated anti-human IgG and its substrate solution.

Fetal Blood Sampling

Cordocentesis was performed both for fetal blood sampling and for intra-uterine platelet transfusions. The method was adapted from that used for the intra-uterine transfusion of red blood cells in haemolytic disease of the newborn, as previously described [33, 34].

Platelet Concentrates

Platelet concentrates were prepared by plateletpheresis of unrelated PI^{A1}-negative donors using the Haemonetics V50 cell separator with surge. All donors were CMV-seronegative. Each platelet concentrate was gamma-irradiated with 1,500 cGy to prevent graft-versus-host disease. Approximately 150 ml of each donation was concentrated by centrifugation to produce a final concentrate of between 50 and 90 ml. Each platelet concentrate was transfused using a standard platelet-giving set; the volume and platelet count of each concentrate is shown in table 1.

The volume of the platelet concentrate for transfusion on each occasion was calculated using the formula: Volume of concentrate = (desired increment × feto-placental blood volume)/platelet count of concentrate.

The feto-placental blood volume for gestational age was derived from previously constructed charts [35].

Case Study

Patient C. R.

Past history. She first became pregnant at the age of 16. This pregnancy was terminated for psychosocial reasons. At the age of 23 she again became pregnant and subsequently delivered a 2.5-kg male infant by spontaneous vaginal delivery at 38 weeks gestation. The infant was found to be profoundly thrombocytopenic and had a left-sided hemiparesis and developmental delay due to intracranial haemorrhage. Further investigation revealed that the mother's platelets typed as PI^{A1}-negative, the baby's as PI^{A1}-positive and that the mother's serum contained platelet-specific antibodies of anti-PI^{A1} specificity. The maternal HLA type was: A1, A3, B7, B8, Bw6, DR3, DR4, DRw52, DRw53, DQW2, DQW3.

Third Pregnancy. She became pregnant again at the age of 24. The father's platelet type was found to be homozygous PI^{A1}/PI^{A1} using the PIFT and immunoblotting. This pregnancy was followed carefully with regular ultrasound scans from 20 weeks gestation. At 26 weeks, fetal blood sampling revealed severe fetal thrombocytopenia (platelet count 32×10^9/l).

Intra-uterine transfusions of PI^{A1}-negative platelets were given at 26, 27 and 30 weeks. Good immediate platelet increments were obtained but the platelet count had always fallen to a low level by the time of the next transfusion. The mother was also treated with high-dose intravenous immunoglobulin for 5 days during the 29th week but without any effect on the fetal platelet count. At 30 weeks, the mother fell on an icy pavement and a few days later fetal death was diagnosed. She delivered a 1.2-kg stillborn infant and post-mortem examination did not reveal any evidence of haemorrhage. This pregnancy has been briefly described previously [25].

Fourth Pregnancy. Her next pregnancy was at the age of 25. The fetus was monitored with regular ultrasound scans from 16 weeks. At 29 weeks fetal blood sampling revealed severe thrombocytopenia (platelet count 17×10^9/l).

Intra-uterine transfusions of PI^{A1}-negative platelets were started at 29 weeks gestation and continued at weekly intervals for 6 weeks; a greater number of platelets were given with each transfusion than in her

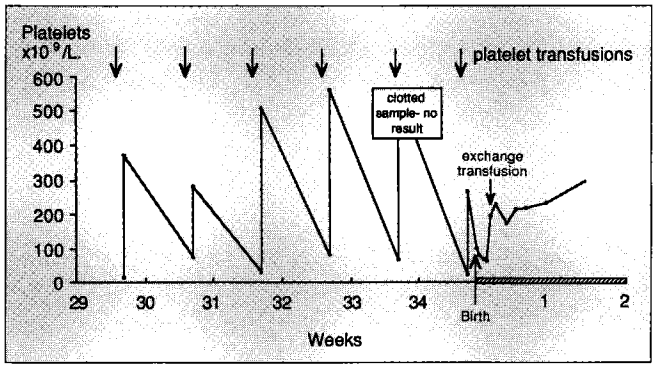

Fig. 1. Fetal and post-natal platelet counts in the fourth pregnancy of patient C. R.

third pregnancy. Good immediate platelet increments were again obtained (table 1). In contrast to the previous pregnancy, platelet counts after 1 week were successfully maintained above 30×10^9/l in all but one case (fig. 1) After the 5th transfusion, fetal distress was noted with brief episodes of bradycardia and tachycardia. One week later, after the 6th transfusion at 34 weeks and 5 days gestation, the fetus again had bradycardia. A 2.1-kg female infant was delivered by Caesarean section on the following day. Cord blood sampling after delivery revealed a haemoglobin of 6.8 g/dl and a platelet count of 102×10^9/l. The baby's platelet count was 66×10^9/l on the next day. The baby had mild respiratory distress and was given a red cell exchange transfusion and a further platelet transfusion; after this procedure the haemoglobin was 13.3 g/dl and the platelet count was 198×10^9/l. A satisfactory platelet count was maintained without further transfusions and the baby left hospital 7 days after birth with a platelet count of 235×10^9/l. Follow-up examinations have shown no evidence of neurological damage.

Platelet Serology. No change in the titre of maternal anti-PI^{A1} antibodies (1:8) occurred in the last two pregnancies, and maternal HLA antibodies were detected for the first time at the and of the second pregnancy. HLA and platelet-specific antibodies were not detectable in fetal blood samples taken prior to each platelet transfusion in both the third and fourth pregnancies, apart from on one occasion at 32 weeks in the fourth pregnancy when weak anti-PI^{A1} of maternal origin was found.

Discussion

Although it is an uncommon problem, ANT causes considerable morbidity and mortality [5, 6]. It had been assumed that the greatest risk of intracranial haemorrhage was at the time of birth and for this reason Caesarean section has been advocated [36, 37]. However, there have been increasing numbers of reports of intracranial haemorrhage occurring prior to delivery suggesting the need for prenatal treatment [3, 7–19]. Further data are required about the natural history of ANT, particularly the incidence, severty and timing of haemorrhage, to allow a rational approach to antenatal management.

With the advent of fetal blood sampling, it has become possible to confirm the diagnosis of ANT and its severity in the fetus; in addition, platelet concentrates may be transfused to the fetus to correct the thrombocytopenia prior to delivery [23]. In most affected pregnancies, fetal thrombocytopenia is already present at 20 weeks gestation [38]. The possibility that repeated platelet transfusions from 20 weeks until term might provide complete protection from intrauterine haemorrhage has been discounted because of the putative need for transfusions every 4 or 5 days and the risk of transfusion-transmitted infection [39]. On the other hand, some cases of ANT do not develop severe thrombocytopenia until after 20 weeks gestation [$\frac{20}{dl}$, 40] and there are only two documented cases of intra-uterine haemorrhage before 30 weeks gestation [3, 16], suggesting that the greatest risk of haemorrhage may be in the last trimester of pregnancy. This provides support for the use of repeated platelet transfusions beginning between the 26th and 30th weeks of pregnancy and continuing until fetal maturity is reached when an elective Caesarean section is performed.

In the fourth pregnancy of patient C. R. described in the present paper, it was possible to maintain the fetal platelet count above 30×10^9/l for almost the whole of the last trimester of pregnancy by increasing the number of transfused platelets. Nicolini et al. [24] have also used this approach; they found that the fetal platelet count had always fallen below 50×10^9/l (and often much lower) before the next transfusion. Furthermore, Mueller-Eckhardt et al. [19] successfully used the same procedure to manage a high risk pregnancy following the occurrence of severe intracranial haemorrhage in a previous fetus with ANT who had been managed conservatively [19]. However, further data are needed to confirm the efficacy of this approach in preventing prenatal haemorrhage. An alternative platelet transfusion strategy would be to give a single platelet transfusion just before delivery [18, 22, 23]. This option might be considered suitable for pregnancies thought to be at low risk of prenatal haemorrhage; such pregnancies are difficult to identify and this approach would not protect against the risk of thrombocytopenic bleeding in the last trimester.

An important practical part of the management using repeated platelet transfusions is the calculation of the volume of platelet concentrate required to maintain the platelet count for one week at the required 'safe' level. The calculation is based on a simple mathematical formula which takes account of the desired platelet increment, the estimated feto-placental blood volume and the platelet count of the platelet concentrate. An additional factor which needs to be considered is the half-life of the tranfused platelets and this was found to be approximately 3 days.

The fact that the immediate platelet increment was found to be only about 50% of that expected (i.e. 50% recovery of transfused platelets) also needs to be taken into consideration in calculating the volume of platelet concentrate. The lower than expected immediate platelet increment (table 1) might be due to pooling of transfused platelets in the fetal spleen and placental circulation and to the dilution associated with the significant increase in fetal blood volume produced by the transfusion.

Intra-uterine platelet transfusions are not without risk to the fetus, and repeated transfusions obviously increase the likelihood of complications. Although transfusion-transmitted infection may be avoided by the use of maternal platelets [22], this approach is not practical for repeated transfusions [39]. The risk may be minimised by careful screening of donations from Pl^{A1}-negative donors, including CMV antibody testing. A logistical problem may be the identification of sufficient numbers of such donors, particularly if the platelet antibody specificity is not anti-Pl^{A1}. In addition, in the fourth pregnancy of patient C. R. described in this report, there was a progressive fall in the fetal haemoglobin level. This may have been the result of repeated fetal blood sampling and dilution. If intra-uterine platelet transfusions are started earlier in pregnancy, then fetal anaemia may necessitate intra-uterine transfusion of red cells. Another possible complication of repeated transfusions is the development of alloantibodies to platelet antigens resulting in poor responses to subsequent platelet transfusions, but there was no evidence that this occurred in the pregnancy described in this report. Moreover, a recent study has demonstrated the failure of neonates to form red cell alloantibodies after multiple red cell transfusions [41].

Non-invasive methods for prenatal treatment of ANT have also been attempted. Daffos et al. [39] reported an apparent increase in fetal platelet count after maternal treatment with prednisolone 10 mg daily from the 23rd week of pregnancy until delivery. Bussel et al. [42] reported elevation of the fetal platelet count and absence of bleeding in seven cases of ANT treated by weekly maternal administration of high-dose intravenous IgG with or without dexamethasone, although in three other cases of ANT the use of high-dose IgG alone had no effect on the fetal platelet count [22, 25, 43].

In conclusion, the optimal management to prevent severe intracranial haemorrhage in ANT is not certain; the use of weekly intra-uterine platelet transfusions commencing between the 26th and 30th weeks of pregnancy to maintain the fetal platelet count above at least 30×10^9/l is one approach which may be expected to result in a successful outcome, although it is associated with the complications described above and further data about the natural history of ANT and the efficacy of this treatment are needed. For logistic reasons it may not be possible to offer this approach in all cases and the use of maternal treatment with intravenous IgG and/or steroids should be further evaluated as initial treatment to prevent prenatal haemorrhage in ANT. However, if non-invasive methods fail to raise the platelet count, intra-uterine platelet transfusions are a reliable way of achieving this.

Acknowledgements

We are grateful fo Sister Jane Allen's invaluable help with the platelet transfusions. We would like to thank Professor T. A. Lister and Sister Jennifer Sterlini for undertaking plateletpheresis of Pl^{A1}-negative donors in the ICRF Department of Medical Oncology at St. Bartholomew's Hospital and also the North-East Thames Regional Blood Transfusion Centre for providing some of the Pl^{A1}-negative platelet donors.

References

1 Shulman, N. R.; Marder, V. J.; Hillar, M. C.; Collier, E. M.: Platelet and leucocyte isoantigens and their antibodies. Serologic, physiologic and clinical studies. Prog. Haematol. *4:* 222–304 (1964).
2 Von dem Borne, A. E. G. Kr.; van Leeuwen, E. F.; von Riesz, L. E.; van Boxtel, C. J.; Engelfriet, C. P.: Neonatal alloimmune thrombocytopenia: detection and characterization of the responsible antibodies by the platelet immunofluorescence test. Blood *57:* 649–656 (1981)
3 Reznikoff-Etievant, M. F.: Management of alloimmune neonatal and antenatal thrombocytopenia: Vox Sang. *5:* 193–201 (1988).
4 Blanchette, V. S.; Peters, M. A.; Pegg-Feige, K.: Alloimmune thrombocytopenia. Review from a neonatal intensive care unit. Curr. Stud. Hemat. Blood Transfus., Vol. 52, pp. 87–96 (Karger, Basel 1986).
5 Pearson, H. A.; Shulman, N. R.; Marder, V. J.; Cone, T. E.: Isoimmune neonatal thrombocytopenic purpura. Clinical and therapeutic considerations. Blood *23:* 154–177 (1964).
6 Muller, J. Y.; Reznikoff-Etievant, M. F.; Patereau, C.; Dangu, C.; Chesnel, N.: Thrombopénies néonatal alloimmunes. Etude clinique et biologique de 84 cas. Presse méd. *14:* 83–86 (1985).
7 McIntosh, S.; O'Brien, R. T.; Schwartz, A. D.; Pearson, H. A.: Neonatal isoimmune purpura. Response to platelet infusions. J. Paediat. *82:* 1020–1027 (1973).
8 Zalneraitis, E. L.; Young, R. S. K.; Krishnamoorthy, K. S.: Intracranial haemorrhage in utero as a complication of isoimmune thrombocytopenia. J. Paediat. *95:* 611–614 (1979).
9 Jesurun, C. A.; Levin, G. S.; Sullivan, W. R.; Stevens, D.: Intracranial haemorrhage in utero re thrombocytopenia. J. Paediat. *97:* 695–696 (1980).
10 Naidu, S.; Messmore, H.; Caserta, V.; Fine, M.: CNS lesions in neonatal isoimmune thrombocytopenia. Archs Neurol. *40:* 552–554 (1983).
11 Sia, C. G.; Amigo, N. C.; Harper, R. G.; Farahani, G.; Kochen, J.:

Failure of cesarean section to prevent intracranial haemorrhage in siblings with isoimmune neonatal thrombocytopenia. Am. J. Obstet. Gynec. *153:* 79–81 (1985).
12 Friedman, J.M.; Aster, R.H.: Neonatal alloimmune thrombocytopenic purpura and congenial porencephaly in two siblings associated with a 'new' maternal antiplatelet antibody. Blood *65:* 1412–1415 (1985).
13 Lam, A.H.; Shulman, L.A.: Ultrasound in congenital intracranial haemorrhage secondary to isoimmune thrombocytopenia. Pediatr. Radiol. *15:* 8–11 (1985).
14 Morales, W.J.; Stroup, M.: Intracranial haemorrhage in utero due to isoimmune neonatal thrombocytopenia. Obstet Gynec. *65:* 20S–21S (1985).
15 Deaver, J.E.; Leppert, P.C.; Zaroulis, C.G.: Neonatal alloimmune thrombocytopenic purpura. Am. J. Perinat. *3:* 127–131 (1986).
16 Herman, J.H.; Jumbelic, M.I.; Ancona, R.J.; Kickler, T.S.: In utero cerebral haemorrhage in alloimmune thrombocytopenia. Am. J. Pediat. Oncol. *8.* 312–317 (1986).
17 Burrows, R.F.; Caco, C.C.; Kelton, J.G.: Neonatal alloimmune thrombocytopenia: spontaneous in utero intracranical haemorrhage. Am. J. Hematol. *28:* 98–102 (1988).
18 De Vries, L.S.; Connell, J.; Bydder, G.M.; Dubowitz, L.M.S.; Rodeck, C.H.; Mibashan, R.S.; Waters, A.H,: Recurrent intracranial haemorrhages in utero in an infant with alloimmune thrombocytopenia. Case report. Br. J. Obstet. Gynaecol. *95:* 299–302 (1988).
19 Mueller-Eckhardt, C.; Kiefel, V.; Jovanovic, V.; Kunzel, W.; Becker, T.; Wolf, H.; Zeh, K.: Prenatal treatment of fetal alloimmune thrombocytopenia. Lancet *ii:* 910 (1988).
20 Blanchette, V.; Decary, F.; Chan, L.; Hogan, V.: Fetomaternal Pl^{A1} incompatibility: assessment of risk factors for alloantibody formation. XXI Congr. int. Soc. Haemat. XIX Congr. int. Soc. Blood Transfus. Sydney 1986 (abstract) p. 595 (1986).
21 Shulman N.R.; Jordan, J.V.: Platelet immunology in: Colman, Hirsh, Marder, Salzmann, Haemostasis and thrombosis: basic principles and clinical practice; pp. 274–342 (J.B. Lippincott, Philadelphia 1982).
22 Kaplan, C.; Daffos, F.; Forestier, F.; Cox, W.L.; Lyon-Caen, D.; Dupuy-Montbrun, M.C.; Salmon C.: Management of alloimmune thrombocytopenia: Antenatal diagnosis and in utero transfusion of maternal platelets. Blood *72:* 340–343 (1988).
23 Daffos, F.; Forestier, F.; Muller, J.Y.; Reznikoff-Etievant, M.F.; Habibi, B.; Capella-Pavlovsky, M.; Maigret, P.; Kaplan, C.: Prenatal treatment of alloimmune thrombocytopenia. Lancet *ii:* 632 (1984).
24 Nicolini, U.; Rodeck, C.H.; Kochenour, N.K.; Greco, P.; Fisk, N.M.; Letsky, E.; Lubenko, A.: In utero platelet transfusion for alloimmune thrombocytopenia. Lancet *2:* 506 (1988).
25 Waters, A.H.; Ireland, R.; Mibashan, R.S.; Murphy, M.F.; Millar, D.S.; Chapman, J.F.; Metcalfe, P.; De Vries, L.E.; Rodeck, C.H.; Nicolaides, K.H.: Fetal platelet transfusions in the management of alloimmune thrombocytopenia. Thromb Haemostasis *58:* 323 (1987).
26 Mittal, K.K.: Workshop report: standardisation of the HLA-typing method and reagents. Vox Sang. *34:* 58–63 (1978).
27 Von dem Borne, A.E.G.Kr.; Verheugt, F.W.A.; Oosterhof, F:, von Riesz, E.; Brutel de la Riviere, A.; Engelfriet, C.P.: A simple immunofluorescence test for the detection of platelet antibodies. Br. J. Haematol. *39:* 195–207 (1975).
28 Taaning, E.; Killman, S.-A.; Morling, N.; Ovesen, H.; Svejgaard, A.: Post-transfusion purpura (PTP) due to anti-Zw^b(-Pl^{A2}): the significance of IgG3 antibodies in PTP. Br. J. Haemat. *64:* 217–225 (1986).
29 Nordhagen, R.; Flaathen, S.T.: Chloroquine removal of HLA antigens from platelets for the platelet immunofluorescence test. Vox Sang. *48:* 156–159 (1985).
30 Laemmli, U.K.: Cleavage of structural proteins during assembly of the head of bacteriophage T4. Nature, Lond. *227:* 680–685 (1970).
31 Harper, D.R.; Kangro, H.O.; Argent, S.; Heath, R.B.: Reduction in immunoreactivity of varicella-zoster virus proteins induced by mycoplasma contamination. J. virol. Meth. *20:* 65–72 (1988).
32 Chapman, J.F.; Murphy, M.F.; Berney, S.I.; Ord, J.; Metcalfe, P.; Amess, J.A.L.; Waters, A.H.: Post-transfusion purpura associated with anti-Bak^a and anti-Pl^{A2} antibodies and delayed haemolytic transfusion reaction. Vox Sang. *52»* 313–317 (1987).
33 Nicolaides, K.H.; Rodeck, C.H.; Soothill, P.W.; Campbell, S.: Ultrasound-guided sampling of umbilical cord and placental blood to assess fetal wellbeing. Lancet *i:* 1065–1067 (1986).
34 Nicolaides, K.H.; Soothill, P.W.; Rodeck, C.H.; Clewell, W.: Rh disease: intravascular fetal blood transfusion by cordocentesis. Fetal Therapy *i:* 185–192 (1986).
35 Nicolaides, K.H.; Clewell, W.H.; Rodeck, C.H.: Measurement of human fetoplacental blood volume in erythroblastosis fetalis. Am. J. Obstet, Gynec. *157:* 50–53 (1987).
36 Mennuti, M.; Schwarz, R.H.; Gill, F.: Obstetric management of isoimmune thrombocytopenia. Am J. Obstet. Gynec. *118:* 565–566 (1974).
37 Sitarz, A.L.; Driscoll, J.M.; Wolff, J.A.: Management of isoimmune neonatal thrombocytopenia. Am. J. Obstet. Gynec. *124:* 39–42 (1976).
38 Daffos, F.; Forestier, F.; Kaplan, C.; Cox, W.: Prenatal diagnosis and management of bleeding disorders with fetal blood sampling. Am. J. Obstet. Gynec. *158:* 939–946 (1988).
39 Daffos, F.; Forestier, F.; Kaplan, C.: Prenatal treatment of fetal alloimmune thrombocytopenia, Lancet *ii:* 910 (1988).
40 Lynch, L.; Bussel, J.; Goldberg, J.D.; Chitkara, U.; Wilkins, I.; MacFarland, J.; Berkowitz, R.L.: The in utero diagnosis and management of alloimmune thrombocytopenia. Prenat. Diag. *8:* 329–331 (1988).
41 Ludvigsen, C.W.; Swanson, J.L.; Thompson, T.R.; McCullough, J.: The failure of neonates to form red blood cell alloantibodies in response to multiple transfusions. Am. J. clin. Path. *87:* 250–251 (1987).
42 Bussel, J.B.; Berkowitz, R.L.; McFarland, J.G.; Lynch, L.; Chitkara, U.: Antenatal treatment of neonatal alloimmune thrombocytopenia. New Engl. J. Med. *319:* 1374–1378 (1988).
43 Mir, N.; Samson, D.; House, M.J.; Kovar, I.Z.: Failure of antenatal high-dose immunoglobulin to improve fetal platelet count in neonatal alloimmune thrombocytopenia. Vox Sang. *55:* 188–189 (1988).

Received: January 27, 1989
Revised manuscript received: May 19, 1989
Accepted: June 6, 1989

Prof. A. H. Waters
Department of Haematology
St. Bartholomew's Hospital
GB–London ECIA 7BE (UK)