Assessment and management of immune thrombocytopenia in pregnancy and in neonates

D L Cohen, T P Baglin

Department of Paediatrics, Addenbrooke's Hospital, Cambridge, and 48th Medical Group (USAF) RAF Lakenheath, Suffolk
D L Cohen

Department of Haematology, Addenbrooke's Hospital, Cambridge
T P Baglin

Correspondence to: Dr D L Cohen, Department of Paediatrics, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

The use of electronic cell counters has led to the recognition that pregnancy is frequently associated with thrombocytopenia. As well as disorders that cause thrombocytopenia in the non-pregnant state, a reduction in the circulating platelet count may result from the pregnancy itself, either as an incidental consequence, so-called 'gestational thrombocytopenia', or as a manifestation of pregnancy associated pathology, such as pre-eclampsia. Until recently autoimmune thrombocytopenia (ATP or ITP) was regarded as a common cause of a low platelet count in pregnancy, but it now seems that most mild thrombocytopenias in pregnancy are simply benign gestational thrombocytopenia, with no implications for morbidity in either mother or fetus.¹ Furthermore, it is now apparent that ITP in pregnancy is associated with considerably

less morbidity to the fetus or neonate than was previously realised.

Neonatal illness is frequently and non-specifically associated with thrombocytopenia whilst the distinct entity of neonatal allo-immune thrombocytopenia (NAIT) has been well characterised, and the high morbidity and mortality of this condition has been clarified.²

Understanding the complex association between maternal and fetal-neonatal thrombocytopenia and the distinction between auto- and alloimmune platelet destruction is critical to the management of affected mothers and infants. Several papers published during the past few years have clarified many confusing issues relating to the diagnosis and management of these conditions.¹⁻¹² The purpose of this review is to summarise current concepts of immune thrombocytopenia in pregnancy and in the fetus or neonate, and in particular to emphasise the distinction between auto- and alloimmune thrombocytopenia and the implications of this knowledge for management.

Thrombocytopenia in pregnancy

Figure 1

Maternal thrombocytopenia and implications for neonatal morbidity

The assessment and management of thrombocytopenia in pregnancy is summarised in fig 1.

Thrombocytopenia of less than $150 \times 10^9/l$ occurs in about 6–8% of pregnancies.³⁻⁵ If a platelet count above $70 \times 10^9/l$ is detected in a healthy pregnant woman with no evidence of systemic disease or a history of ITP, the most likely diagnosis is benign gestational thrombocytopenia. This thrombocytopenic syndrome is non-immune and is not associated with either maternal or fetal or neonatal morbidity or mortality. Affected pregnancies are not complicated by excessive haemorrhage, and the infants are not thrombocytopenic. The condition resolves within a few weeks of delivery. A recent large study of 15 932 neonates identified only one infant with a platelet count of less than $50 \times 10^9/l$ born to 756 mothers with presumed benign gestational thrombocytopenia.³ The platelet count was greater than $20 \times 10^9/l$ and the infant had Down's syndrome and congenital marrow dysfunction.

However, thrombocytopenia associated with systemic disease must always be excluded before diagnosing gestational thrombocytopenia, because an alternative diagnosis may have major implications for mother and child. Maternal hypertensive disorders (including

pre-eclampsia), diabetes mellitus, systemic lupus erythematosus, hyperthyroidism, thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), HIV infection, and sepsis must be considered. Consumption coagulopathy caused by amniotic fluid embolism or intrauterine fetal death should be considered in thrombocytopenic women who are ill. Occasionally primary haematological disease such as leukaemia may present in pregnancy.¹³ Bone marrow examination is not necessary in patients with stable thrombocytopenia of $>70 \times 10^9/l$ and no other features suggestive of primary marrow pathology. However, patients with platelet counts of less than $70 \times 10^9/l$, or with any other haematological abnormality, should have a bone marrow examination to exclude marrow disease such as acute leukaemia.

ITP should be considered in otherwise healthy women with thrombocytopenia, particularly if there is a history of this disorder. ITP is a common disorder in young women. With isolated thrombocytopenia for which there is no apparent cause, the diagnosis is primarily one of exclusion. A rapid increase in platelets following administration of corticosteroid or high dose immunoglobulin confirms the immune mechanism of platelet destruction, but immune thrombocytopenia secondary to HIV infection or the antiphospholipid syndrome is also responsive, and these conditions should be considered before diagnosing isolated primary platelet specific autoimmunity. Measurement of platelet associated immunoglobulin does not reliably differentiate ITP from gestational thrombocytopenia as it is neither sensitive nor specific. Increased platelet associated immunoglobulin is frequently detected in normal women with no haematological abnormality as well as in women with gestational thrombocytopenia and other thrombocytopenic syndromes. These measurements are therefore of little if any value in the assessment of mild or moderate thrombocytopenia.¹⁴ Women with a history of ITP which precedes pregnancy or who have incidentally detected thrombocytopenia with a platelet count of $<70 \times 10^9/l$ should not be regarded as having simple gestational thrombocytopenia because ITP is more likely at this level of thrombocytopenia. Women with suspected ITP should be managed in accordance with haematological guidelines designed to prevent morbidity. Pregnant women with platelet counts of $>50 \times 10^9/l$ have minimal bleeding risk and rarely require active intervention. When the platelet count is $<50 \times 10^9/l$ an assessment must be made regarding the degree of bleeding risk for the level of thrombocytopenia with respect to the stage of pregnancy, the anticipated mode of delivery, the need for epidural anaesthesia and the presence of other complications. Our practice is to use standard corticosteroid treatment with prednisolone at 0.25 mg/kg as first line treatment for pregnant women at risk of bleeding.¹⁵ Most women are responsive and tolerate this relatively low steroid dose without

any subsequent side effects. A maintenance dose that will achieve a haemostatic platelet count can then be used until delivery. It is important to appreciate that complete normalisation of the maternal platelet count is not required and low steroid doses can therefore be maintained. Patients who are at risk of bleeding and who do not respond or tolerate steroids may require alternative treatment.¹⁶

ITP in pregnancy is caused by the production of maternal autoantibodies specific for distinct epitopes on platelet membrane glycoproteins, particularly the IIb/IIIa and Ib/IX/V complexes.¹⁷ The immune sensitised platelets are removed from the circulation via binding to Fc receptors expressed on the surface of reticuloendothelial cells, primarily in the spleen. The fetus is at risk of immune platelet destruction as the maternal autoantibody is actively transported to the fetal circulation via Fc receptors on the cells of the syncytiotrophoblast. However, the degree of fetal thrombocytopenia does not correlate with the amount of platelet reactive antibody in cord blood.¹⁸ Clearly, the degree of immune sensitisation of the platelet surface is not the only factor that determines the circulating platelet count, and the productive capacity of the fetal marrow and maturity of the reticuloendothelial system are likely to be influential factors. Fetal thrombocytopenia is common, but only rarely have well documented cases of intracranial haemorrhage been reported in neonates born to mothers with ITP.⁸

Until recently there has been considerable concern regarding the prevention of intrapartum or postpartum neonatal intracranial haemorrhage but no method of assessing fetal wellbeing in terms of thrombocytopenia has proved useful in this setting. However, it is now clear that although 5–10% of infants born to women with ITP may have platelet counts of $<50 \times 10^9/l$, they rarely if ever have any disease.³ The incidence of intracranial haemorrhage in infants born to mothers with ITP has been considered to be as high as 1–2%⁸ but this may be an overestimate. This event now seems to be so unusual in thrombocytopenic infants born to mothers with ITP that the possibility of coexistent NAIT should be considered. Maternal platelet antigen and alloantibody response should be determined in a reference laboratory to identify a cause for severe thrombocytopenia other than the transplacental passage of maternal autoantibody in neonates with severe thrombocytopenia born to mothers with ITP. This is particularly important as the incidence of NAIT has probably been underestimated.²

There is now a rational basis for minimal intervention in women with ITP in pregnancy. Fetal morbidity is low but intrauterine assessment and treatment are difficult. There is no consistent correlation between neonatal platelet counts and maternal platelet antibody titres or maternal platelet counts.¹⁸ Furthermore, administration of corticosteroids or high dose immunoglobulin to the mother has not been shown conclusively to affect fetal platelet counts or outcome.^{12 19 20} Similarly, removal of the spleen may result in normalisation of maternal

Neonatal thrombocytopenia

Figure 2

platelet counts but the autoantibody may still be produced and the fetus or neonate may still be affected. The measurement of fetal scalp platelet counts during labour is unreliable and often underestimates the fetal platelet count, possibly leading to inappropriate intervention.²¹ Given the exceedingly small risk of spontaneous intrauterine haemorrhage percutaneous umbilical blood sampling (PUBS) is not justified, particularly as there is no effective therapeutic product that can be administered in utero if fetal bleeding occurs as the panspecific autoantibody renders all platelets incompatible. Caesarean section may not be less traumatic than vaginal delivery and would be unwarranted for most infants with normal or mildly reduced platelet counts. The need for caesarean section should be an obstetric decision based on the haemostatic and obstetric condition of the mother and the progress of the labour. The relative safety of this procedure in the context of fetal thrombocytopenia is not known. While contention regarding the risk and optimal therapeutic strategy remains,^{8,11} there is increasing conservatism with respect to both investigation and intervention.^{1,12} Mothers and obstetricians who wish to be reassured must understand that even though determination of fetal platelet counts can be accomplished during pregnancy, without a specific treatment such as exists for alloimmune thrombocytopenia, the risk of the diagnostic procedure – for example, PUBS – may outweigh any benefit should severe thrombocytopenia be detected.

In contrast to ITP, in which mothers and their fetuses may both be affected to some degree, women who become sensitised to their fetuses' dissimilar platelet antigens do not generally have thrombocytopenia during their pregnancies, although the alloantibodies can, and often do, cause severe fetal and neonatal thrombocytopenia with associated haemorrhagic morbidity, including intracranial

haemorrhage and death – NAIT. Thus gestational thrombocytopenia, maternal autoimmune thrombocytopenia with transplacental passage of platelet autoantibody, and pregnancy related maternal allosensitisation of women against fetal platelet antigens with consequent NAIT are very distinct entities with vastly different implications for management.

Neonatal immune thrombocytopenia

The assessment and management of thrombocytopenia in the neonate is summarised in fig 2.

The mean (SEM) platelet count in fetuses is $187 (47) \times 10^9/l$ at 15 weeks' gestation and increases to $274 (47) \times 10^9/l$ at 40 weeks' gestation.²² The normal infant at birth should have a platelet count which falls within the normal adult range and which therefore should be in excess of $150 \times 10^9/l$. The incidence of thrombocytopenia (defined as a platelet count $<150 \times 10^9/l$) in non-selected neonates is about 0.8–1.0%.²³ Though thrombocytopenia can be a manifestation of many disorders, the mechanisms responsible are often multifactorial and not fully understood. Elements of production, destruction, intravascular aggregation, sequestration or endothelial margination may all have some role in producing thrombocytopenia. Thrombocytopenia, substantial enough to cause morbidity ($<50 \times 10^9/l$), occurs much less frequently, with an incidence of 0.12% (95% confidence interval 0.07 to 0.19%).³ On the other hand, at least 20% of infants in special care baby units have platelet counts of less than $150 \times 10^9/l$ and about 4% have counts of less than $50 \times 10^9/l$.⁷ About half of these infants have increased platelet associated IgG. This is due to various mechanisms, including specific targeting of platelet antigens in the minority and non-specific adherence in the majority. It is not known what contribution, if any, the platelet associated immunoglobulin makes to platelet survival in most of these cases. Generally, the thrombocytopenia worsens after two to three days but resolves by day 10 in most infants whose underlying medical conditions are improving.

Neonatal thrombocytopenia has been associated with many conditions.⁷ Sepsis (with or without disseminated intravascular coagulation), congenital infections, intrauterine growth retardation, necrotising enterocolitis, polycythaemia, pre-eclampsia, asphyxia, respiratory distress syndrome, persistent pulmonary hypertension, mechanical ventilation, phototherapy, hyperalimentation, exchange transfusion, haemolytic disease and other conditions characterised by clinical instability in sick neonates are frequently associated with thrombocytopenia. HIV infection can cause thrombocytopenia in infants, though the incidence of this in neonates without other causes of thrombocytopenia has not yet been clarified. Rare congenital marrow disorders may result in amegakaryocytic thrombocytopenia – for example, the syndrome of thrombocytopenia and absent radii (TAR).²⁴

The Kasabach-Merritt syndrome with consumptive thrombocytopenia may occur with visceral haemangiomas in the absence of cutaneous manifestations. Fetal or neonatal thrombocytopenia has also been reported in association with maternal disease, including hypertension, thyroid disease, diabetes mellitus and systemic lupus erythematosus.

Immune thrombocytopenia should be considered in any infant with bleeding in whom commonly associated illnesses associated with thrombocytopenia have been excluded. It should also be considered in well term infants with isolated thrombocytopenia. Most infants identified as having thrombocytopenia in the absence of systemic disease or a defined congenital syndrome associated with thrombocytopenia usually have either autoimmune or alloimmune thrombocytopenia. The platelet serves as a target for antibody, usually IgG derived from the mother via transplacental transfer. Mild or moderate thrombocytopenia in a neonate whose mother has thrombocytopenia suggests autoimmune thrombocytopenia and hence a low risk of morbidity. However, women whose spleens have been removed may have persistent antibody production but low clearance of platelets while clinically important platelet destruction can occur in the fetus. It is also now recognised that infants may have autoimmune thrombocytopenia in the absence of maternal autoimmune thrombocytopenia, so-called occult autoimmunity.²⁵ Nevertheless, neonatal thrombocytopenia with a normal maternal platelet count in the absence of previous spleen removal in the mother strongly suggests alloimmune thrombocytopenia.

NAIT is very different from autoimmune thrombocytopenia, with major morbidity and a substantial risk of mortality. Up to 30% or more of fetuses or neonates may experience intracranial haemorrhage and die, or survive with variable long term morbidity as sequelae to porencephaly, hydrocephalus, developmental retardation or seizure disorders.²⁶ Improved laboratory techniques are useful for differentiating autoimmune from alloimmune thrombocytopenia.^{27,28} The HPA platelet alloantigen system is responsible for 75% of cases of NAIT in Caucasians²⁹ with other platelet membrane glycoproteins with biallelic autosomal dominant inheritance involved in other cases. Class II MHC molecules function as immune response modifiers to platelet alloantigens with the risk of development of NAIT closely linked to the DRW52 locus.² It has also been suggested that HLA antigens may serve as primary targets for alloantibody mediated fetal thrombocytopenia although this proposal requires further study.³⁰ While analogous to Rhesus isosensitisation of red cells in terms of antibody production, the condition is different in its effects as it frequently occurs in the first pregnancy. About 50% of infants with NAIT are first births and 97% of subsequent pregnancies are affected.² Thus recurrence in subsequent siblings is very common and is the rule rather than the exception. As maternal thrombocytopenia is not present and platelet antigen and alloantibody screening are not

yet routinely performed the only predictive factor for this condition may be a history of a previously affected child or a more remote positive family history.

The true incidence of HPA alloimmunisation has been presumed to be of the order of 1 in 500–1 in 2000, but comprehensive population data are only now becoming available. Similarly, the actual morbidity and mortality caused by this disorder are now being clarified. In contrast to autoimmune thrombocytopenia, specific treatment is available for affected fetuses. Protocols using fetal ultrasound examinations beginning early in gestation, blood sampling (via percutaneous umbilical blood sampling), fetal platelet transfusions, maternal steroids and intravenous gamma-globulin have been developed and have resulted in improved outcomes, both in terms of platelet counts and morbidity in fetuses and infants born to mothers with a previously affected pregnancy.^{31–35} Early delivery as soon as fetal maturity is achieved shortens the risk period for haemorrhage. Administration of high dose immunoglobulin to the mother results in an increase in the fetal platelet count.³² Intrauterine platelet transfusion is effective in increasing fetal platelet counts and preventing haemorrhage but may have to be started as early as 18 weeks.³⁶ Prospective screening programmes have now shown that NAIT usually develops in neonates born to women with detectable antiplatelet antibody.³⁷ On the basis of these recent observations, Flug *et al* have suggested that all pregnant women should have their HPA status determined.² Those who are homozygous for HPA2 with detectable anti-HPA1 antibody should have PUBS performed at 20 weeks. If the fetal platelet count is $<100 \times 10^9/l$ the mother should receive weekly intravenous immunoglobulin. If the repeat PUBS six weeks later reveals a count of $>30 \times 10^9/l$ treatment should be continued; if it is $<30 \times 10^9/l$ intrauterine antigen negative platelet transfusions should be administered to the fetus at weekly intervals. Homozygous HPA2 women without detectable antibody should be retested at monthly intervals and if antibody becomes detectable they should be managed in the above manner. A count of $50 \times 10^9/l$ has been suggested as a discriminant level for deciding on vaginal delivery or elective section.² Ongoing studies should determine if this is a feasible approach but there may be logistic problems of access to PUBS and the cost effectiveness of this approach may have to be proved.

Affected infants usually present at birth or soon after with purpura or evidence of intracranial haemorrhage. It has been assumed that outcome following intracranial haemorrhage subsequent to immune thrombocytopenia usually has a poor prognosis but a more favourable outcome in neonates affected by immune thrombocytopenia has recently been reported.³⁸ When a neonate is found to have NAIT an urgent management decision is required based on the degree of thrombocytopenia and the extent of haemorrhage.

Infants with severe thrombocytopenia and haemorrhagic manifestations should receive antigen negative platelets using either the mother's washed platelets or antigen typed, non-maternal, donor platelets. Intravenous immunoglobulin should also be considered and may be effective in increasing the platelet count.³⁹ An infant with purpura and severe thrombocytopenia requires rapid intervention and a cranial computed tomography scan. Platelet products should ideally be irradiated to prevent graft versus host disease GvHD and should preferably be from a cytomegalovirus (CMV) negative donor. The use of irradiated platelets or CMV negative blood will be determined by the degree of thrombocytopenia and institutional guidelines.

Autoimmune neonatal thrombocytopenia is essentially a maternal disease which occurs in the neonate as a result of the transplacental passage of maternally produced autoantibody directed against various glycoproteins on the platelet surface. Thrombocytopenia in affected infants is usually mild and the rare instances of severe morbidity nearly always occur in infants whose mother's ITP produced the current pregnancy. Intracranial haemorrhage is rare. Treatment of the affected infants is rarely necessary or advisable in the absence of bleeding. If treatment is necessary then intravenous immunoglobulin or oral prednisolone should be considered in the first instance. Platelet transfusions are unlikely to be helpful as the antibody target is common to all platelets but may be useful adjunctively after intravenous immunoglobulin in a few patients with severe haemorrhage.

Conclusion

ITP in pregnant women is essentially a maternal disease with a very low risk of morbidity to the fetus. Intervention should be in response to the needs of the mother, recognising that severe thrombocytopenia caused by transfer of maternal autoantibody to the fetus or neonate is exceptional. In contrast, in NAIT alloimmunisation of the maternal immune system results in transplacental transfer of alloantibody with high affinity typically for the platelet membrane glycoprotein IIIa. Platelet destruction is severe and thrombocytopenia with a high risk of major haemorrhage is common. Specific effective treatment is available and therefore NAIT should be diagnosed and treated as soon as possible to prevent neonatal morbidity and mortality. Screening women in their first pregnancy for HPA2 homozygosity and detection of anti-HPA1 antibody may permit identification of high risk fetuses and intervention in utero to prevent antepartum intracranial haemorrhage.

- 1 Aster R. Gestational thrombocytopenia, a plea for conservative management. *N Engl J Med* 1990; 323: 264-6.
- 2 Flug F, Karpatkin M, Karpatkin S. Should all pregnant women be tested for their platelet PLA (Zw, HPA-1) phenotype? *Br J Haematol* 1994; 86: 1-5.
- 3 Burrows R, Kelton J. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N Engl J Med* 1993; 329: 1463-6.
- 4 Burrows R, Kelton J. Incidentally detected thrombocytopenia in healthy mothers and their infants. *N Engl J Med* 1988; 319: 142-5.

- 5 Burrows R, Kelton J. Thrombocytopenia at delivery. *Am J Obstet Gynecol* 1990; 162: 731-4.
- 6 Bussell J, Kaplan C, McFarland J. Recommendation for the evaluation and treatment of neonatal autoimmune and alloimmune thrombocytopenia. *Thromb Haemostas* 1991; 65: 631-4.
- 7 Andrew M. The hemostatic system in the infant. In: Nathan D, Oski F, eds. *Hematology of infancy and childhood*. 4th edn. Philadelphia: WB Saunders & Co, 1993: 115-27.
- 8 Samuels P, Bussell J, Braitman L, Tomaski A, Druzin M, Mennuti M, et al. Estimation of the risk of thrombocytopenia in the offspring of pregnant women with presumed immune thrombocytopenic purpura. *N Engl J Med* 1990; 323: 229-35.
- 9 Kaplan C, Daffos F, Forestier F, Tertian G, Catherine N, Pons J, et al. Fetal platelet counts in thrombocytopenic pregnancy. *Lancet* 1991; 336: 979-82.
- 10 Bussell J, Druzin M, Cines D, Samuels P. Thrombocytopenia in pregnancy. *Lancet* 1991; 337: 251.
- 11 McCrae K, Samuels P, Schreiber A. Pregnancy-associated thrombocytopenia: pathogenesis and management. *Blood* 1992; 80: 2697-714.
- 12 Burrows R, Kelton J. Thrombocytopenia in pregnancy. In: Greer I, Turpie A, Forbes C, eds. *Haemostasis and thrombosis in obstetrics and gynaecology*. London: Chapman & Hall, 1992: 407-29.
- 13 Roy V, Gutteridge C, Nysenbaum A, Newland A. Combination chemotherapy with conservative obstetric management in the treatment of pregnant patients with acute myeloblastic leukaemia. *Clin Lab Haematol* 1989; 11: 171-8.
- 14 Kelton J, Powers P, Carter C. A prospective study of the usefulness of the measurement of platelet-associated IgG for the diagnosis of idiopathic thrombocytopenic purpura. *Blood* 1982; 60: 1050-3.
- 15 Bellucci S, Charpak Y, Chastang C, Tobelem G, Purpura C, and the Cooperative Group on Immune Thrombocytopenic Purpura. Low doses v conventional doses of corticoids in immune thrombocytopenic purpura (ITP). *Blood* 1988; 71: 1165-9.
- 16 Manoharan A. Treatment of refractory idiopathic thrombocytopenic purpura in adults. *Br J Haematol* 1991; 79: 143-7.
- 17 Van Leeuwen E, Van der Van J, Engelfriet C, von dem Borne A. Specificity of autoantibodies in autoimmune thrombocytopenia. *Blood* 1982; 59: 23-6.
- 18 Scott J, Rote N, Cruikshank D. Antiplatelet antibodies and platelet counts in pregnancies complicated by autoimmune thrombocytopenia. *Am J Obstet Gynecol* 1983; 145: 932-9.
- 19 Karpatkin M, Porges R, Karpatkin S. Platelet counts in infants of women with autoimmune thrombocytopenia, effect of steroid administration to the mother. *N Engl J Med* 1981; 305: 936-8.
- 20 Christiaens G, Niewenhuis H, Von den Borne A, Ouwehand W, Helmerhorst F, Van Dalen C, et al. Idiopathic thrombocytopenic purpura in pregnancy: a randomised trial on the effect of antenatal low dose corticoids on neonatal platelet count. *Br J Obstet Gynaecol* 1990; 97: 893-8.
- 21 Christiaens G, Helmerhorst F. Validity of intrapartum diagnosis of fetal thrombocytopenia. *Am J Obstet Gynecol* 1987; 157: 864-5.
- 22 Van den Hof M, Nicolaides K. Platelet count in normal, small and anemic fetuses. *Am J Obstet Gynecol* 1990; 162: 735-9.
- 23 Dreyfus M, Morel-Kopp M, Verdy E, Schlegel N, Kaplan C, Tchernia G. Immune neonatal thrombocytopenia: Unexpected results of a multicentric prospective study in non selected patients. *Blood* 1993; 82 (suppl 1): 582a.
- 24 Hall J, Levin J, Kuhn J, et al. Thrombocytopenia with absent radius. *Medicine* 1969; 48: 411-39.
- 25 Tchernia G, Morel-Kopp M, Yvart J, Kaplan C. Neonatal thrombocytopenia and hidden maternal autoimmunity. *Br J Haematol* 1993; 84: 457-63.
- 26 Naidu S. Central nervous system lesions in neonatal isoimmune thrombocytopenia. *Arch Neurol* 1983; 40: 552-4.
- 27 Clemenceau S, Perichon B, Elion J, Kaplan C, Krishnamoorthy R. An improved DNA based identification of fetuses at risk for HPA-1a (PLA1) neonatal alloimmune thrombocytopenia. *Br J Haematol* 1994; 86: 198-200.
- 28 Pao M, Karłowicz M, Kickler T, Zinchan W. Importance of platelet serologic testing for defining the cause of neonatal thrombocytopenia. *Am J Ped Hematol Oncol* 1991; 13: 71-6.
- 29 Von Dem Borne A, Van Leeuwen W, Von Riesz I, Van Boxtel C, Engelfriet C. Neonatal alloimmune thrombocytopenia: Detection and characterisation of the responsible antibodies by the platelet immunofluorescence test. *Blood* 1981; 57: 649-56.
- 30 Lalezari P, Dimitrova A, Diwan A, Einarson M. HLA incompatibility is the most common cause of neonatal alloimmune thrombocytopenia. *Blood* 1993; 82 (suppl 1): 203a.
- 31 Bussell J, Berkowitz R, McFarland J, Lynch L, Chitkara U. Antenatal treatment of neonatal alloimmune thrombocytopenia. *N Engl J Med* 1988; 319: 1374-8.
- 32 Lynch L, Bussell J, McFarland J, Chitkara U, Berkowitz R. Antenatal treatment of neonatal alloimmune thrombocytopenia. *Obstet Gynecol* 1992; 80: 67-71.
- 33 Bussell J, McFarland J, Berkowitz R. Antenatal management of fetal alloimmune and autoimmune thrombocytopenia. *Transfusion Medicine Review* 1990; 2: 49-62.

- 34 Nicolini U, Rodeck C, Kochenour N, Greco P, Fisk NM, Letsky E, *et al.* In-utero platelet transfusion for allo-immune thrombocytopenia. *Lancet* 1988; **ii**: 506.
- 35 Daffos F, Forestier F, Muller J, Reznikoff-Etievant MF, Habibi B, Capella-Parlovsky M, *et al.* Prenatal treatment of alloimmune thrombocytopenia. *Lancet* 1984; **ii**: 632.
- 36 Murphy M, Metcalfe P, Waters A, Ord J, Hambley H, Nicolaides K. Antenatal management of severe fetomaternal alloimmune thrombocytopenia: HLA incompatibility may affect responses to platelet transfusions. *Blood* 1993; **81**: 2174–9.
- 37 McFarland J, Frenzke M, Aster R. Testing of maternal sera in pregnancies at risk for neonatal alloimmune thrombocytopenia. *Transfusion* 1989; **29**: 128–33.
- 38 Bussel J, Tanli S, Peterson Hart de C. Favourable outcome in 7 cases of perinatal intracranial haemorrhage due to immune thrombocytopenia. *Am J Ped Hematol Oncol* 1991; **13**: 156–9.
- 39 Linder N, Shapiro S, Moser A, Roitman J, Engelhard D. Treatment of thrombocytopenia with high dose intravenous gamma globulin. *Dev Pharmacol Ther* 1990; **14**: 205–8.ii8