To transfuse or not to transfuse: iatrogenic compromise of women's reproductive careers

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INTRODUCTION

Transfusing young women can have serious consequences for their reproductive function. Red cell alloimmunization is a potential risk, causing fetal haemolysis in subsequent pregnancies. Alternative management strategies for non-life-threatening anaemia should be sought whenever possible.

DO WE TRANSFUSE TOO OFTEN?

As a result of increasing public awareness of transfusion transmitted disease, a less liberal attitude towards the administration of blood products has developed (Goodnough et al, 1999). However, patients are still being transfused when other therapeutic options, such as iron therapy, are feasible. This seems to occur particularly when health-care providers are faced with moderate to severe anaemia, and fail to take into account that, when developing chronically over a long period of time, even very low haemoglobin concentrations are well tolerated and drug treatment rather than blood transfusion may be appropriate.

Apart from infection and transfusion reactions, red cell alloimmunization poses a significant problem in the group of population that is most likely to be affected by iron deficiency anaemia (IDA): women of child-bearing age.

CASE REPORT

A 21-year-old Indo-Asian woman, who had arrived in the UK 5 months before presentation, consulted her general practitioner because of tiredness and shortness of breath on climbing stairs. There were no significant factors in her history, except that she did not eat red meat. Initial investigation revealed a severe anaemia with a haemoglobin (Hb) concentration of 4.6 g/dl, mean cell volume (MCV) of 49.4 fl, mean cell haemoglobin (MCH) of 11.5 pg, white cell count of 7.4 x 10^9/litre and a platelet count of 583 x 10^9/litre. She was promptly referred as an emergency to a general medical ward in a teaching hospital for further management. On admission, physical examination revealed pallor and a tachycardia of 110 beats/minute, but there ware no other significant findings. Her electrocardiogram was normal and there was no evidence of cardiac failure on chest X-ray. She was transfused three units of packed red cells. Subsequently she underwent further investigations, including Hb electrophoresis, vitamin B_{12} and folate levels, ferritin and transferrin levels, serum urea and electrolytes, liver function tests, blood film for malarial parasites, endomysial and gliadine antibodies, and comprehensive gastrointestinal tract work-up. All investigations were negative with the exception of a positive anti-gliadine immunoglobulin G. The diagnosis of iron deficiency anaemia of unknown cause was made. The patient was given dietary advice and was discharged back under her GP's care 6 months later, having maintained a normal Hb.

A year later she attended an antenatal clinic at 15 weeks gestation. Her initial Hb was 11.4 g/dl with an MCV of 74 fl. Her blood group was O RhD positive. However, her antenatal serology testing detected anti-E and anti-c (32 iU/ml) antibodies. Her husband was heterozygous for the gene c and homozygous for e. The patient's antibody titres were checked every 2 weeks as recommended by the National Blood Transfusion Service, and are shown in *Figure 1*. Fetal wellbeing was assessed at 2-weekly intervals, using ultrasound and umbilical and middle cerebral artery Doppler. All tests remained within normal limits. As the antibody titre rose steeply at 33 weeks gestation, amniocentesis and amniotic fluid spectrophotometry at optical density 450 were performed. The results indicated minimal or no fetal haemolysis. However, in view of the continuing increase in anti-c titres, the decision was made to deliver at 36 weeks gestation. A male infant (3.32 kg) was delivered by caesarean section following failed induction of labour. Although not anaemic, he was jaundiced at birth and required admission to the neonatal intensive care unit, where he underwent two exchange transfusions.

This case report shows the need for careful consideration of the indication for blood transfusion in this group.

IS ANAEMIA IN YOUNG WOMEN AN ISSUE?

Despite the continuing decline in the incidence of IDA, up to 25% of the world population are still affected. While the bulk of this figure represents widespread and severe IDA in developing countries, the prevalence of IDA in the western world reaches 10% (DeMaeyer and Adiels-Tegman, 1985), with women in the reproductive age group 15 times more frequently affected than men (Cook et al, 1986). In the UK, average iron intake in adolescent girls is well below the reference nutrient intake, leading to IDA which may persist into reproductive years. Racial differences exist, and young Asian girls are twice as likely to have IDA than their Caucasian counterparts (Nelson et al, 1994).

Consequently, particularly in areas with large Asian communities, both primary care providers and hospital practitioners will continue to encounter young women with varying degrees of IDA, and will have to offer them advice on the most appropriate management. As exemplified in the above case report, when faced with severe, albeit only mildly to moderately symptomatic anaemia, doctors may be inclined to transfuse the patient before investigating its underlying cause.

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RISKS OF TRANSFUSING YOUNG WOMEN

This mode of management can no longer be considered appropriate. It remains difficult to reliably estimate the proportion of avoidable blood transfusions, but it is widely acknowledged that patients with asymptomatic IDA should only be transfused if they fail to respond to adequate iron therapy, or if they are to undergo immediate surgery (Davies and Williamson, 1998).

Although careful cross-matching procedures minimize transfusion reactions, there are immunological consequences to blood transfusion which may have potentially detrimental effects. These involve mismatch of various factors expressed on cellular blood components or in plasma, e.g. complement components, histocompatibility leukocyte antigens, tissue specific and membrane alloantigens, immunoglobulins and heat shock proteins (Petranyi et al, 1997).

In young women red cell alloimmunization is a further serious risk, which may significantly compromise their future reproductive career by subsequently causing fetal and neonatal haemolysis. The true incidence of red cell alloimmunization following blood transfusion is probably higher than previously thought, and has been reported to be as high as 8.6% (Redman et al, 1996). Moreover, women may be at a higher risk of sensitization than men (Spielmann and Seidl, 1974), and rates of alloimmunization may be higher in non-Caucasians (Luban, 1989).

ALLOIMMUNIZATION AND PREGNANCY

While the incidence of RhD sensitization as a result of a transfusion mismatch has diminished (Tovey, 1988), other red cell antigens, which are not always matched in routine cross-match procedures, now have a relatively more prominent role (*Table 1*). This is particularly true in Rhesus positive individuals. Anti-c, which featured in this case report, has been reported to account for up to 10% and anti-Kell for up to 22% of antibodies detected in alloimmunized blood samples after blood transfusion (Hundric-Hasple et al, 1994).

Among the non-D antibodies found in pregnancy, anti-c and anti-Kell are probably most frequently associated with significant fetal and neonatal haemolysis. There are thought to be about 1100 anti-c and anti-Kell pregnancies annually in England and Wales, although only few result in substantial morbidity (Bowell et al, 1986). However, the potential risks and the need for serial, frequently invasive investigations generate considerable anxiety and cost.

CONCLUSION

There is a need for increased awareness regarding the issues concerning the management of IDA in women of childbearing age, both among primary care providers and specialists. Of course the management in individual cases will depend on the cause of anaemia and severity of symptoms; however, the threshold for blood transfusion ought to be reconsidered, particularly with the women's future reproductive function in mind. In the presence of identifiable aetiological factors, such as menstrual disorders or dietary deficiency, correction of the underlying cause with concomitant iron therapy should be the first-line management. HM

Figure 1. Maternal serum anti-c titres between 15 and 35 weeks gestation.

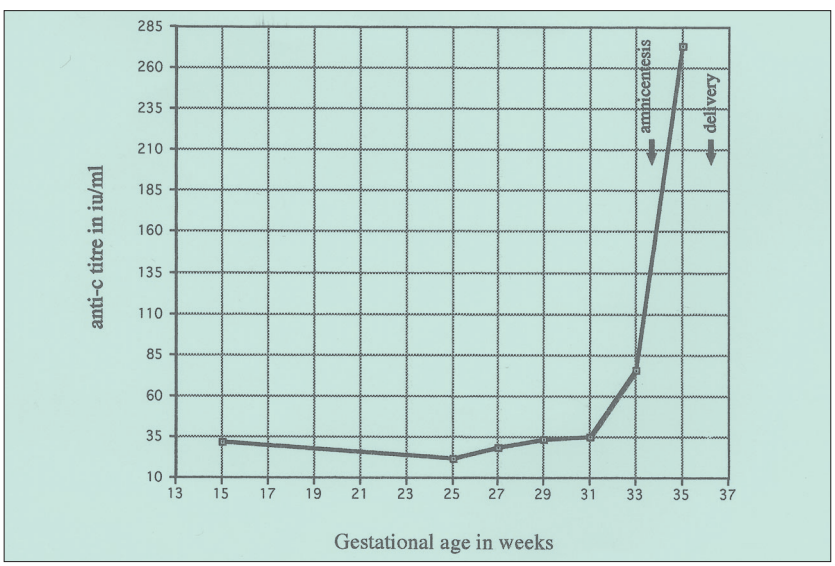

TABLE 1.
Red cell antibodies implicated in fetal and neonatal haemolysis

Common	Infrequent	Rare, severe haemolysis unlikely
D, C, c, E, e, Kell	$Kp^{a/b}$, k, S, Jk^{a} (Kidd), Fy^{a} (Duffy)	Do^{a}, $Di^{a/b}$, Fy^{b}, Hutch, Jk^{b}, Lu^{a}, M, N, s, U, Yt^{a}

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