# Preventing RhD haemolytic disease of the fetus and newborn: where to next?

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Non-invasive fetal RhD genotyping will enable ethical and cost-effective targeting of prophylaxis

There are many unique and inspiring aspects to the story of haemolytic disease of the fetus and newborn. This once common, mysterious, and potentially devastating disease has been known for centuries. It may have been the reason for the shocking obstetric history of Katherine of Aragon, the first wife of Henry VIII; the course of British history might have been very different had anti-RhD been available in Tudor England.[1]

In the course of 30 years (1932–1962), haemolytic disease of the fetus and newborn was clinically defined, its pathophysiology clarified and causation elucidated, treatment developed, and prevention initiated. This story shows the importance of Evidence-based medicine, the Ethics of human beings altruistically helping each other, and the Economic drivers of cost-effectiveness in health care, illustrating how society responds to the challenges of establishing and stabilising this triangle without jeopardising any of its three essential components.

Hydrops fetalis and kernicterus were recognised in 1932 by Louis Diamond (1902–1999) and his associates as being different aspects of the same disease (Box).[2] Six years later, pathologist Ruth Darrow (1895–1956), whose baby had died of kernicterus, proposed that the disease had its origin in the materno-fetal passage of maternal alloantibodies produced in response to the feto-maternal passage of red blood cells.[3] Fetal haemoglobin was initially suspected to be the offending antigen, but, after Karl Landsteiner and Alexander Wiener discovered the Rh blood group system, Philip Levine (1900–1987) identified RhD as the causative antigen.[4] As the suppression of alloimmune responses had been understood since the early 1900s, it is surprising that anti-D prophylaxis was not subsequently developed until two decades after the pathophysiology and cause of the disease had been established.

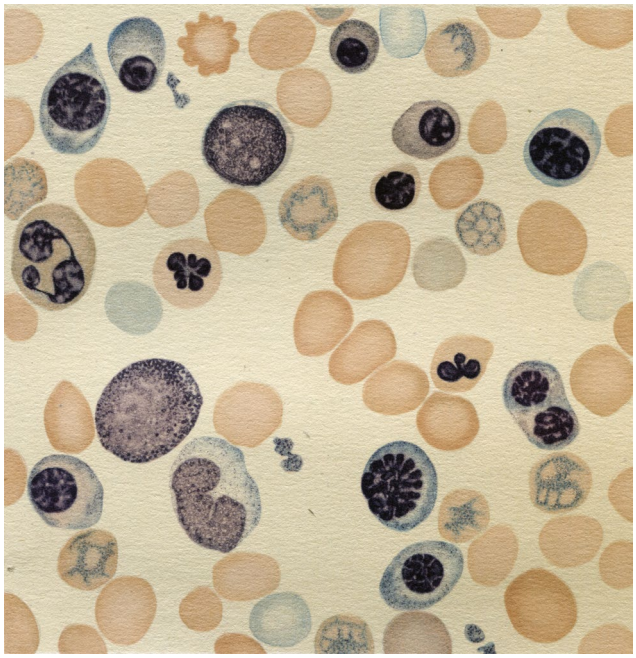
Randomised controlled trials of post-delivery anti-D prophylaxis confirmed its efficacy and safety, reducing the alloimmunisation rate from 15% to 1%.[5] Evidence for the benefit of antenatal prophylaxis is drawn from large observational studies which found that single and two-dose regimens further reduced the alloimmunisation rate to 0.2%.[6,7]

Transfusion medicine has humans at each end of the demand and supply chain. Altruistic blood donors volunteer to provide a unique component of their blood, in most cases after being actively stimulated to produce the anti-D that has almost totally eliminated RhD alloimmunisation when administered during pregnancy. Attempts to develop therapeutic monoclonal or recombinant anti-D have not yet borne fruit, and for the foreseeable future prophylaxis will depend upon Australian blood donors if importation of commercial product is to be avoided.

In this issue of the *MJA*, White and his colleagues[8] report a trial of routine antenatal anti-D prophylaxis (RAADP) that compared the outcomes of single and two-dose regimens. The primary outcome was the detection of circulating anti-D in the mother at delivery, a surrogate marker of prophylaxis efficacy that has not been validated. A better but logistically more difficult and expensive approach would have been to use flow cytometry to assess clearance of fetal RhD cells from maternal circulation. The mechanism by which anti-D prophylaxis suppresses immunisation is not entirely clear, but the correlation between red blood cell clearance and the prevention of the antibody response is strong.[9]

Can the trial reported by White and colleagues[8] inform decision making regarding advice in clinical practice guidelines about the relative benefits of single and two-dose RAADP regimens? The authors reported better compliance with single dose treatment

**Erythroblastosis fetalis or hemolytic anemia of the newborn; severe form**



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(although the difference was not not statistically different), and this might be more important than measurable anti-D levels at delivery. Single-dose RAADP has been employed in some countries for more than 20 years without evidence of higher rates of alloimmunisation. The case for the Australian guidelines continuing to recommend the two-dose schedule should perhaps be re-assessed in light of experience overseas.

It is important to note that the evidence for the benefits and risks of anti-D prophylaxis is soundly based on studies of the combination of antenatal and post-delivery prophylaxis. Level I evidence for the superiority of the two-dose schedule in averting anti-D formation will be elusive, not only because enormous numbers of participants would be needed for an adequately powered randomised controlled trial, but also because of the ethical problems of such a study. The most practical alternative may be to analyse post-marketing observational data from multiple centres.

Where to next? The ultimate challenge for clinical practice guidelines after the highest level of achievable Evidence has been reached is prioritising Ethics and Economics when updating the guidelines, as well as ensuring that they are implemented. The main areas of focus should be self-sufficiency and stewardship of the product. To reduce unnecessary use of anti-D immunoglobulin, non-invasive fetal RhD genotyping should be adopted to allow antenatal prophylaxis to be restricted to RhD-negative women carrying RhD-positive fetuses.[10] But cost-effectiveness, historically not a major driver in transfusion medicine, remains a particularly complex challenge because of the ethics of deliberately stimulating blood donors to produce anti-D.

**Competing interests**: James Isbister is a member of the Independent Advisory Committee of the Australian Red Cross Blood Service and Chair of the National Blood Authority Patient Blood Management Implementation Steering Committee. Amanda Thompson is a member of the National Blood Authority expert reference group for development of a clinical practice guideline on the use of RhD immunoglobulin in maternity care.

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