

Routine antenatal anti-D: *an overview of the evidence*

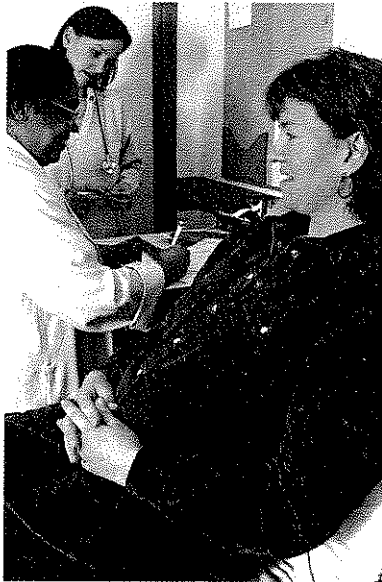
Anti-D was developed thirty years ago in response to the problem of rhesus disease. In simple terms, it is a synthetic pharmaceutical product manufactured from human blood which is designed to prevent rhesus negative women from developing antibodies to rhesus positive blood. In most areas, anti-D is routinely offered to rhesus negative women who have given birth to a rhesus positive baby, and to rhesus negative women who experience a 'sensitising event' during pregnancy, where it is feared that some of the baby's blood may have entered her bloodstream.

While the postnatal administration of anti-D immunoglobulin to rhesus negative women who have given birth to a rhesus positive baby has been considered by many as an acceptable and beneficial routine intervention for the last 30 years, the question of whether it is appropriate to offer routine antenatal administration of this product has been hotly debated for almost as long. There is little question that women who experience potentially sensitising events in pregnancy should be given appropriate information and offered this as an option. Rather, the debate concerns the issue of so-called 'silent' fetomaternal transfusion — the existence (or otherwise) of which phenomenon forms part of the basis for arguments in favour of routine antenatal prophylaxis.

The debate surrounding the routine administration of anti-D during pregnancy began in 1969, when Zipursky and Israels¹ suggested that antenatal anti-D administration may prove to reduce the rate of sensitisation. Bowman and Pollock² followed this up with the specific recommendation that anti-D should be administered to all rhesus negative women at 28 weeks to prevent sensitisation in pregnancy. The debate continued throughout the 1980s and 1990s, with opinions divided between those who saw antenatal anti-D as a wholly beneficial intervention, which would save babies, and those who urged caution for a variety of reasons. Antenatal anti-D has been offered routinely in some countries, including the USA³ and Germany, for a number of years. Yet Britain's first active discussion of this matter occurred in 1997, when a consensus conference⁴ decided to recommend routine antenatal administration in the UK; an issue which is currently being debated on practical, professional and political levels.

Why offer antenatal anti-D?
Proponents of routine antenatal

administration base their arguments around evidence suggesting that current protocols for the administration of anti-D do not prevent all cases of isoimmunisation. They feel that routine antenatal administration is the best way forward in moving closer to 100% protection from isoimmunisation. For example, Hughes *et al*⁵ carried out research in Scotland and concluded that,



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Antenatal anti-D has been debated for the past three decades

in 53 of the 80 babies with rhesus disease, this had been caused by the failure of the current guidelines to protect against maternal isoimmunisation.

The effectiveness of the antenatal anti-D programme in Derbyshire — where women having their first baby are already offered antenatal anti-D at 28 and 34 weeks of pregnancy — was evaluated by Mayne *et al*⁶ who showed a fall in the mean overall sensitisation rate from 1.12% in 1988–91 (before the onset of the antenatal programme) to 0.28% in 1993–95.

Another research study by McSweeney *et al*⁷ not only provides evidence in

support of antenatal administration, but also highlights part of the argument against this. While these researchers estimate that over 80% of women who became isoimmunised might not have experienced this had they been offered antenatal anti-D, they also found that professionals failed to offer anti-D in 48% of cases where women experienced potential sensitising events in the antenatal period. This is one of the strongest arguments against routine administration of antenatal anti-D.

The fact that most of the studies cited in support of routine antenatal anti-D are retrospective proves problematic. The use of women's case notes in such research is known to cause difficulties; many aspects of care are not always well documented by professionals and this can lead to bias in the results of the study. For instance, if a clinician had not documented the occurrence of a potentially sensitising event, or perhaps not even asked the woman about these, then it would look as if the woman had experienced silent fetomaternal haemorrhage if she then became isoimmunised.

Much of the evidence cited in this area, although interesting and useful in other ways, does not look at the effectiveness of antenatal anti-D in the light of prospective, randomised controlled trials. Only two antenatal anti-D trials of any real size and quality have been conducted — although it should be noted that neither of these was single or double-blinded. Lee and Rawlinson⁸ gave women in the treatment group two doses of 50mg (250 international units) of anti-D at 28 and 34 weeks, and showed no statistically significant difference between their outcomes and women in the group who had not received antenatal anti-D. However, researchers in Huchet *et al*'s study⁹ gave a larger dose of anti-D (500 international units) at 28 and 34 weeks and showed a clear reduction in

the incidence of isoimmunisation at between two and twelve months, although no data which considered subsequent pregnancy in those women were available. In response to these data, Cochrane reviewers concluded that there was still a need for consideration of other issues, such as cost and supply of anti-D.¹⁰ Of course, we should bear in mind that, even if we feel that the evidence shows antenatal anti-D administration to be effective, this does not automatically mean it is either necessary or beneficial for all women; this is another issue entirely.

Is there evidence for caution?

There are two main arguments against the routine administration of antenatal anti-D. Although cost is a major issue, this will not be considered here — discussion of this can be found elsewhere.¹¹ The first of these arguments concerns the difficulty that exists with trying to establish how effective antenatal anti-D would be when there are still questions and problems regarding the current programme of routine postnatal administration and antenatal administration in response to a potentially sensitising event. Ghosh and Murphy's Scottish study¹² showed that just over 30% of women who had experienced an antenatal sensitising event had not been offered anti-D. Tovey¹³ showed that 22% of the women in his study became sensitised as a result of 'failure of administration' and Howard *et al*¹⁴ also propose that closer adherence to the 1991 recommendations¹⁵ might further reduce the incidence of isoimmunisation. For example, their study found that only 20% of women who had experienced abdominal trauma had been offered anti-D and there was only 95% adherence to the recommendations in the area of postnatal administration.

Clearly, it is not helpful to begin a prophylactic antenatal programme if a proportion of the women who are becoming sensitised during pregnancy are facing this as a result of professional failure to offer anti-D after a potentially sensitising event. Rather than subjecting all women to antenatal anti-D because some clinicians fail to offer this to the women that really need it, we need to consider how this trend can be reversed. We also need to establish how many

women are becoming sensitised as a result of failure to implement the current guidelines, and not include these women in figures which are being used to promote the uptake of routine antenatal prophylaxis.

It is not just midwifery and obstetric departments which are failing to offer anti-D. Huggon and Watson¹⁶ sampled 29 women who arrived in accident and emergency departments following a threatened miscarriage. Only eight women were tested to establish their blood group on admission and none of those women who were rhesus negative were offered anti-D. Gilling-Smith *et al*¹⁷ built on this small-scale study and researched 88 accident and emergency units, which treated women who experienced bleeding in early pregnancy. Of these, 77 failed to administer anti-D when this was

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appropriate, and 37% reported not even having access to Kleihauer testing to determine whether a woman had experienced a larger bleed than would be covered by the standard dose.

What are the risks?

The second argument against routine antenatal anti-D concerns the potential risks of this, both to the woman and to her unborn baby (who will not benefit from this — anti-D effectively being a protective measure for future siblings). The fact that there has been no research investigating the effects of anti-D on the unborn child is one of the factors of concern to those currently calling for caution.^{18,19} Gaskin cites several potential risk factors where babies are exposed to anti-D, including immune system compromise and potential problems during later reproduction for rhesus negative baby girls exposed to anti-D *in utero*.¹⁸

Two further potential risks of antenatal anti-D are discussed in the medical literature; this does not, however, mean that these are the only possible risks as there may be others not yet predicted. The first risk is that of augmentation, or enhanced anti-D immunisation,⁴ where a woman who is given passive anti-D during the antenatal period could, upon exposure to rhesus positive cells (via transplacental haemorrhage), mount a primary immune response to these.

The second concern is the effect of passive anti-D on the unborn baby. There has been no systematic study which looks at the short and long-term side effects of anti-D in babies.⁴ Although Gaskin's evidence¹⁸ concerning immune system compromise seems to have been ignored, other risks to the baby have been discussed in the literature. Some of these concern the fact that about 10% of the anti-D given to the mother will cross the placenta to the baby.^{4,20} Studies have shown that this causes a proportion of babies to test positive for antiglobulins (via a direct Coombs test) after they are born.^{2,13,21} The few studies which have looked at this have suggested that, while babies may suffer some anaemia, this does not require treatment in the immediate postnatal period.

Although Romm²² points out that the manufacturers of anti-D clearly state that this should not be given to babies, no-one has considered the question of whether there are long term consequences of this. It should be remembered that unborn babies will also be exposed to the risks which women face, such as that of virus transmission.²³ This can only be exacerbated by the fact that the optimal dose of antenatal anti-D is not known; women and babies may be exposed to more of this product than they need.

Debating the issues

In 1997, a consensus conference was held so that a group of experts could determine national recommendations for antenatal anti-D administration.⁴ These experts gathered to assess the evidence, including many of the studies cited here, to make recommendations to the Royal College of Obstetricians and Gynaecologists and the Royal College of Physicians of Edinburgh. This group included haematologists, obstetricians, general practitioners and even a medical

journalist. Significantly, a number of groups were not represented; no consumer-focused childbirth organisations or childbearing women were invited for their opinions, and there was no clinical midwifery representation in the group. This may seem undemocratic to some, as it is women who receive the product and usually midwives who inform them of the issues and administer it.

In relation to current failures of implementation, the conference noted their concern that, 'there is abundant evidence that the recommendations are not being fully applied'.⁴ They did not, however, feel that this issue warranted further investigation before making the decision to recommend routine antenatal anti-D. Another recommendation concerned the suggestion that, 'information leaflets concerning the recommendations should be given to rhesus-negative women and their partners'. This may be an issue which the midwifery profession needs to debate in relation to informed choice and the need for balanced information; the vast majority of the information leaflets currently available — mostly donated by the pharmaceutical companies producing anti-D — are biased towards women's acceptance of anti-D rather than the facilitation of informed choice. If more midwives became involved in the process of writing and evaluating this kind of information, women may have more of a foundation upon which to make their choices.

CONCLUSIONS

The Royal College of Midwives and the UKCC have raised concerns about the guidelines advocating the use of anti-D in the antenatal period,^{19,24} specifically the lack of testing of the product for routine use and the lack of sound evidence which suggests that antenatal administration is beneficial. Coombes¹⁸ is also among those who have highlighted the fact that around 40% of the 100,000 or so women who would receive antenatal anti-D each year in the UK would be carrying rhesus negative babies, and therefore would have received this unnecessarily. Should paternal blood testing be one of the options which women should be offered at this time? Women who are pregnant with their last child are also among those

who would not benefit from antenatal anti-D. Should it become routine practice for midwives to discuss these issues with women in relation to their personal need for anti-D?

Many questions remain which suggest the need for midwives to become more involved in this debate. Is there enough sound evidence to support the routine antenatal administration of anti-D, or should midwives — as women's advocates — be concerned about this prospect? How can the issues be addressed and the remaining questions answered in such a way that we know that the options we are offering women are beneficial rather than harmful and based on what is truly optimal for those women, rather than being deemed necessary as a result of our own failures in other areas? More than ever, midwives need to be able to explain and discuss the evidence with the women who face this decision. Whatever recommendations are put in place, either locally or nationally, women have a right to make their own informed choices and midwives have a duty to enable these choices to be freely made.

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