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# Incidence of maternal sensitisation to Rh(D) in Christchurch, New Zealand and reasons for prophylaxis failures

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**Abstract**

**Aim** To estimate the current incidence of maternal sensitisation to Rh(D) and examine reasons for prophylaxis failures.

**Method** Retrospective chart review of new sensitisations to Rh(D) detected in antenatal records, between 2005 and 2012 in Christchurch, New Zealand and systematic examination of circumstances likely to have caused prophylaxis failures.

**Results** Fifty-four new sensitisations in an at-risk population of about 4624 in 8 years means an incidence of roughly 1.1%. In 86.6% of 45 sensitisations where information was available, there was a recognised sensitising event including previous deliveries while in 13.3% there were none. Of those with recognised sensitising events, 46.1% had anti-D prophylaxis per local guidelines, in 12.8%, prophylaxis was given though it did not conform, entirely, to guideline. No prophylaxis at all was given to 41% despite a sensitising event being recognised.

**Conclusion** The incidence of maternal sensitisation to Rh(D) in Christchurch, New Zealand, is as expected given our prophylaxis regimen. Half the sensitisations were associated with complete or partial failure to follow local guidelines. Better adherence to this may reduce incidence of sensitisation. It is also thrice as high as might be expected with a routine antenatal anti-D prophylaxis (RAADP) program. An economic analysis of RAADP in New Zealand will be useful.

Haemolytic disease of the fetus and newborn (HDFN), which may follow maternal sensitisation to Rh(D), is a serious, but mostly preventable, problem. Prophylaxis with anti-D was initially used postnatally, then antenatally for sensitising events, and since the 1970s, routinely antenatally.[1-3]

Several countries, though not New Zealand, officially recommend routine antenatal anti-D prophylaxis (RAADP).[1,4] In this context it should be noted that though the Royal Australian and New Zealand College of Obstetricians and Gynaecologists guideline recommends RAADP,[5] this is not yet endorsed by the New Zealand Ministry of Health.

We aimed to determine the incidence of sensitisation to Rh(D) in New Zealand given the current prophylaxis regimen[6] and to examine the reasons for the sensitisations that occurred.

## Method

Retrospective chart review of all those with alloantibody to Rh(D), detected for the first time between 2005 and 2012, in the New Zealand Blood Service (NZBS) Christchurch Hospital Blood Bank antenatal records.

Using a specially-designed data collection form we systematically examined the circumstances that might have led to failure of protection against sensitisation to Rh(D)—specifically:

- Was there a recognised antenatal sensitising event?
- If so, at what stage of pregnancy did it occur?
- What dose of prophylactic anti-D, if any, was given to cover this event?
- If indicated, was a Kleihauer (or equivalent) test done to determine if a further prophylactic anti-D dose was indicated?
- Was there any history of transfusion of Rh(D) incompatible blood components e.g. platelets and, if so, was this covered with prophylactic anti-D?

As this study meets the criteria for studies that do not require New Zealand Health and Disability Ethics Committees review, ethics approval was not sought.[7]

## Results

In the antenatal records we found 54 *new sensitisations* to Rh(D) in the 8 years from 2005–2012. All appeared to be related to the pregnancy with none, apparently, related to an Rh(D) incompatible transfusion. The parity of the women involved varied from 0–5. Seven women (13%) were primigravidae. Table 1 summarises our data on sensitisations to Rh(D) and prophylaxis during this period.

**Table 1. Summary of data on sensitisations to Rh(D) and anti-D prophylaxis in Christchurch, 2005–2012**

| | | | Recognised sensitising event (including previous delivery) | | Prophylaxis | | |
|---|---|---|---|---|---|---|---|
| | | | No | Yes | Given per guideline | Given but not per guideline | Not given (not given despite recognised sensitising event) |
| Pregnancy stage when sensitisation first detected | 1st trimester | **13** | 1 | 12 | 5 | 1 | 7 (6) |
| | 2nd trimester | **1** | 0 | 1 | 0 | 0 | 1 (1) |
| | 3rd trimester | **23** | 4 | 19 | 11 | 3 | 9 (5) |
| | Peri-partum / post-natal | **8** | 1 | 7 | 2 | 1 | 5 (4) |
| | No information | **9** | – | – | – | – | – |
| | totals | **54** | 6 | 39 | 18 | 5 | 22 (16) |

To calculate incidence of maternal sensitisation to Rh(D), we estimated the population-at-risk. For this we considered the number of confinements (defined as 'a pregnancy resulting in either live or stillborn children, irrespective of whether a single or multiple birth results'[8]) in Christchurch. There are about 6300 of these annually and 85% of them (about 5355) may be assumed to be in women of European Caucasian origin[8] of whom 18% (about 964) may be expected to be Rh(D) negative.[9]

It should be noted that the other ethnic groups of any size in Christchurch (Māori, Pacific Islander and East Asian) are predominantly Rh(D) positive. It can be calculated that about 60% of all pregnancies in the Rh(D) negative, European Caucasian population (578 pregnancies) will result in an Rh(D) positive fetus the consequence of which may be maternal sensitisation to Rh(D). This assumes that the father is also Caucasian and takes in to account the proportions of Rh(D) positive Caucasian Europeans who are likely to be either heterozygous or homozygous for Rh(D) and the likelihood that only 50% of pregnancies where the father is heterozygous for Rh(D) will result in an Rh(D) positive fetus whereas this will be 100% if the father is homozygous.

Thus, the population-at-risk—the population of Rh(D) negative pregnant women likely to be carrying an Rh(D) positive fetus—in Christchurch can be calculated to be about 578 per year or 4624 for the 8 years from 2005–2012. We can then calculate a rough incidence proportion of 54/4624 or 1.1% for this 8 year period and an incidence rate of about 1.4 per 1000 person years in this population.

For 9/54 (16.6%) sensitisations in our study, no clear information on timing of sensitisation, events predisposing to this, or prophylaxis, was available. These will, essentially, not be considered further. Thirteen (24%) new sensitisations to RhD were detected during the 1$^{st}$ routine antenatal blood tests (around 10–12 weeks gestation), one (1.8%) in the 2$^{nd}$ trimester, 23 (42.5%) in the 3$^{rd}$ trimester, and 8 (14.8%) in the peri-partum or post-natal periods.

Among the 45 sensitisations where information was available, 39 (86.6%) were preceded by a documented sensitising event, including previous deliveries, while for six (13.3%) there were no documented events. Table 2 summarises the nature of sensitising event depending on stage of pregnancy when sensitisation was first detected.

Of the 39 with a recognised sensitising event, 18 (46.1%) had anti-D prophylaxis per NZBS guidelines. In a further 5, (12.8%), prophylaxis was given though it did not conform entirely to the guideline (all of which were failures to perform a follow-up Kleihauer test to determine the quantum of fetomaternal haemorrhage when indicated). No prophylaxis at all was given to 16/39 (41.0%) women despite a sensitising event being recognised nor is there a record of a Kleihauer test being done in these cases.

Overall, of the 54 new sensitisations to Rh(D), at least 18 (33.3%) appear to have occurred despite the standard, local anti-D prophylaxis guideline being adhered to, at least five (9.2%) with partial non-adherence to the NZBS guideline and 22 (40.7%) with anti-D never having been administered. As stated, for nine (16.6%), information was inadequate.

**Table 2. Likely sensitising event in the 45 women in Christchurch sensitised to Rh(D), 2005–2012 for whom this information was available**

| Pregnancy stage when sensitisation first detected | Sensitising event | Number |
|---|---|---|
| 1st trimester: | Previous delivery only | 8 |
| | Miscarriage* | 2 |
| | Still-birth* | 1 |
| | Massive fetal haemorrhage* | 1 |
| | No sensitising event | 1 |
| 2nd trimester: | Previous delivery only | 1 |
| 3rd trimester: | Previous delivery only | 14 |
| | Miscarriage* | 1 |
| | PV spotting* | 1 |
| | Uterine rupture* | 1 |
| | Intrauterine death (29/40)* | 1 |
| | Termination of pregnancy* | 1 |
| | No sensitising event | 4 |
| Per-partum / post-natal: | Previous delivery only | 3 |
| | Miscarriage* | 1 |
| | Fall on to abdomen* | 1 |
| | Amniocentesis* | 1 |
| | Termination of pregnancy* | 1 |
| | No sensitising event | 1 |

* previous delivery was also a potential sensitising event in these cases

## Discussion

The incidence proportion of maternal sensitisation to Rh(D)–the major cause of HDFN—used to be about 13–14% before any prophylaxis was available, this fell to 1–2% after routine post-natal prophylaxis was started in the 1960s, to about 1% after antenatal prophylaxis for sensitising events and further to about 0.2–0.3% after the introduction of RAADP in the 1970s.[1–3]

In contrast to some countries, RAADP is not official policy in New Zealand.[1,4] Though some practitioners use it, its application here is patchy at best.[10]

From our data it would appear that the calculated incidence proportion in Christchurch is at least 1.1% of the population at risk per year or 6.3 women per year. These figures may in fact be slightly higher because in some instances sensitisation may only be detectable following re-stimulation by the antigen—for instance in a subsequent pregnancy[11] and this may not have happened. Nevertheless, the calculated incidence is roughly what one might expect with prophylaxis for antenatal sensitising events and routine post-natal prophylaxis (conventional prophylaxis) but without RAADP and is at least thrice as high as might be expected if an RAADP programme was also in place.

Because less than half the sensitisations with a documented sensitising event (18/39) had anti-D prophylaxis per guideline, improved adherence to protocol, supported by continuing education and, perhaps, checklists may reduce incidence of sensitisation.

An NZBS audit of anti-D prophylaxis showed that greater than 95% of all post-natal indications for anti-D prophylaxis audited were covered appropriately in terms of initial dose and its timing. However this audit also highlighted the overall poor, and very variable, adherence to the guidelines for the Kleihauer test as also the overall low (5% of eligible candidates), and variable, use of RAADP.[10] It should be kept in mind that this audit was concerned with the way anti-D was used *when it was used*. It does not address, as does the present study, the incidence of sensitisations and the causes of prophylaxis failures.

In 41% (16 / 39) of sensitisations with a documented sensitising event, anti-D prophylaxis was simply not administered. If an RAADP programme had been in place, it is likely that some of these sensitisations might have been prevented. Why anti-D prophylaxis was omitted in these 16 women is unclear excepting in the case of two Jehovah's Witnesses who refused prophylaxis.

In nearly half the sensitisations with a documented sensitising event (18 / 39), prophylaxis was administered per guideline. This suggests that other, unrecognised, sensitising events—perhaps not covered with prophylaxis—also occurred. It is reasonable to think that some of these sensitisations too may have been prevented through an RAADP programme.

In 6/45 sensitisations where the clinical record appeared to be complete, no sensitising event had been recorded—not even a previous delivery. We are not sure what the mechanism of sensitisation in these cases was. Some women may not truly have been primigravidae; some primigravidae may have failed to report a sensitising event and, in some sensitisation could have occurred without obvious exposure to Rh(D) positive RBC—through pregnancy, transfusion, or other means. Mechanisms by which this might occur include the sensitisation of Rh(D) negative mothers during fetal life by exposure to Rh(D) positive RBC from *their* mothers or what's been called the 'grandmother hypothesis'.[12,13]

A similar audit was performed in the UK covering a period when RAADP was not yet standard practice (1988–1991). In this study, of 129 women with 312 pregnancies and 98 potentially sensitising events between them, information was inadequate for 40% of events, 52% of women with Rh(D) sensitisation had not had a recognised sensitising event (other than a prior delivery), sensitisation occurred after 20% of

events despite anti-D prophylaxis per local protocol and 48% of events were associated with complete or partial failure to follow local guidelines.[14]

Experience shows that even with an RAADP programme sensitisation to Rh(D) still occurs.[4,15] These may be due to failure to adhere to the RAADP protocol, refusal to accept prophylaxis, and, possibly, biological reasons for failure to respond as expected to prophylaxis.

Nevertheless, a recent bias-adjusted meta-analysis has confirmed that RAADP, in addition to conventional prophylaxis, is more effective than conventional prophylaxis alone.[16] There are several studies of cost-benefit analysis of RAADP, additional to conventional prophylaxis, compared to the latter alone. These take in to account the additional costs of the anti-D for the RAADP, and of administering it, compared to the costs, if RAADP was not used, of managing sensitised pregnancies and neurodevelopmental problems in affected children. Even without reckoning societal and other costs, RAADP is believed to be economically attractive—especially for primigravidae but also if used in all eligible women.[17-19]

To summarise, the incidence of maternal sensitisation to Rh(D) in Christchurch, New Zealand, is about 1.1%. Between 2005–2012, 44 neonates in the Christchurch region were affected by Rh isoimmunisation. Consequently, 13 fetuses received intrauterine transfusions and 7 neonates, exchange transfusions. This is as expected given our prophylaxis regimen. Half of all sensitisations appeared to be associated with complete or partial failure to follow the current guideline. Better adherence to this may reduce incidence of sensitisation. The incidence is three times higher than it might be if an RAADP program was also in place.

With such a programme, the number of new sensitisations in Christchurch can be expected to drop from about 6.3 to about 2 per year. An economic analysis of RAADP in New Zealand, comparing various models of RAADP with the status quo, will be useful.

**Competing interests:** Nil.

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