RESEARCH ARTICLES

Emergency clinicians' interpretation and application of Anti-D guidelines

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ABSTRACT

Objective: The objective of this study was to audit the use of anti-D immunoglobulin (anti-D) against the current Australian guidelines in one large inner-city referral hospital over three years and critique the practice identified.

Background: Pregnant patients who have a D-negative (RhD negative) blood type are at risk of D alloimmunisation if a potentially sensitising event occurs during pregnancy or birth. The administration of anti-D Ig can prevent complications related to alloimmunisation. Potentially sensitising events commonly present to the emergency department requiring the administration of anti-D Ig in line with current guidelines.

Study Design and Methods: This is a retrospective cohort study of all patients who received anti-D Ig in a large inner-city emergency department (ED) over three years (July 2014 – June 2017). Indications for administration were scrutinised against current guidelines by experienced clinicians.

Results: A total of 228 patients received anti-D Ig, with the majority being less than twelve weeks in gestation (169, 74.1%). Anti-D Ig was administered without support from the guidelines in 81 (35.5%) patients, with a lack of documented sensitising event in 77 (95%) of these cases.

Discussion and Conclusion: There were inconsistencies amongst clinicians who prescribe anti-D Ig in the ED, and a lack of the application of current guidelines. This may stem from a lack of empirical evidence about the need for anti-D Ig in the most common group presenting to EDs, those under twelve weeks in gestation. Current guidelines also fail to take into consideration future need, which could be incorporated in future, ED specific anti-D Ig guidelines.

Implications for research, policy, and practice: This audit identified overuse of anti-D Ig in the ED. This may stem from the absence of evidence for its use in pregnant patients under 12 weeks in gestation. To reduce unsupported use, further data on alloimmunisation rates following potentially sensitising events in early pregnancy would be helpful. Additional guidelines specific to patients under 12 weeks in gestation, and presenting to the emergency department may reduce some unsupported usage.

What is already known about the topic?

- Pregnant patients who have an D-negative blood type are at risk of D alloimmunisation when a sensitising event occurs.

- It is common for patients to present to the emergency department with complications in early pregnancy
- Previous work has shown that there is variation in anti-D Ig administration in the emergency department.

What this paper adds:
- There is significant use of anti-D Ig in the emergency department that is outside of current guidelines.
- The current guidelines may not serve the needs of the majority of presentations in the emergency department.
- Further data on alloimmunisation rates following potentially sensitising events in patients less then twelve weeks of gestation would be useful.

Keywords: anti-D immunoglobulin, Rh(D) alloimmunisation, Pregnancy, Complications of Pregnancy, Emergency Department.

INTRODUCTION

Pregnant patients who have an RhD-negative (D-negative) blood type are at risk of D alloimmunisation if a potentially sensitising event occurs during pregnancy or birth. Alloimmunisation can only occur if the fetus is D positive, and these fetal red cells enter the maternal circulation. This can cause the pregnant patient to develop anti-D which can lead to recurrent miscarriage or the development of hemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies[1]. Routine administration of anti-D immunoglobulin (anti-D Ig) during pregnancy and postnatally aims to decrease the risk of alloimmunisation.

Acute administration of anti-D Ig is required when potentially sensitising events occur. The emergency department (ED) commonly treats pregnant patients with complications in early pregnancy and, therefore, is required to identify D negative patients and treat those who have experienced a potentially sensitising event. Historically, EDs have been poor at identifying patients at risk of D alloimmunisation and administering anti-D Ig, despite its widespread availability since the 1970s.[2] Evidence-based guidelines exist in almost every jurisdiction on the recommendations for both the routine and acute administration of anti-D Ig, in Australia, these are issued by the Royal Australasian College of Obstetricians and Gynecologists (RANZCOG) and supported by the National Blood Authority.[3]

EDs have been reported as having deficiencies in the assessment of the D type and antibody status (D status) of pregnant people with potentially sensitising events. In the early 1990s, it was reported that most pregnant women presenting to ED's did not have their D status tested or have anti-D Ig administered before discharge.[2] These results have continually been reported since, although by 2012 it was reported that D status was being measured in approximately 70% of pregnant patients and 56 - 62.5% of D negative pregnant patients with potentially sensitising events received anti-D Ig.[4,5] The underutilisation of anti-D Ig in the ED had led to several authors recommending that all D negative pregnant ED patients with potentially sensitising events receive a dose of anti-D Ig.[1,6,7]

The reported lack of application of guidelines in the ED may be representative of the level of evidence for the use of anti-D Ig in the most common group of patients seen in the ED, those under 12 weeks of gestation. There is evidence that 7% of pregnant patients under 12 weeks will have fetal cells in the maternal circulation, and that this can occur as early as five weeks of gestation however, there is no evidence that this causes maternal sensitisation.[8,9] The use of anti-D Ig in patients under 12 weeks of gestation, although recommended in Australia, is not supported by high-quality evidence.[9,10] The RANZCOG guidelines identify that pregnant women under 12 weeks of gestation should be offered 250IU of anti-D Ig if a sensitising event occurs. Sensitising events include miscarriage, termination of pregnancy (either surgical or medical) and ectopic pregnancy. The RANZCOG guidelines state that there is insufficient evidence to recommend administering anti-D Ig to those people with a threatened miscarriage before 12 weeks' gestation.[3]

The lack of high-quality evidence of the possibility of sensitisation in the first trimester has led authors to recommend blanket administration to all D negative pregnant people with a possible sensitising event. This recommendation can lead to some pregnant people receiving anti-D Ig in the ED that is not supported by current guidelines. This study aims to review all administrations of anti-D Ig to pregnant patients in the large inner-city ED of the busiest public maternity hospital in Queensland, Australia over three years, and compare the indications for the administration to the current RANZCOG guidelines to define if the usage of anti-D outside of current guidelines is occurring and to which patient group this may be occurring.

METHODS

This study took the form of a retrospective cohort review/audit of all pregnant patients who had anti-D Ig (Rh(D) immunoglobulin) issued for administration in the ED over three years (July 2014 – June 2017) in a single large inner-

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city hospital. Information on the patients who received anti-D Ig was collected from the pathology information system (blood group antibodies, previous administration of anti-D Ig), electronic medical record of the ED (presenting problems, history and assessment of the patient), and radiology information system (results of ultrasound scan, if attended). Two independent clinicians (JB, MS) reviewed each case. They assessed administration against the RANZCOG guidelines when they disagreed the case was reviewed by a third clinician (AA) to make the final determination. Patients who were administered anti-D Ig are described using descriptive statistics (frequencies and percentages, medians and interquartile range), differences between patients who have anti-D Ig administered within and outside of current are assessed using non-parametric inferential statistics. The inter-rater reliability between the two reviewers is presented as a Cohen's Kappa statistic. To quantify the level of variability of the application of the guidelines, all five authors assessed the same 17 cases before the commencement of the study, and the inter-rater reliability across the five authors was compared using Fleiss' Kappa.

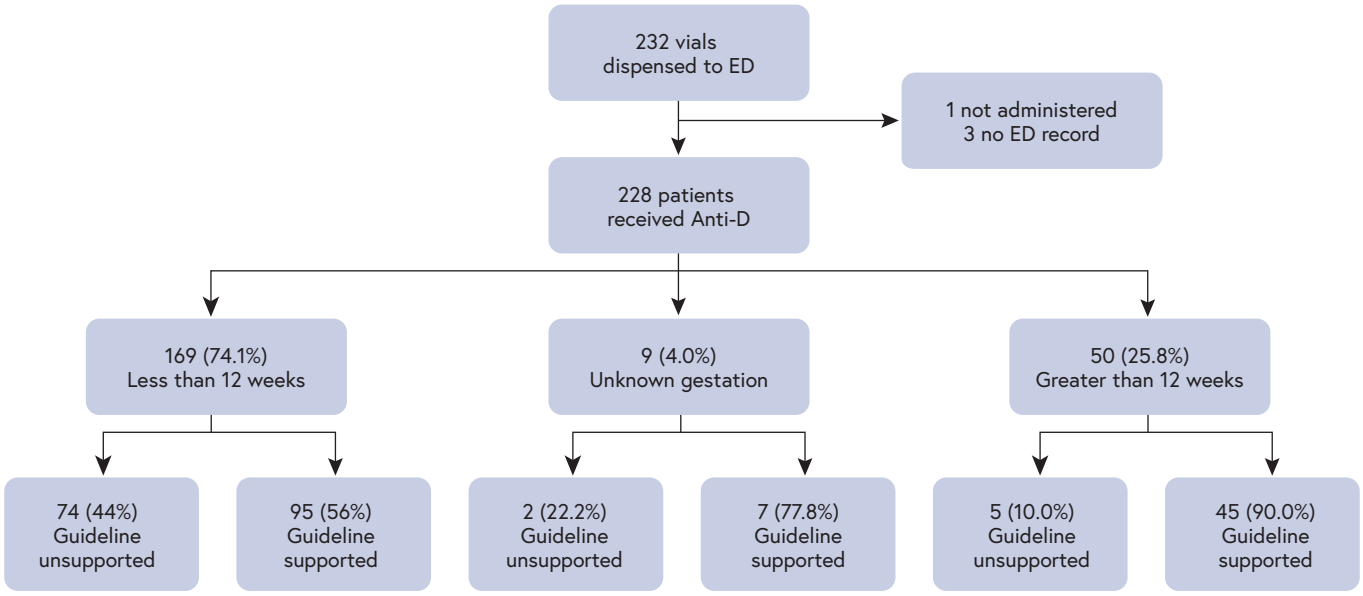
The data abstracter was familiar with the data and databases being interrogated, was blinded to the hypothesis, and was not part of the investigatory team. Data that could be collected from preexisting fields were collected and joined by the ED data manager. Other information was abstracted from free text fields in line with data definitions set out in the study protocol. Missing data were identified and reported on, variables with substantial (>5%) missing data were assessed for randomness via logistic regression. This study was reviewed and approved by the hospital human research ethics committee, and access to patient-level data without consent was approved under the Public Health Act.

RESULTS

There was a total of 228 patients who received anti-D Ig in the ED over these three years. Five variables: previous pregnancies (4, 1.8%); current gestation (9, 4.0%); previous administration of anti-D Ig (1, 0.4%); blood group (3, 1.3%); and antibody screen (7, 3.1%) all had missing data. As none of these met the 5% threshold; therefore, no further analysis was performed, and the missing data remain in the dataset. The majority (169, 74.1%) were under 12 weeks of gestation and were eventually discharged home from the ED or the ED Short Stay Unit (201, 88.2%) (see Table One). Anti-D Ig was administered without support from the RANZCOG guidelines in 81 (35.5%) of all cases over three years. The majority of administrations unsupported by the guidelines were in patients under 12 weeks in gestation ($c^2$19.954 (2), p<0.001). The most common reason for administration unsupported by the guidelines was the lack of an identified sensitising event (77, 95.0%).

Almost all of the patients reviewed in this study received an ultrasound scan (USS) (188, 82.5%) a further 23 (10.1%) arrived in the ED with a recently completed USS leaving only 17 (7.4%) not receiving a USS. Blood group and antibody screen was completed in the ED or privately before arrival in 223 (97.8%) of all cases. Further details on the patients and treatment provided are summarised in Table One below.

There was significant variation in the application of the RANZCOG guidelines among clinician authors of this work. All five authors reviewed the same 17 patients who had anti-D Ig administered in the ED before the commencement of data collection. There was only moderate agreement amongst raters (κ0.596, z=8.04, p<0.001). There was better cohesion between the two raters that reviewed all cases (κ0.876, z=13.5, p<0.001); however, discrepancies still occurred in 13 (5.7%) of all cases.



ED = emergency department

FIGURE ONE: THE BREAKDOWN OF THE POPULATION INCLUDED IN THE STUDY

TABLE ONE: CHARACTERISTICS OF THE POPULATION RECEIVING ANTI-D IN THE EMERGENCY DEPARTMENT.

	Total	Guideline Supported	Guideline Unsupported
Age (median, IQR) years	32 (28–37)	33 (28–38)	30 (27–36)
Discharge Location			
Discharged Home	98 (43.0%)	58 (39.5%)	40 (49.4%)
ED Short Stay Unit	103 (45.2%)	63 (42.9%)	40 (49.4%)
Admitted to hospital	18 (7.9%)	18 (12.2%)	0 (0.0%)
Obstetric Review Centre	8 (3.5%)	8 (5.4%)	0 (0.0%)
LAMA	1 (0.4%)	0 (0.0%)	1 (1.2%)
Referral			
General Practitioner	147 (64.5%)	89 (60.5%)	58 (71.6%)
Obstetrician	39 (17.1%)	38 (25.9%)	1 (1.2%)
Nil	42 (18.4%)	20 (13.6%)	22 (27.2%)
Diagnosis			
Miscarriage – Threatened	113 (49.6%)	55 (37.4%)	58 (71.6%)
Miscarriage – Inevitable	47 (20.6%)	44 (29.9%)	3 (3.7%)
Miscarriage – Complete	13 (5.7%)	11 (7.5%)	2 (2.5%)
Abnormal Vaginal Bleeding	9 (3.9%)	4 (2.7%)	5 (6.2%)
Pregnancy	9 (3.9%)	1 (0.7%)	8 (9.9%)
Ectopic Pregnancy	5 (2.2%)	5 (3.4%)	0 (0.0%)
Other	32 (14.0%)	27 (18.4%)	5 (6.2%)
Gestation[+]			
Less than 12 weeks	169 (74.1%)	95 (64.6%)	74 (91.4%)
Greater then 12 Weeks	50 (21.9%)	45(30.6%)	5 (6.2%)
Antibodies			
Anti-D	1 (0.5%)	1 (0.7%)	0 (0.0%)
Passive Anti-D	13 (5.9%)	10 (7.0%)	3 (3.8%)
Anti-M	1 (0.5%)	1 (0.7%)	0 (0.0%)
Nil	206 (93.2%)	131 (91.6%)	75 (96.2%)
Prescriber			
Medical Officer	211 (92.5%)	135 (91.8%)	76 (93.8%)
Nurse Practitioner	17 (7.5%)	12 (8.2%)	5 (6.2%)
Documented Consent			
Yes	33 (14.5%)	25 (17.0%)	8 (9.9%)
No	195 (85.5%)	122 (83.0%)	73 (90.1%)

ED = emergency department
LAMA = left against medical advice
IQR = Interquartile range
Nine patients had an unknown gestation

DISCUSSION

Anti-D Ig administration is occurring in the department that is not guideline supported in up to 35.5% of all patients. The majority of use that is not guideline supported is in patients under 12 weeks in gestation, without an identified potential sensitising event. The current guidelines present a poor level of evidence for the most common presentation (threatened miscarriage, 49.6%) in the most common gestation (less than 12 weeks, 74.1%) to the ED. Therefore, clinicians may be hesitant to not administer anti-D Ig given the perceived safety (adverse event rate of less than 1:80000[1]) and limited availability outside of the hospital environment. Both British and Australian guidelines identify that there is insufficient evidence to administer anti-D Ig in threatened miscarriages less than 12 weeks of gestation[1,3] and recommend by consensus[3] or by grade 2C evidence[1] that anti-D Ig should only be administered in Chorionic villus sampling, miscarriage, termination of pregnancy or ectopic pregnancy in patients of gestation less than 12 weeks. There is no accommodation in the guidelines for future need; therefore ED clinicians may also administer anti-D Ig to patients who may require it and are referred back to a general practitioner for further care as general practitioners have limited access to anti-D Ig. Antibody screening and USS were completed in almost all cases studied, a significant improvement from previous work,[4] however there was some evidence that anti-D Ig was administered before USS in many cases; therefore consideration of identification of sensitising event was not given, and this should be explored further in future work. Although the Australian guidelines do not discuss the urgency of anti-D Ig administration after the potential sensitising event, other guidelines do discuss that ideal administration is within 72 hours but can be given up to 10 days post-event, in almost all cases this would allow sufficient time to obtain a USS (generally available two-three hours after presentation).[1] Documentation of consent for administration was low, and any intervention that aims to improve anti-D Ig use should include improving the rates of consent for administration.

In the absence of further empirical evidence of the potential for sensitisation in early pregnancy (less than 12 weeks), specific application of current knowledge and guidelines to the ED cohort may reduce administration that is not needed. Guidelines that incorporate pathways, including the timing of administration, required investigations, the potential for future need, consent and risks stratification are likely to improve the use of this therapy. Appropriate use of this therapy is desirable; despite a low adverse event rate, there are significant supply constraints. The Australian anti-D Ig supply coming from only a few donors and supplies, at times of high demand, needing to be sourced from overseas to maintain supplies.

LIMITATIONS

The findings of this audit are limited in that they reviewed cases from only one metropolitan ED. The audit was retrospective and in some cases there may have been further information available that influenced the clinical decision to give anti D Ig that was not documented in the clinical record. This audit did not examine cases where people who required a dose of anti D Ig, did not receive it in the ED. Future work should review all patients who present to the emergency department with miscarriage, not just those receiving anti-D Ig.

CONCLUSION

This audit has highlighted the inconsistencies amongst clinicians in the ED to follow guidelines when prescribing anti-D Ig to pregnant patients. Accentuating this issue and improved signposting to the national guidance for ED staff would potentially improve practice. The creation of ED specific guidelines, or a subsection of existing guidance focusing on first-trimester pregnancy with reference to the ED, may further assist ED clinicians in their decision making. These guidelines would consider where the person has to follow up treatment and their access to anti D Ig and specific ultrasound findings. They may also include the consideration of new technology being increasingly accessed in assessing the fetal D type in early pregnancy. Further improvement into good clinical practice would include gaining signed consent for the administration of anti-D Ig. Further research into the risk of first-trimester D alloimmunisation would be optimal; however, the authors acknowledge that this recommendation has been made consistently for several decades and has yet to occur in view of the difficulty designing and performing sufficiently powered studies.

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Conflicts of Interest: The authors have no conflicts of interest to declare.

Author Contributions: MS and JB conceived the study. MS supervised data collection with assistance from JH. JH obtained ethics and governance approval for the conduct of the study. All authors contributed to the application of the guidelines. JH provided statistical assistance. The manuscript was prepared by JH, MS and JB with significant specialist input from KL and AA.

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