

**GUIDELINES FOR THE USE OF
ANTI-D IMMUNOGLOBULIN
FOR
RHESUS PROPHYLAXIS**

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CREST

CLINICAL RESOURCE EFFICIENCY SUPPORT TEAM

This booklet has been published by the Clinical Resource Efficiency Support Team (CREST) which is a small committee of health care professionals established under the auspices of the Central Medical Advisory Committee. Its aim is to promote clinical efficiency in the health service in Northern Ireland while ensuring the highest possible standard of clinical practice is maintained.

CREST wishes to thank Dr Jim Dornan and the Working Group for producing this guidance. Special thanks are due to Dr Margaret Boyle for the major contribution she made to the production of this booklet.

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GUIDELINES FOR THE USE OF ANTI-D IMMUNOGLOBULIN FOR RHESUS (Rh) PROPHYLAXIS

1. BACKGROUND

An audit of the management of women¹, in Northern Ireland, who were RhD negative and who gave birth in 1996 was undertaken during 1998. All maternity units were included. When the audit findings were presented it was recommended that guidelines should be developed *for the use of Anti-D immunoglobulin for Rh prophylaxis in Northern Ireland*.

The guidance contained in this booklet is largely based on updated guidelines produced, in 1999, by a joint Working Group of the British Blood Transfusion Society (BBTS) and the Royal College of Obstetricians and Gynaecologists (RCOG)² and the RCOG guidelines³ published in 1999. Account has also been taken of the Northern Ireland 1998 Audit findings.

2. ANTENATAL PROPHYLAXIS

The 1999 RCOG guidelines recommend the introduction of routine antenatal prophylaxis for RhD negative women. The Department of Health in England has passed these guidelines to the National Institute for Clinical Excellence (NICE) for its consideration. CREST will review the position regarding routine antenatal prophylaxis when NICE has considered the RCOG guidelines.

3. INTRODUCTION

Approximately 17% of women in Northern Ireland are RhD negative. The development of anti-D antibodies generally results from feto-maternal haemorrhages (FMH) occurring in RhD negative women who carry a RhD positive fetus. Post delivery immuno-prophylaxis using anti-D immunoglobulin (anti-D Ig) began in the United Kingdom in 1969 and in 1981 anti-D Ig was recommended⁴ following all potentially sensitising events. Since its introduction the number of deaths attributed to RhD alloimmunisation has decreased dramatically; from 46/100,000 births before 1969 to 1.6/100,000 in 1990⁵. However RhD alloimmunisation still occurs. The 1998 Northern Ireland Audit of current practice against the 1991 guidelines⁶ indicated that these guidelines were not being fully adhered to, particularly in the antenatal period.

4. IDENTIFICATION OF RhD NEGATIVE WOMEN

All pregnant women should have their ABO blood group, RhD type and antibody titres checked at booking, ideally before 16 weeks gestation, and repeated at 28-32 weeks ([Appendix 2](#)). Those who are RhD negative should have this recorded in a prominent place in their antenatal chart. A short proforma ([Appendix 3](#)) for recording antibody titres and any history of sensitising events and action taken should be held inside the front cover of their chart. Information relating to previous pregnancies should also be recorded.

When the results become available all women should be given written information confirming their ABO blood group and RhD type. The implications of this should also be explained. For those who are RhD negative without anti-D antibodies, informed verbal consent should be obtained before the administration of anti-D Ig. If anyone declines, it should be recorded in their notes.

5. POTENTIALLY SENSITISING EVENTS

Anti-D Ig must be given to RhD negative women without anti-D antibodies as soon as possible following any of the events listed below. **Before** 20 weeks' gestation 250iu should be given. **After** 20 weeks' gestation blood should be taken for the Kleihauer test to estimate the size of the FMH and 500iu of anti-D Ig given ([Appendix 2](#)).

- termination of pregnancy (medical or surgical)
- evacuation of the uterus (medical or surgical)
- ectopic pregnancy
- threatened miscarriage after 12 weeks
- invasive prenatal procedures, eg,
 - amniocentesis
 - chorion villus sampling
 - fetal blood sampling
- antepartum haemorrhage
- external version of the fetus
- closed abdominal injury
- intrauterine death
- stillbirth
- delivery of a RhD positive infant.

6. PROPHYLAXIS FOLLOWING FETAL LOSS OR THREATENED MISCARRIAGE

6.1 *Spontaneous miscarriage*

- **Anti-D is not required** if a spontaneous miscarriage occurs **before** 12 weeks' gestation as long as medical or surgical methods have not been used to evacuate the products of conception. The risk of sensitisation in such circumstances is negligible.
- **Anti-D Ig should be given** to all non-sensitised RhD negative women who have a spontaneous complete or incomplete abortion **after** 12 weeks of pregnancy.
- **Anti-D Ig should be given** to all non-sensitised RhD negative women who have a **medical or surgical evacuation** of the uterus **regardless of gestational age**.

6.2 *Therapeutic termination of pregnancy*

- **Anti-D Ig should be given** to all non-sensitised RhD negative women having a therapeutic termination of pregnancy, whether **by medical or surgical methods, regardless of gestational age.**

6.3 *Ectopic pregnancy*

- **Anti-D Ig should be given** to all non-sensitised RhD negative women who have a diagnosis of ectopic pregnancy.

6.4 *Threatened miscarriage*

- Evidence that women are sensitised after uterine **bleeding in the first 12 weeks** of pregnancy where the fetus is alive and the pregnancy continues is scant⁷ though there are very rare examples³. Against this background, **routine administration of anti-D Ig cannot be recommended.**
- It may be prudent to administer **anti-D Ig to all non-sensitised RhD negative women with a threatened miscarriage before 12 weeks of pregnancy where bleeding is heavy or repeated and where there is associated abdominal pain.** The period of gestation should be confirmed by ultrasound.
- **Anti-D Ig should be given** to all non-sensitised RhD negative women with a threatened miscarriage **after 12 weeks of pregnancy.** Where bleeding continues intermittently after 12 weeks' gestation, anti-D Ig should be repeated at 6-weekly intervals.

7. **POSTNATAL PROPHYLAXIS**

7.1 *Tests required and prophylaxis following delivery*

- At delivery cord blood should be taken from all RhD negative women to determine the ABO group and RhD type of the infant. Cord blood should also be drawn for haemoglobin, bilirubin and a Coomb's test ([Appendix 2](#)).
- At least 500iu of anti-D Ig should be given to every non-sensitised RhD negative woman as soon as possible and within 72 hours of delivery of a RhD positive infant. Maternal blood for Kleihauer testing should be taken (as soon as possible, within two hours of delivery and prior to administration of anti-D Ig) to determine if the FMH is greater than 4mls. If a large FMH has occurred, the hospital blood bank which carried out the Kleihauer test will, where indicated, prescribe the amount of additional anti-D Ig required ([Appendix 4](#)).

7.2 *Delivery of macerated fetus*

- Occasionally, where a macerated fetus from a non-sensitised RhD negative mother is delivered following intrauterine death, the RhD type cannot be determined. In these circumstances a Kleihauer test should be performed to exclude a large spontaneous FMH and anti-D Ig given to the mother.

8. RHESUS D NEGATIVE WOMEN WHO BECOME SENSITISED

If a RhD negative woman who is already sensitised becomes pregnant or becomes sensitised during pregnancy, she should be referred to an obstetric unit where she can be managed by a consultant obstetrician with the necessary experience of the condition.

9. REPEAT DOSES OF ANTI-D IMMUNOGLOBULIN

For most cases of **recurrent bleeding, anti-D Ig every 6 weeks will be sufficient**. However, if another **significant** sensitising event occurs within 6 weeks of the previous dose, additional anti-D Ig should be given. Where anti-D Ig is administered after 20 weeks a Kleihauer test must be done ([Section 10](#)).

10. TEST FOR THE SIZE OF THE FETO-MATERNAL HAEMORRHAGE (FMH)

Studies have shown that 99.2%-99.3% of women have a FMH less than 4ml at delivery and that up to 50% of the larger FMHs occur after normal deliveries⁸. However, the following clinical circumstances are more likely to be associated with a large FMH:

- abdominal trauma during the third trimester
- unexplained hydrops fetalis
- multiple pregnancies (at delivery)
- stillbirths and intrauterine deaths
- instrumental deliveries and caesarean section
- manual removal of the placenta

The Kleihauer acid elution test is used to detect fetal red cells in the mother's circulation. It detects fetal red cells by detecting fetal haemoglobin (HbF). A Kleihauer screening test should be performed on women of 20 weeks or more gestation in order to identify those, with a large FMH, who need additional anti-D Ig. The recommended policy in the UK is to obtain an anticoagulated blood sample within two hours of the delivery or as soon as possible after the sensitising event occurs. If a large FMH has occurred, the hospital blood bank which carried out the Kleihauer test will, where indicated, prescribe the amount of additional anti-D required ([Appendix 4](#)).

11. FOLLOW UP OF WOMEN WITH A LARGE FMH

Where a large FMH (greater than 4ml) has been identified the woman should be advised of the need to have a further plasma sample taken six months after the sensitising event for testing for the presence of anti-D antibodies. This allows early identification of sensitisation and alerts to the possibility of a subsequent high risk pregnancy.

12. ADMINISTRATION OF ANTI-D IMMUNOGLOBULIN

Intramuscular anti-D Ig is best given into the **deltoid muscle** as injections into the gluteal region often only reach the subcutaneous tissues and absorption may be delayed.

For successful immunoprophylaxis, anti-D Ig should be given as soon as possible after the sensitising event but **always within 72 hours**. If it is not given before 72 hours, every effort should still be made to administer the anti-D Ig, as a dose given within 9-10 days may provide some protection. Women who are already sensitised should **not** be given anti-D Ig. If a large FMH has occurred, the hospital blood bank which carried out the Kleihauer test will, where indicated, prescribe the amount of additional anti-D Ig required ([Appendix 4](#)).

13. COMMUNICATION

The effective management of RhD negative women is crucial to ensure a continuing reduction in the number of sensitised women. This can best be achieved by all professionals who care for such women sharing details of the screening results and the management of sensitising episodes. General Practitioner records, community midwifery and hospital obstetric/gynaecology records, and patient held records must have the RhD negative status clearly identified. As the patient held record is the common link to all professional care given, the date and time of sensitising events, Kleihauer testing, and anti-D Ig administration should be recorded in it in addition to any other records held by hospitals or professionals in the community.

All pregnant women should be given written information confirming their ABO blood group and RhD type. All RhD negative women should, in addition, be given a list of potentially sensitising events and guidance as to what they should do should such an event occur.

There should be regular multiprofessional educational updates, on this topic, for all health care professionals engaged in the care of pregnant women.

14. SUPPLY OF ANTI-D IMMUNOGLOBULIN

Anti-D Ig was previously collected by apheresis from volunteer donors who had anti-D Ig in their blood. Concern about the theoretical risk of contracting variant CJD from blood products led the UK Committee on Safety of Medicines to advise in 1998 that UK plasma should no longer be used to make plasma-derived products (including anti-D Ig). Recently, imported anti-D Ig has been to make plasma-derived products (including anti-D Ig). Recently, imported anti-D Ig has been licensed in the UK. It should be noted that the imported products may be prepared from plasma collected from paid donors within and outside the EC ([Appendix 5](#)).

15. RECOMMENDATIONS

1. All units (including A&E Departments) offering advice and care to pregnant women should have written guidelines, complying with the CREST guidance, on the management of RhD negative women during pregnancy.
2. All relevant staff working in such units should be aware of the guidance and understand when anti-D Ig should be given and when a Kleihauer test should be carried out.
3. All pregnant women should have their ABO blood group, RhD type and antibody titres checked at booking. Those who are RhD negative should have this recorded in a prominent place in their antenatal chart.
4. All pregnant women should be given written information confirming their ABO blood group and RhD type once the results become available.
5. All non-sensitised RhD negative women should be informed as to why anti-D Ig may be required.
6. All non-sensitised RhD negative women should be given anti-D as soon as possible after a potentially sensitising event.
7. If the sensitising event occurs before 20 weeks of pregnancy 250 iu of anti-D Ig should be given. For all events after 20 weeks blood should be taken for a Kleihauer test and 500 iu of anti-D Ig should be given. Depending on the result of the test, additional anti-D Ig should be given as required.
8. All RhD negative women should have their antibody titres checked at 28-32 weeks' gestation.
9. Anti-D Ig is best given by injection into the deltoid muscle.
10. Anti-D is not required if a complete spontaneous miscarriage occurs before 12 weeks' gestation.
11. Anti-D Ig does not need to be given in cases of uncomplicated threatened miscarriage of less than 12 weeks' gestation.
12. Any woman who has a medical or surgical evacuation of her uterus should have her RhD type checked and if RhD negative without antibodies anti-D Ig should be given.
13. At delivery all RhD negative women need to have taken:
 - a) Cord blood for the baby's ABO blood group, RhD type, haemoglobin, bilirubin and Coomb's test.
 - b) Maternal blood within 2 hours of delivery for Kleihauer testing.

In the event of the baby being RhD positive, 500iu of anti-D Ig should be given as soon as possible and within 72 hours, to the mother if she is non-sensitised. If the Kleihauer indicates a FMH of more than 4mls, additional anti-D Ig should be given.

14. Where a large FMH has been identified the woman should be advised of the need to have a further plasma sample taken six months after the sensitising event for testing for the presence of anti-D antibodies.
15. If a RhD negative woman who is already sensitised becomes pregnant or becomes sensitised during pregnancy, she should be referred to an obstetric unit where she can be managed by a consultant obstetrician with the necessary experience of the condition.
16. All professionals providing maternity care should undertake regular audits of their practice against the current guidelines.
17. There should be regular multiprofessional education updates on the use of anti-D immunoglobulin for Rh prophylaxis.

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CHART I

IDENTIFICATION AND MANAGEMENT OF RHESUS/RED CELL ANTIBODY STATUS IN ALL PREGNANT WOMEN

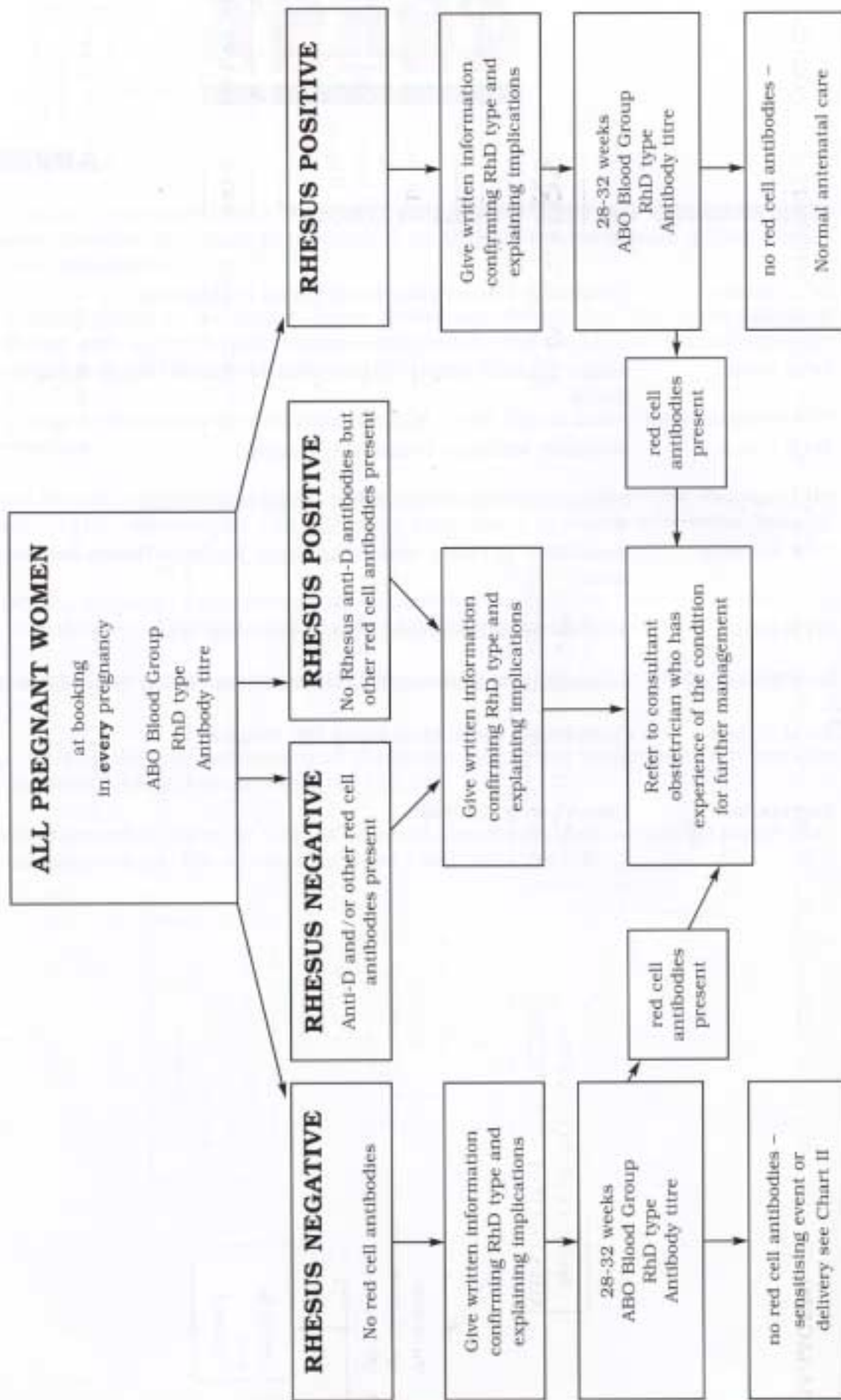
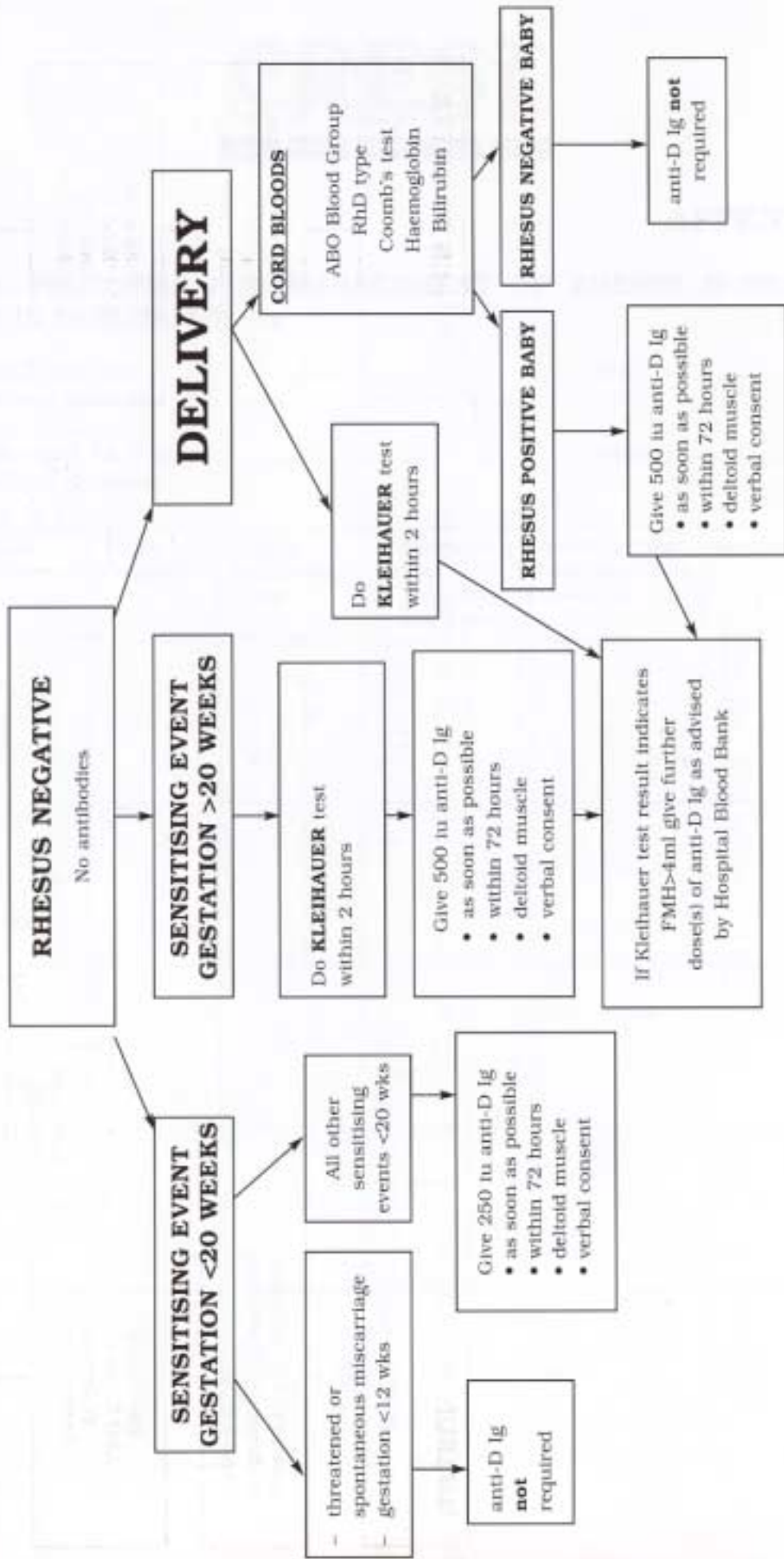


CHART II

MANAGEMENT OF ANTENATAL SENSITISING EVENTS AND DELIVERY IN Rh NEGATIVE WOMEN WITHOUT ANTIBODIES



SAMPLE PROFORMA FOR MANAGEMENT OF RHESUS D NEGATIVE WOMEN IN PREGNANCY

Booking ABO, RhD type _____ Date _____
and presence of antibodies

28-32 Weeks ABO, Rh D type _____ Date _____
and presence of antibodies

Date	Weeks Pregnant	Type of Sensitising Event	Kleihauer Test Date/ Time and Result	Anti-D Ig given Dose/Date /Time	Signature

ESTIMATION OF THE SIZE OF FETO MATERNAL HAEMORRHAGE (FMH) AND AMOUNT OF ANTI-D IMMUNOGLOBULIN REQUIRED

Criteria for performing a FMH estimation

A FMH estimation should be performed:

- i. following a potentially sensitising event after 20 weeks gestation in a RhD negative woman;
- ii. in a RhD negative woman where the fetal RhD type cannot be determined (eg macerated fetus); and
- iii. if a RhD negative woman has delivered a RhD positive baby.

FMH assessment is not indicated if preformed immune anti-D is present in the mother's plasma/serum (ie the mother is already sensitised).

Management of women with a FMH.

A minimum dose of 500iu anti-D Ig must be given – based on a dose recommendation of 125iu per ml of fetal red cells. When there is a FMH of more than 15ml it is preferable to use a larger anti-D Ig i.m. preparation (2500iu or 5000iu).

For any FMH greater than 4ml an appropriate supplementary dose of anti-D Ig must be given immediately. A repeat estimation of the FMH should be carried out 48 hours following an initial anti-D Ig injection. The serum/plasma should also be screened for anti-D.

Protocol for the follow up of a woman with FMH of more than 4mls

<u>Acid elution/ flow cytometry</u>	<u>Serum/Plasma</u>	<u>Action</u>
No fetal cells present	Free anti-D	No further action
Fetal cells present	No free anti-D	Quantify and give appropriate further dose of anti-D Repeat FMH assessment in 48 hours
Fetal cells present	Free anti-D	Repeat FMH assessment in 48 hours
No fetal cells present	No free anti-D	Give further dose of anti-D Re-test the serum/plasma for presence of free anti-D in 48 hours

It is recommended that where possible a FMH of greater than 4ml should be confirmed by flow cytometric analysis. If this method is not available then a separate operator should confirm the FMH by the Kleihauer technique or if this is not possible, eg out of routine working hours, a new film should be examined.

ANTI-D IMMUNOGLOBULIN PREPARATIONS AVAILABLE IN THE UK.

Until 1994, only anti-D Ig prepared from immune plasma donated by unpaid UK volunteer donors, either by the Bio Products Laboratory (BPL) or by the Scottish Plasma Fractionation Laboratory (PFC), was available in the UK. Recently imported anti-D Ig has been licensed in the UK. It should be noted that imported products may be prepared from plasma collected from paid donors within and outside the EC. The currently available preparations are:

BPL (Intramuscular)

- (i) 250iu (50mcg)
- (ii) 500iu (100mcg)
- (iii) 2500iu (500mcg)

PFC (Intramuscular)

- (i) 250iu (50mcg)
- (ii) 500iu (100mcg)
- (iii) 5000iu (1000mcg)

IMPORTED

- (i) Intramuscular 1250iu (250mcg) "Partobulin" from IMMUNO (licensed in the UK).
- (ii) Intravenous 600iu (120mcg) or 1500iu (300mcg) from WINRHO (not licensed in the UK)

TRANSFUSION OF RhD POSITIVE BLOOD COMPONENTS

RhD positive platelet transfusions

It should usually be possible to provide RhD negative platelets for women of childbearing age who need a platelet transfusion. Occasionally, if an appropriate product is not available, it may be necessary to use RhD positive platelets. In these circumstances, prophylaxis against possible Rh alloimmunisation by red cells containing the platelet product should be given¹.

250iu anti-D IG should be given following every two adult doses (i.e. derived from up to 8 routine donations) of platelets. Patients who have marked thrombocytopenia should be given the anti-D Ig subcutaneously to avoid the possibility of haematoma following intramuscular injection.

Inadvertent transfusion of RhD positive blood

When less than 15ml of RhD positive blood have been transferred to a RhD negative woman capable of childbearing, the appropriate dose of anti-D Ig should be given. When more than 15ml have been transfused, it is preferable to use the larger anti-D Ig i.m. preparation (2500iu or 5000iu). The dose should be calculated on the basis that 500iu of anti-D Ig will suppress immunisation by 4ml of RhD positive blood.

When more than two units of RhD positive blood have been transfused, consideration should be given to undertaking an exchange transfusion to reduce the load of RhD positive red blood cells in the circulation and the dose of anti-D Ig required to suppress immunisation. In this situation, the patient should be counselled regarding the implications of both non intervention (for future pregnancies) and of treatment, including any hazards from receiving donated blood, the exchange procedure itself and of larger doses of anti-D Ig including i.v. anti-D.

Immediate exchange transfusion will reduce the load of RhD positive red cells (a one-blood-volume exchange will achieve a 65-70% reduction in RhD positive cells; a two-volume exchange 85-90%). Following exchange transfusion, the residual volume of RhD positive red cells should be estimated using flow cytometry or rosetting. Intravenous anti-D Ig is the preparation of choice, achieving adequate plasma levels immediately and being more effective microgram for microgram than intramuscular anti-D at clearing red cells. The dose to be administered should assume that 500iu of anti-D Ig i.v. will suppress immunisation by 8-10mls of fetal red cells. Up to a maximum 10,000iu should be given in any 24 hour period. Intravenous anti-D Ig is available for use in the UK on a named-patient basis only from WINRHO (Canada). Intramuscular anti-D Ig **must not** be given intravenously. An appropriate combined dose of intravenous and intramuscular anti-D should be determined in discussion with a specialist in Transfusion Medicine. Follow up tests for RhD positive red cells should be undertaken every 48 hours and further anti-D Ig given until all RhD positive red cells have been cleared from the circulation. Free anti-D in the patient's serum does not necessarily reflect adequate prophylaxis and anti-D Ig treatment should be continued until RhD positive red cells are no longer detectable.

Passive anti-D Ig given in large doses may be detectable for up to six months or more and tests for immune anti-D may not be conclusive for 9-12 months.

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