Guideline for the prophylactic use of Rh D immunoglobulin in pregnancy care

Summary of recommendations and expert opinion points

The Expert Reference Group (ERG) developed recommendations (Rs) where sufficient evidence was available from the systematic review of the literature. The recommendations have been carefully worded to reflect the strength of the body of evidence. Each recommendation has been given a grade in accordance with Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The definitions of each grade are provided in Chapter 2 of the Guideline.

The ERG also developed expert opinion points (EOPs) for material that was outside the scope of the systematic review, and for guidance for which no new systematic review was conducted. The EOPs are based on consensus among the members of the ERG.

Identifier	Guidance – recommendations and expert opinion points	Relevant section of Guideline
Blood group and antibody screening in all pregnant women		
EOP1	All women should have an ABO / Rh D type and antibody screen performed early in pregnancy. Rh D positive pregnant women do not require Rh D immunoglobulin.	3.1.1
EOP2	If antibody screening identifies anti-D in an Rh D negative pregnant woman, consideration of clinical history and laboratory findings is required to determine whether the anti-D is likely to be preformed (due to sensitisation) or passive (due to administration of Rh D immunoglobulin in the past 12 weeks).[a] In cases of likely preformed anti-D antibodies, seek specialist obstetric advice, manage as Rh D sensitised and consider NIPT for fetal *RHD* status. [a] See EOP3	1.1 3.1.1
EOP3	Rh D immunoglobulin should not be given to Rh D negative pregnant women with preformed anti-D antibodies. However, if it is unclear whether the anti-D detected in the mother's blood is preformed (due to sensitisation) or passive (due to administration of Rh D immunoglobulin in the past 12 weeks), the treating clinician should be consulted. If there is continuing doubt, Rh D immunoglobulin should be administered.	3.1.1
Non-invasive prenatal testing for fetal RHD in all Rh D negative pregnant women		
R9	The ERG **recommends** the testing of maternal blood to determine fetal *RHD* genotype in all Rh D negative pregnant women to enable targeted antenatal Rh D immunoprophylaxis.[a] (*Strong recommendation, high certainty of evidence about the accuracy of the test*) [a] The ERG's recommendation on the use of NIPT for fetal *RHD* is not a policy statement on funding and supply arrangements for the national provisions of NIPT for blood group genotyping to determine the Rh D status of the fetus.	3.3.1
R10	The ERG **recommends** that test sensitivity be at least 99% in order to minimise the number of Rh D positive fetuses being missed by the test. (*Strong recommendation, high certainty of evidence about the accuracy of the test*)	3.3.1
R11	The ERG **recommends** NIPT for fetal *RHD* from 11^{+0} weeks of pregnancy because of higher test accuracy than at earlier weeks. (*Strong recommendation, high certainty of evidence about the accuracy of the test*)	3.3.1

Identifier	Guidance – recommendations and expert opinion points	Relevant section of Guideline
Targeted immunoprophylaxis in Rh D negative pregnant women		
R6	The ERG **recommends** that antenatal Rh D immunoprophylaxis in Rh D negative pregnant women with no preformed anti-D antibodies be targeted to those predicted to be carrying an Rh D positive fetus, based on NIPT for fetal *RHD*. This applies to both routine and sensitising event immunoprophylaxis, if the result of fetal *RHD* genotyping is available.[a] (*Strong recommendation, low certainty of evidence about the size of effect*) [a] See EOP3 and EOP7	3.3.1
R7	If fetal *Rh D* status is not available or is uncertain, the ERG **recommends** that antenatal Rh D immunoprophylaxis be offered to Rh D negative pregnant women with no preformed anti-D antibodies. (*Strong recommendation, low certainty of evidence about the size of effect*)	3.3.1
Routine antenatal immunoprophylaxis in Rh D negative pregnant women		
R1	The ERG **recommends** access to antenatal Rh D immunoglobulin for the prevention of Rh D alloimmunisation in Rh D negative pregnant women with no preformed anti-D antibodies.[a] (*Strong recommendation, low to very low certainty of evidence about the size of effect*) [a] See R6	3.1.1
Routine dosage regimens in Rh D negative pregnant women		
R2	The ERG **recommends** that administration of Rh D immunoglobulin 625 IU at 28 and 34 weeks of pregnancy[a] continue in Rh D negative pregnant women with no preformed anti-D antibodies unless NIPT for fetal *RHD*[b] has predicted that they are not carrying an Rh D positive fetus. The ERG does not currently suggest changing to a single dose of Rh D immunoglobulin 1500 IU. (*Weak recommendation, low to very low certainty of evidence about the size of effect*) [a] A woman's pregnancy care schedule and clinical discretion may warrant the administration of Rh D immunoglobulin within 2 weeks before or after the recommended 28 and 34 weeks of pregnancy. However, if the second dose of Rh D immunoglobulin is given before 34 weeks and the pregnancy goes beyond the due date, the risk of inadequate anti-D coverage at birth increases. [b] All women should have an ABO/Rh D type and antibody screen performed early in pregnancy. Women who are Rh D negative should be retested at 28 weeks unless NIPT for fetal *RHD* has predicted that they are not carrying an Rh D positive fetus. The specimen should be collected before giving prophylactic Rh D immunoglobulin; however, the immunoglobulin can be given before the results are available.[1]	3.1.1
Sensitising event immunoprophylaxis in the first 12 weeks of pregnancy in Rh D negative women		
R3	After the following sensitising events in the first 12 weeks of singleton or multiple pregnancy: miscarriage, termination of pregnancy (medical after 10 weeks gestation or surgical), ectopic pregnancy, molar pregnancy and chorionic villus sampling, the ERG **recommends** that a dose of Rh D immunoglobulin 250 IU be given to all Rh D negative women with no preformed anti-D antibodies to prevent Rh D alloimmunisation. (*Strong recommendation, very low certainty of evidence about the size of effect*)	3.2.1
R4	In the setting of medical termination of pregnancy before 10 weeks of gestation there is insufficient evidence to suggest the routine use of Rh D immunoglobulin.[2, 3] *(Discretionary (weak) recommendation, expert consensus)*	3.2.1

Identifier	Guidance – recommendations and expert opinion points	Relevant section of Guideline
Sensitising event immunoprophylaxis in the first 12 weeks of pregnancy in Rh D negative women *(cont.)*		
R5	In Rh D negative women with an ongoing pregnancy who have uterine bleeding in the first 12 weeks of pregnancy there is insufficient evidence to support the routine use of Rh D immunoglobulin. However, where the bleeding is repeated, heavy or associated with abdominal pain or significant pelvic trauma, immunoprophylaxis may be administered to women with no preformed anti-D antibodies. (*Qualified (weak) recommendation, expert consensus*)	3.2.1
EOP4	At all times when Rh D immunoglobulin is being administered for a sensitising event, it should be given as soon as practical within 72 hours. If delayed beyond 72 hours, the dose should be given up to 10 days from the sensitising event, but may have lower efficacy.	3.2.1
EOP5	For repeated sensitising events in the first 12 weeks of pregnancy, there is no evidence to guide practice. Specialist obstetric consultation is advised regarding further administration of Rh D immunoprophylaxis. For new sensitising events a repeated dose of Rh D immunoglobulin may be indicated. For ongoing uterine bleeding alone, a repeat dose of Rh D immunoglobulin (250 IU if during the first 12 weeks and 625 IU if after) may be appropriate after an interval of 6 weeks.[4,5]	3.2.1
Sensitisting event immunoprophylaxis beyond the first 12 weeks of pregnancy in Rh D negative women		
EOP7	A dose of Rh D immunoglobulin 625 IU should be offered to every Rh D negative woman with no preformed anti-D antibodies, unless NIPT for fetal *RHD* has predicted the fetus to be Rh D negative, to ensure adequate protection against alloimmunisation for the following indications after 12^{+6} weeks of pregnancy: • genetic studies (chorionic villus sampling, amniocentesis and cordocentesis) • abdominal trauma considered sufficient to cause FMH, even if FMH testing is negative • each occasion of revealed or concealed antepartum haemorrhage. Where the woman suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage (and the need for immunoprophylaxis) should be considered • external cephalic version (successful or attempted) • miscarriage or termination of pregnancy.	3.5.1
EOP8	For sensitising events after 20 weeks of pregnancy, the magnitude of FMH should be assessed, and further doses of Rh D immunoglobulin administered if required.[a,b,c] [a] The first dose of the Rh D immunoglobulin should be given without waiting for the result of the test for FMH. [b] Taken from Point 4.3 of the BCSH *Guidelines for the estimation of fetomaternal haemorrhage.*[6] [c] See Appendix C of the Guideline for guidance on dosing.	3.5.1
EOP9	For ongoing uterine bleeding alone beyond 12 weeks' gestation a further dose of Rh D immunoglobulin (625 IU) may be appropriate at 6 weekly intervals.[7] New sensitising events should be managed with a further dose of Rh D immunoglobulin (625 IU) and assessment of FMH (after 20 weeks or where otherwise indicated) with additional dosing to cover large volume FMH if required (100 IU for each mL of fetal red cells beyond 6 mL).[a] [a] See Appendix C of the Guideline for guidance on dosing.	3.5.1

Identifier	Guidance – recommendations and expert opinion points	Relevant section of Guideline
Sensitisting event immunoprophylaxis beyond the first 12 weeks of pregnancy in Rh D negative women *(cont.)*		
EOP10	In reference to antenatal sensitising events after 20 weeks of pregnancy and after giving birth, a maternal sample to assess the volume of FMH should be taken before administration of Rh D immunoglobulin. However, at no time should Rh D immunoglobulin be delayed based on, or pending, the results of testing to quantitate FMH. Between 13 and 20 weeks of pregnancy, the magnitude of FMH may be assessed at clinical discretion.	3.5.1
EOP11	The magnitude of the FMH should be assessed by a method capable of quantifying a haemorrhage of ≥6 mL of fetal red cells (equivalent to 12 mL of whole blood). Flow cytometry is accepted as the most accurate quantitative test for FMH and is the method of choice for quantitation if readily available. Where FMH quantitation shows that FMH greater than that covered by the dose already administered has occurred, an additional dose or doses of Rh D immunoglobulin sufficient to provide immunoprophylaxis must be administered as soon as practical within 72 hours.[a] If delayed beyond 72 hours, the dose should be given up to 10 days from the sensitising event, but may have lower efficacy. [a] See Appendix C of the Guideline for guidance on dosing.	3.5.1
EOP12	For large bleeds ≥ 6 mL of fetal red cells (equivalent to 12 mL of whole blood), follow-up testing should be performed on a sample collected 48 hours post intravenous Rh D immunoglobulin administration or 72 hours post intramuscular Rh D immunoglobulin administration, to determine whether further dosing is required. Supplemental Rh D immunoglobulin should be administered if the test for FMH is still positive.[a] If testing for fetal cells is negative on a follow-up sample, no further testing is required. [a] See Appendix C of the Guideline for guidance on dosing.	3.5.1
Targeted immunoprophylaxis in postnatal Rh D negative women		
R8	The ERG currently **recommends** that postnatal Rh D immunoprophylaxis (Rh D immunoglobulin 625 IU) continue to be administered to all Rh D negative women with no preformed anti-D antibodies who have a baby who is predicted to be Rh D positive based on NIPT for fetal *RHD*, or cord blood or neonatal Rh D typing. The cord blood or neonatal testing should be performed regardless of the results of NIPT for fetal *RHD*, but need not delay administration of Rh D immunoprophylaxis when the fetus has been shown to be *RHD* positive by NIPT testing. If the baby is Rh D positive, administer Rh D immunoglobulin even if the NIPT predicted an Rh D negative baby. *(Strong recommendation, high certainty of evidence)*	3.3.1
High BMI		
R12	The ERG **does not currently support** an increased dose of Rh D immunoglobulin or changes in laboratory testing on the basis of high BMI in Rh D negative pregnant women. *(Weak recommendation, very low certainty of evidence about the size of effect)*	3.4.1
EOP6	Rh D immunoglobulin must be given by deep intramuscular injection. For women with a BMI of more than 30, particular consideration should be given to factors that may affect the adequacy of the injection (e.g. the site of administration and the length of the needle used).	3.4.1

BMI: body mass index, EOP: expert opinion point, ERG: Expert Reference Group, FMH: fetomaternal haemorrhage, IU: international units, NIPT: non-invasive prenatal testing, R: recommendation;

anti-D - refers to circulating antibodies, *RHD* - refers to genotype, Rh D immunoglobulin - refers to the product, Rh D positive/negative - refers to blood type

Summary of clinical guidance on the use and timing of pathology testing

Test	Timing	Target group	Relevant section of document
ABO/Rh D type and antibody screen	First visit (at approximately 10 weeks)	All pregnant women	3.1.1
NIPT for fetal *RHD*	From 11^{+0} weeks of pregnancy	All Rh D negative pregnant women	3.3.1
Magnitude of FMH[a]	• After 20 weeks of pregnancy • At delivery	Rh D negative women following birth or a sensitising event during pregnancy (after 20 weeks)	3.5.1
Rh D type and antibody screen (Retest)	28 weeks (prior to administration of Rh D immunoglobulin)	Rh D negative pregnant women (unless NIPT for fetal *RHD* has predicted that they are not carrying an Rh D positive fetus)	3.1.1
Cord blood or neonatal testing for Rh D type and direct antiglobulin titre	At delivery	All babies of Rh D negative women	3.3.1
Follow up testing for large FMH[b]	48 hours post IV Rh D immununoglobulin adminstiation (or 72 hours post IM Rh D immunoglobulin administration)	Rh D negative women following FMH ≥ 6 mL of fetal red cells (equivalent to 12 mL of whole fetal blood)	3.5.1

FMH: fetomaternal haemorrhage, IM: intramuscular, IV: intravenous, NIPT: non-invasive prenatal testing

anti-D - refers to circulating antibodies, *RHD* - refers to genotype, Rh D immunoglobulin - refers to the product, Rh D positive/negative - refers to blood type.

[a,b] The magnitude of FMH should be assessed by a method capable of quantifying a haemorrhage of ≥6 mL of fetal red cells (equivalent to 12 mL of whole blood). Flow cytometry is accepted as the most accurate quantitative test for FMH and is the method of choice for quantitation if readily available (Refer to EOP11).

Summary of clinical guidance on the use and timing of Rh D immunoglobulin

Clinical indication	Rh D immunoglobulin dose and timing	Target group	Relevant section of Guideline
Routine immunoprophylaxis			
Routine antenatal immunoprophylaxis	625 IU At 28 and 34 weeks of pregnancy	Rh D negative pregnant women with no preformed anti-D antibodies (unless NIPT for fetal *RHD* has predicted that they are not carrying an Rh D positive fetus)	3.1.1
Routine postnatal immunoprophylaxis	625 IU After giving birth	All Rh D negative women with no preformed anti-D antibodies after giving birth to an Rh D positive baby (based on cord blood or neonatal Rh D typing[a]). If the baby is Rh D postive, administer Rh D immunoglobulin even if the NIPT predicted an Rh D negative baby [a] Cord blood or neonatal testing should be performed regardless of NIPT results for fetal *RHD*.	3.3.1

FMH: fetomaternal haemorrhage, IM: intramuscular, IU: international units, NIPT: non-invasive prenatal testing

anti-D - refers to circulating antibodies, *RHD* - refers to genotype, Rh D immunoglobulin - refers to the product, Rh D positive/negative - refers to blood type.

Summary of clinical guidance on the use and timing of Rh D immunoglobulin

Clinical indication		Rh D immunoglobulin dose and timing	Target group	Relevant section of Guideline
Sensitising event immunoprophylaxis				
Sensitising event immunoprophylaxis in the first 12 weeks of pregnancy	• Miscarriage • Termination of pregnancy (medical after 10 weeks gestation or surgical) • Ectopic pregnancy • Molar pregnancy • Chorionic villus sampling	250 IU As soon as practical within 72 hours. If delayed beyond 72 hours, the dose should be given up to 10 days from the sensitising event, but may have lower efficacy For ongoing uterine bleeding alone, a repeat dose of Rh D immunoglobulin (250 IU if before 12 weeks and 625 IU if after) may be appropriate after an interval of 6 weeks	All Rh D negative women with no preformed anti-D antibodies	3.2.1
Sensitising event immunoprophylaxis after 12^{+6} weeks of pregnancy	• Genetic studies (chorionic villus sampling, amniocentesis and cordocentesis) • Abdominal trauma considered sufficient to cause fetomaternal haemorrhage, even if FMH testing is negative • Each occasion of revealed or concealed antepartum haemorrhage. Where the woman suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage (and the need for immunoprophylaxis) should be considered. • External cephalic version (successful or attempted) • Miscarriage or termination of pregnancy	625 IU As soon as practical within 72 hours. If delayed beyond 72 hours, the dose should be given up to 10 days from the sensitising event, but may have lower efficacy For ongoing uterine bleeding alone, a repeat dose may be appropriate at 6 weekly intervals	All Rh D negative women with no preformed anti-D antibodies (unless NIPT for fetal *RHD* has predicted the fetus to be Rh D negative)	3.5.1
Large FMH ≥6 mL of fetal red cells (equivalent to 12 mL of whole blood)	• Antepartum • Postpartum	625 IU as soon as possible Follow laboratory or specialist obstetric advice for additional doses of IM Rh D immunoglobulin or IV Rh D immunoglobulin, and for follow-up testing	All Rh D negative women with no preformed anti-D antibodies (unless NIPT for fetal *RHD* has predicted the fetus to be Rh D negative)	3.5.1

FMH: fetomaternal haemorrhage, IM: intramuscular, IU: international units; IV: intravenous, NIPT: non-invasive prenatal testing

anti-D - refers to circulating antibodies, *RHD* - refers to genotype, Rh D immunoglobulin - refers to the product, Rh D positive/negative - refers to blood type

References

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