Rh D negative women and pregnancy

IMPORTANT: *Consider individual clinical circumstances. Consult a pharmacopeia for complete drug information. Refer to the QCG position statement on gender associated language Read the full disclaimer at www.health.qld.gov.au/qcg*

Introduction

Aspect	Consideration
Rh D associated definitions	• **Alloimmunisation**: Rh D sensitisation–refer to Alloimmunisation • **Anti-D antibody:** circulating Rh D antibodies (passive or preformed)[1] • **Rh D Ig** (Rh D immunoglobulin)**:** blood product administered to Rh D negative woman for immunoprophylaxis • **Rh D** *(previously known as Rhesus D):* **positive or negative** blood group[1] (if positive the D antigen is present on red cells[2]) • **Rh incompatibility:** mother and fetus incompatible for Rh D group • **Haemolytic disease of the fetus and newborn** (HDFN)**:** maternal Ig G antibodies cause destruction of baby's red cells, and if severe anaemia and hydrops • **Immunoprophylaxis:** occurs when Rh D Ig (administered to the woman) destroys fetal Rh D positive red cells in the maternal circulation before alloimmunisation can occur[3]
Non-invasive prenatal test for Rh D (Rh D–NIPT)	• Available free of charge to all Rh D negative pregnant women who are eligible for Medicare Benefits Schedule (MBS) (introduced late 2024) • Aims to support targeted rather than universal antenatal Rh D immunoprophylaxis[4] • Recommend to all non-alloimmunised Rh D negative pregnant women from 15 weeks gestation • Predicts fetal Rh D phenotype (i.e. if fetus Rh D positive or negative) • Cautions[4]: o Maternal Rh D variants interfere with ability to determine fetal Rh D status o Risk of false negative result approximately 0.2% o Not validated for women with multiple pregnancy
Non-invasive prenatal analysis (NIPA)	• Indicated for Rh D negative pregnant women from 12 weeks gestation who: o Are Rh D alloimmunised o Have obstetric indications (e.g. severe fetomaternal haemorrhage, intrauterine death) o Are non-alloimmunised but have relative contraindications to antenatal Rh D immunoprophylaxis (e.g. prior allergic reaction to Rh D immunoglobulin, cultural/religious objection) • Predicts fetal blood group phenotype (ABO/Rh type) for the antigens of interest (D, C, c, E, K, k, Fya, Fyb) • Can determine if current pregnancy at risk of HDFN • Can replace invasive direct sampling methods for fetal DNA, (e.g. amniocentesis or chorionic villus sampling) • Validation and study data suggest accuracy of 100% with 95% CI (97.2-100%)
Other Rh D associated tests	• **Direct antiglobulin test (DAT):** determines whether there is binding of maternal immunoglobulin antibodies (Rh D antibodies) to baby's red cell antigens[5] (known historically as direct Coombs test (DCT)) • **Flow cytometry:** most accurate and method of choice for quantification of feto-maternal haemorrhage (FMH)[1] • **Kleihauer-Betke test:** detects and quantifies FMH[6]
Clinical standards	• Refer to Queensland Clinical Guideline *Standard care*[7] for care considered 'usual' or 'standard'—includes for example: privacy, informed consent, decision making, sensitive communication, medication administration, staff education and support, culturally appropriate care and documentation

Alloimmunisation

Aspect	Consideration
Importance	• Early pregnancy screening, recognition of risk and timely management reduces incidence of fetal death and adverse neonatal outcomes[8] • Rh D negative women are at risk of alloimmunisation that may affect future pregnancies[9] • In Australia, approximately 15% of Australians are Rh D negative[10,11]
Pathophysiology	• An immune system response of an Rh D negative woman to Rh D positive fetal red cells that express the Rh D antigen[1,9,12] • D antigen is expressed on fetal red cells by 38 days of gestation in Rh D positive fetus • If maternal alloimmunisation occurs as a result of sensitising event, anti-D IgG antibodies cross the placenta and may affect an Rh D positive fetus in subsequent pregnancies[9]
Incidence	• If no immunoprophylaxis, the rate of alloimmunisation in Rh D incompatible pregnancy is approximately 16%[13] • Rate of alloimmunisation in Rh D negative women in Queensland due to feto-maternal haemorrhage of greater than 6 mL is approximately 4%[14]
Risk factors	• Incompatible blood groups—occurs if Rh D negative woman has an Rh D positive fetus • Sensitising events in pregnancy [refer to Sensitising events] • Incompatible blood transfusion (including IV drug use/needle sharing)
Maternal and fetal outcomes	• HDFN[15] • Severe anaemia resulting from HDFN[16,17]–if anti-D level[18] o Between 4–15 international units (IU) per mL, moderate risk of HDFN (unlikely severe) o Greater than 15 IU per mL, HDFN may be severe • If other blood group antibodies, HDFN incidence and the critical antibody titres for risk are different—if alloimmunisation suspected, consult with a specialist obstetrician • Hydrops fetalis[19] • Fetal thrombocytopenia[20] • Generally no apparent adverse maternal health outcomes[1], unless severe HDFN causing hydrops when maternal mirror syndrome may develop[21]

Anti-D products

Aspect	Consideration
Consent	• Informed consent required prior to administration of anti-D product o Refer to Queensland Clinical Guideline *Standard care*[7] • Documentation–record the name of product and batch number in woman's medical record
Clinical circumstances	• Body mass index (BMI) greater than or equal to 30 kg/m^2 o No additional dose required[1] o Consider length of needle[1] and administration site (deltoid is suggested) o Consider Rhophylac®* intravenous (IV) injection[22] • No minimum interval required between IM (intramuscular) Rh D Ig administration and vaccination for measles, mumps, rubella and/or varicella[23] • Same dose and regimen (routine prophylaxis and sensitising events) for singleton and multiple pregnancies[1]
Administration safety[22,24]	• Interacts with other medications–do not mix with medications or diluents • Observe woman for at least 20 minutes post administration • No fetal effects of prophylactic anti-D products, suitable to use if breastfeeding
Rh (D) immunoglobulin-VF (single vial)[1,24]	• Human Anti-D Rh_0 immunoglobulin • Bring to room temperature before use • Administer by slow, deep intramuscular (IM) injection o Draw back to ensure not in blood vessel o Best sites are deltoid or anterolateral thigh[25] • Divide doses of more than 5 mL volume • Do **not** administer IV • If extra dose(s) for FMH round up volume to nearest full vial or vials • If more than two IM injections are required, consider IV Rhophylac®
Rhophylac® (prefilled syringe)[1,22]	• Human Anti-D (Rh_0) immunoglobulin • Usually used for large fetal maternal haemorrhage (greater than 6 mL of fetal cells) • Bring to room temperature immediately before administration • Administer IM or IV injection (if dose larger than 5 mL) • Consider IV use for woman who has haemorrhagic disorder precluding IM injection

Antenatal management

Aspect	Consideration
All women	• Recommend testing for ABO/Rh blood group and antibody status (e.g. anti-D, anti-C, Kell) to all women at the first appointment (ideally before 10 weeks gestation)[26]
If Rh D negative	• Assess risk of Rh D alloimmunisation (e.g. previous baby requiring blood transfusion, or known to have had HDFN)[27] • Recommend Rh D–NIPT to all non-alloimmunised Rh D negative women from 15 weeks gestation • Recommend repeat ABO/Rh blood group and antibody status to Rh D negative women without preformed anti-D antibodies at approximately 28 weeks gestation (cluster with other routine blood tests) • If transfusion required, use Rh D negative blood[28] • Offer information about o Rh D status and potential risk to future babies o Blood test surveillance o Sensitising events o Prophylaxis and other indications for Rh D Ig [refer to Sections Routine Rh D immunoglobulin prophylaxis and Sensitising events] o Written consumer information about Rh D Ig; discuss benefits and risks
If Rh D negative and positive anti-D antibody screen[1,29]	• Review clinical history and health records o Previous pregnancies o Blood transfusion o IV drug use/needle sharing o Recent Rh D Ig administration • Determine if anti-D is likely to be: o Preformed (due to sensitisation) *or* o Passive (through the administration of Rh D immunoglobulin in the past 12 weeks) • If preformed anti D o Rh D immunoglobulin not indicated (not effective) o Seek specialist obstetric/maternal fetal medicine advice, including ongoing serial monitoring of antibody titres and regular ultrasound scans[18] o Manage as Rh D sensitised *and* o Consider NIPA for fetal Rh D status • If passive anti-D o Recommend Rh D immunoglobulin • If unknown/uncertain whether anti-D passive or preformed o Seek expert advice o Recommend Rh D immunoglobulin
If Rh D negative fetus predicted from Rh D–NIPT/ NIPA[26]	• Immunoprophylaxis is not indicated for: o Routine immunoprophylaxis or o Sensitising event immunoprophylaxis • All other routine antenatal care indicated • Refer to Postnatal and newborn care for Rh D and DAT testing of baby after birth
If Rh D positive fetus predicted from Rh D–NIPT /NIPA[26]	• Recommend Rh D immunoglobulin to Rh D negative woman with[1] no preformed anti-D antibodies[18] at 28 and 34 weeks gestation o Administer Rh (D) immunoglobulin-VF* 625 international units (IU) IM • If not logistically possible to administer at 28 and 34 weeks o Give as soon as practicable within two weeks of due administration date o If 28 week dose not administered, give as soon as possible and then second dose six weeks later • If sensitising events occur, recommend Rh D immunoglobulin o Refer to Sensitising events • Refer to Postnatal and newborn care for immunoprophylaxis and Rh D and DAT testing of baby after birth
Rh D fetal status unknown[26]	• Recommend Rh D immunoglobulin

Sensitising events

Aspect	Consideration
First 12+6 weeks of pregnancy[1]	• Miscarriage[27] o Excludes threatened miscarriage—consider confirming gestational age by ultrasound scan • Termination of pregnancy[27] (medical or surgical) from 10+0 weeks gestation[26] • Ectopic pregnancy[27] • Molar pregnancy[27] • Chorionic villus sampling[27]
From 13+0 weeks gestation[1]	• Genetic studies[27] o Chorionic villus sampling o Amniocentesis o Cordocentesis • Abdominal trauma[27] • Revealed or concealed antepartum haemorrhage o Consider in woman with unexplained uterine pain—possible concealed antepartum haemorrhage (APH) • External cephalic version (successful or attempted) • Miscarriage or termination of pregnancy[27] • Birth of baby regardless of mode[27]—greatest risk
Sensitising event (or unknown maternal blood group)	• Check maternal blood for: o Blood group (if required) and anti-D antibodies o Quantify FMH size by Kleihauer-Betke or flow cytometry[1,6] • If maternal blood group is Rh D negative, administer Rh D Ig as soon as possible after blood sample taken (most effective within 72 hours of sensitising event[1]) o Do not wait for test results before administering first dose[6] o May be given up to 10 days from sensitising event but may have lower efficacy[1] o Administer for all new sensitising events and regardless of time of routine prophylaxis o Administer routine 28 and 34 week Rh D Ig regardless of extra doses for sensitising event
Measuring FMH	• If 20+1 weeks or more gestation, measure FMH size following sensitising event and at birth for all Rh D negative women[1] • Use method that can quantify a haemorrhage greater than or equal to 6 mL (equivalent to 12 mL of whole blood)[1] • Flow cytometry most useful and accurate quantitative test for FMH[1,30] o If available, method of choice[1] o Includes antenatal and postnatal periods[1] • Offer follow up testing as per laboratory or specialist obstetric advice[1]
Follow up testing	• If large FMH (6 mL or more) repeat flow cytometry after Rh D Ig administration at[1]: o 48 hours post IV administration o 72 hours post IM injection administration
Postnatally	• If baby tests Rh D positive at birth [refer to Postnatal and newborn care] o Obtain maternal bloods to detect and quantify FMH after 45 minutes and within 2–72 hours of birth[6,29] o Collect blood specimen before administering Rh D Immunoglobulin[6]

Rh D immunoglobulin for sensitising event

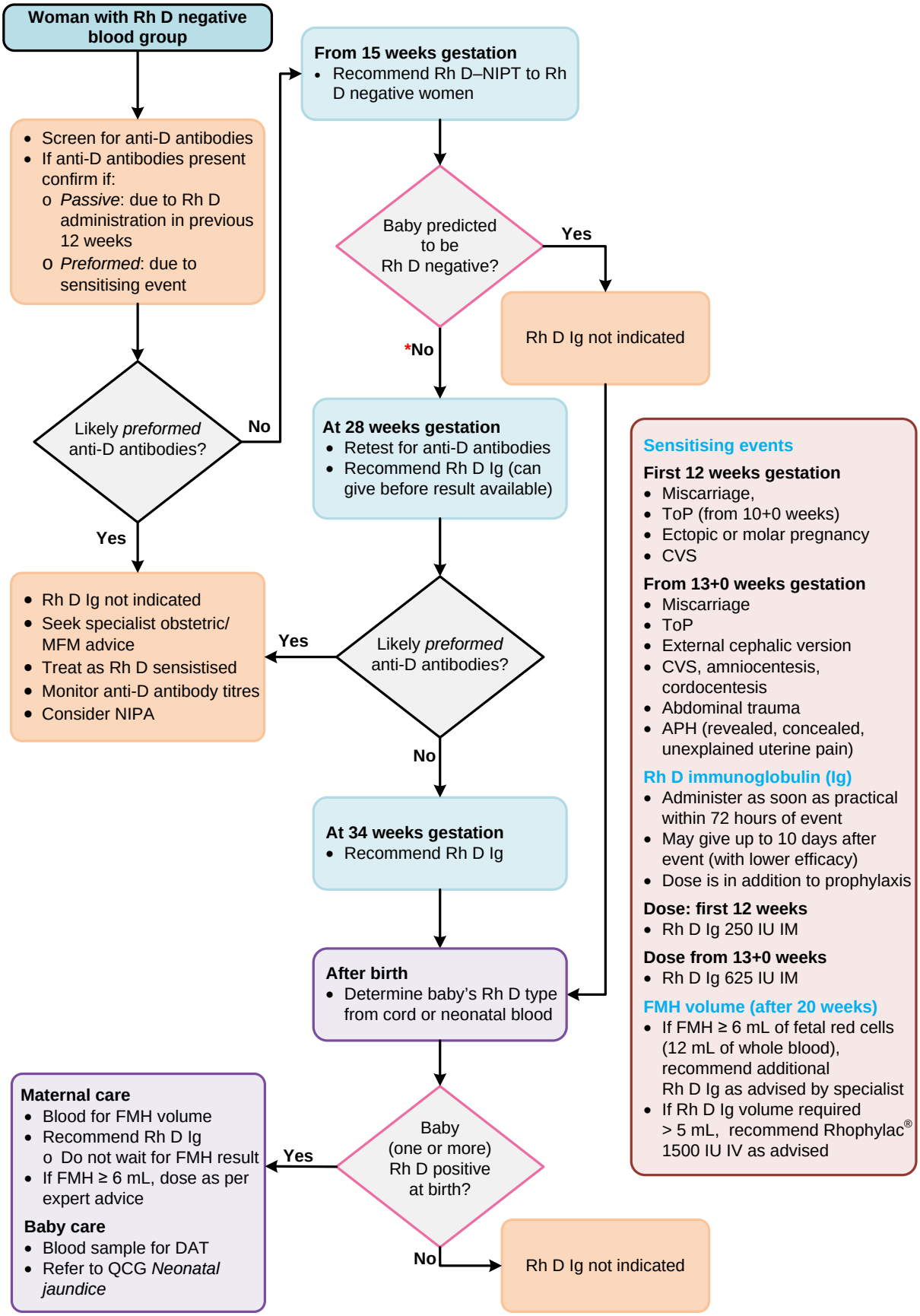
Aspect	Consideration
Context[1]	• Indicated for Rh D negative women with no pre-formed anti-D antibodies and where fetus is predicted to be Rh D positive from Rh D–NIPT or NIPA • Administer dose as soon as practical within 72 hours of sensitising event • If dose not given within 72 hours, may be administered up to 10 days from event o May have lower efficacy • Quantify size of FMH after 20 weeks gestation and after birth
Sensitising event first 12+6 weeks gestation[1]	• If bleeding is repeated, heavy, or associated with abdominal pain or significant pelvic trauma administer Rh D immunoglobulin • Administer Rh (D) immunoglobulin-VF* 250 IU IM injection • If maternal bleeding is ongoing, further dose may be given after interval of six weeks–if less than 13+0 weeks gestation administer Rh (D) immunoglobulin-VF* 250 IU IM injection[24] • Insufficient evidence to support *routine* use of Rh D Ig following threatened miscarriage
Sensitising event from 13+0 weeks gestation[1]	• Administer Rh (D) immunoglobulin-VF* 625 IU IM injection[24] • If ongoing uterine bleeding further doses may be given at intervals of 6 weeks • If gestation unknown and possibly greater than or equal to 13 weeks administer Rh (D) immunoglobulin-VF* 625 IU IM injection[24]
FMH 6 mL or more of fetal cells[1]	• Administer Rh (D) immunoglobulin-VF* 625 IU IM injection • Additional doses following laboratory or specialist obstetric advice o If required, usually an additional dose of Rh (D) immunoglobulin-VF* 100 IU IM injection per 1 mL fetal red cells greater than or equal to 6 mL • If IM injection not practical (e.g. volume of Rh D immunoglobulin to be injected is greater than 5 mL) or is contraindicated (e.g. woman has haemorrhagic disorder) o Administer Rhophylac®* 1500 IU IV injection or as advised by laboratory or specialist obstetrician/feto-maternal specialist[24]
Blood transfusion	• If woman requires blood transfusion—use red cells of the same ABO Rh D group, and K negative[18] • If Rh D negative woman receives Rh D positive blood transfusion, consult with a haematologist for specialist advice regarding individual woman's situation o Rhophylac®* 1500 IU IV injection[22] may be considered *or* other interventions

**Refer to product information*

Postnatal and newborn care

Aspect	Consideration
Screening of baby at birth	• Check Rh D group and DAT of **all** babies born to women who are Rh D negative regardless of immunoprophylaxis or alloimmunisation history[29] o Including if Rh D–NIPT /NIPA test predicted baby to be Rh D negative[1] • If clinically significant antibodies in woman or increased risk of haemolysis–also test cord blood for haemoglobin and bilirubin[18,29]
Newborn care	• Usual newborn baby care and observations • If alloimmunised mother (risk of HDFN), assessment of neurobehavioral state, jaundice and/or anaemia[18] • If weak positive DAT: o May be due to maternal antenatal immunoprophylaxis o Usually no adverse effects on newborn baby o If in doubt about significance of DAT result discuss with testing laboratory or neonatologist/paediatrician • Refer to Queensland Clinical Guidelines: *Routine newborn assessment*[31] and *Jaundice-neonatal*[32]
Maternal postnatal prophylaxis1	• Indicated for all Rh D negative women with no preformed anti-D antibodies who give birth to an Rh D positive baby (Rh D group from cord or neonatal blood) • Administer Rh (D) immunoglobulin-V* 625 international units (IU) intramuscular injection o Administer within 72 hours of birth–regardless of when routine antenatal prophylaxis or sensitising dose given o If not given within 72 hours after birth (preferred), may be given up to 10 days postnatally

Flowchart Routine management of Rh D negative woman



*Includes: not tested, results inconclusive, and baby predicted Rh D positive

APH: antepartum haemorrhage **CVS:** chorionic villus sampling **FMH:** feto-maternal haemorrhage, **Ig:** immunoglobulin **IM:** intramuscular **IV** intravenous **NIPA:** non-invasive prenatal analysis, **Rh D–NIPT:** non-invasive prenatal test for Rh D, **Rh D Ig:** Rh D immunoglobulin-VF **ToP:** termination of pregnancy **≥:** greater than or equal to

Flowchart F23.74-1-V3-R28

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