BMJ Best Practice

Rh incompatibility

Straight to the point of care

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Summary

Rhesus (Rh) incompatibility is a condition where an Rh-negative mother carrying an Rh-positive fetus can produce antibodies against paternally derived Rh antigens on fetal red blood cells. These antibodies can cross the placenta, and destroy fetal red blood cells. It is a leading cause of haemolytic disease of the fetus and newborn, also known as erythroblastosis fetalis.

Effective immunoprophylaxis of Rh-negative at-risk mothers is key to primary prevention.

Intrauterine fetal transfusion is a life-saving treatment for severely affected fetuses.

Survival rates are more than 90%.

Definition

Rh incompatibility occurs in an Rh-negative mother carrying an Rh-positive fetus. If the mother is exposed to the paternally derived Rh antigens on fetal red blood cells (RBCs) she can become sensitised and produce immunoglobulin G (IgG) antibodies, usually against the RhD antigen. These maternally derived antibodies can then freely cross the placenta, binding to and destroying fetal RBCs. This is a leading cause of haemolytic disease of the fetus and newborn (HDN or HDFN, also known as erythroblastosis fetalis), which involves progressive fetal anaemia, and, if untreated, may ultimately lead to hydrops fetalis (collection of fluid in serous compartments) and death.[1][2]

Epidemiology

About 15% of the white population has an RhD-negative blood type.[3] Population data suggest that the incidence of RhD negativity is highest among Basques (36%).[3] Around 6% to 7% of black people and less than 1% of American Indian and Asian people have an RhD-negative blood type.[3] [4] Rh alloimmunisation due to RhD has declined markedly as immunoprophylaxis has become routine practice.[5] [6] Societal factors, such as delayed childbearing and smaller families, may also have contributed to this decline.[5]

In the UK, about 16% of the white population is RhD-negative.[7] In 2013-2014, about 15% of births in England were to RhD-negative women; about 40% of these women had an RhD-negative fetus.[8]

The estimated global prevalence of Rh haemolytic disease is 276/100,000 live births; in countries with well-established perinatal-neonatal care, the prevalence is approximately 2.5/100,000 live births.[9] One survey in Canada estimated that 8/100,000 infants are affected by maternal anti-D antibodies.[10] In the US, the reported incidence of Rh haemolytic disease ranges from 1.0 to 6.8/1000 live births; the higher rate may reflect improved identification and reporting of sensitised women and increasing prevalence of atypical, non-RhD antibodies for which immunoprophylaxis regimens are unavailable.[11] [12] [13]

The relative frequency has been reported for several of these non-RhD antibodies.[11] In a large prospective series including over 300,000 consecutive patients, about 1% of pregnant women had alloantibodies detected in the first trimester.[14] Of these, the prevalence of alloantibodies other than anti-D was 328/100,000, of which 191/100,000 implied a risk for occurrence of haemolytic disease of the fetus and newborn as the father carried the antigen. The most common non-anti-D antibodies were anti-K and anti-c.[14]

Aetiology

Three genes are thought to encode for the Rh blood groups. Two of these genes are located on the short arm of chromosome 1: RhD and RhCE.[15] Study of the RhD gene has revealed significant heterogeneity that may result in a lack of expression of the RhD phenotype. RhD pseudogene has all 10 exons of the RhD, but the gene is not transcribed into a messenger RNA product due to the presence of a stop codon in the intron between exons 3 and 4. Therefore, no RhD protein is synthesised, and the patient is serologically RhD-negative.[16]

Rh incompatibility is caused by destruction of fetal red blood cells (RBCs) from transplacental passage of maternally derived immunoglobulin G antibodies. Passage of fetal cells into the maternal circulation and fetomaternal haemorrhage (FMH) is a frequent occurrence, detectable in 65% of pregnancies either antenatally or in the early postnatal period.[17] Sensitisation of an RhD-negative mother with as little as 0.1 mL of RhD-positive fetal RBCs may elicit a primary immune response.[17] [18] [19]

Placental trauma of varying degrees may lead to sensitising FMH. FMH increases throughout pregnancy (3% first trimester, 43% second trimester, and 64% third trimester).[17] [18] [19] FMH has been found in 1% to 6% of external cephalic versions.[20] [21] [22] Small amounts of FMH (>0.1 mL) are potentially immunising and occur in 2% of patients undergoing amniocentesis.[23] [24] The incidence of FMH at the time of chorionic villus sampling is about 14%.[25] Other invasive procedures, such as cordocentesis, can also cause FMH. Primary prevention of RhD sensitisation can be accomplished with appropriate use of RhD immunoprophylaxis in these clinical settings.[23]

An episode of threatened, spontaneous, or induced abortion can sensitise RhD-negative patients, but the risk of RhD alloimmunisation is very low with pregnancy loss before 12 weeks' gestation.[26] [27] Alloimmunisation has been reported after ectopic pregnancy, and 24% of patients with ruptured ectopic pregnancy have fetal RBCs detectable in the maternal circulation.[28] The risk of RhD alloimmunisation is low in complete molar pregnancy because of absent or incomplete vascularisation of villi and absence of D antigen. Conversely, a partial mole should be viewed as a risk factor for sensitisation.[23][26] [29]

Pathophysiology

Exposure of an RhD-negative mother to RhD-positive fetal red blood cells (RBCs) results in the generation of B lymphocyte clones that recognise the foreign RBC antigen and promote production of immunoglobulin G (IgG). Memory B lymphocytes await the reappearance of RBCs containing the respective antigen, usually in a subsequent pregnancy. When challenged by these antigenic RBCs, the lymphocytes differentiate into plasma cells and produce IgG. Maternal IgG crosses the placenta and attaches to fetal RBCs that have expressed the antigen. These RBCs are then sequestered by macrophages in the fetal spleen, where extravascular haemolysis occurs, producing fetal anaemia. The fetus attempts to compensate by increasing extramedullary haematopoiesis. This results in hepatosplenomegaly, portal hypertension, cardiac compromise, tissue hypoxia, hypoviscosity, and increased brain perfusion. Extreme fetal haemoglobin deficits of ≥70 g/L (≥7 g/dL) can ultimately lead to hydrops fetalis (collection of fluid in serous compartments) and intrauterine fetal death, unless corrected by intrauterine fetal transfusion or neonatal exchange transfusion following delivery.[17] [26] [30]

Classification

Clinical classification[2]

- Rhesus D (RhD) red blood cell (RBC) alloimmunisation
- Haemolysis caused by RhD antigen
- Non-RhD RBC alloimmunisation
- Haemolysis caused by other, atypical RBC antigens (Kell, Rhc, Kidd, Duffy)

Case history

Case history #1

A 32-year-old woman presents at 25 weeks' gestation in her third pregnancy with a positive antibody screen. She is known to be Rh-negative with an Rh-positive partner. Two previous children were born overseas: the first child was carried to term and is healthy. The second child, also born at term, underwent phototherapy in the immediate neonatal period due to jaundice. The patient did not have anti-D prophylaxis given antenatally or postnatally in the previous pregnancies. Physical examination is normal.

Case history #2

A 38-year-old primigravida woman presents for routine antenatal care. Her blood type is known to be Rh-negative with a negative indirect Coombs test, and her partner is Rh-positive. She has been counselled

regarding the need for Rh immunoprophylaxis at 28 weeks of pregnancy and postnatally if her newborn is found to be Rh-positive.

Other presentations

Manifestations of severe erythroblastosis fetalis include ultrasound evidence of significant effusions in serous cavities, organomegaly, polyhydramnios, and extensive skin oedema (anasarca). Anti-RhD antibody titres in severe disease are usually high (>1:32 dilutions). Anti-Kell antibodies may be associated with profound fetal anaemia and hydrops in the presence of low antibody titres due to suppression of erythropoiesis. Evidence suggesting severe fetal anaemia includes high peak systolic velocities on Doppler ultrasound of the middle cerebral artery, low biophysical profile scores, and a sinusoidal fetal heart rate pattern. Although these manifestations of severe fetal disease are usually not detected in a first affected pregnancy, significant fetomaternal haemorrhage from any cause may lead to a secondary immune response and hydrops fetalis, even in a primiparous patient.

Approach

In Rh-negative pregnant women, where Rh paternal phenotype is positive or unknown, the possibility of them becoming alloimmunised and producing red cell antibodies should be considered. Laboratory testing for the presence of red cell antibodies is confirmatory.

Clinical evaluation

All RhD-negative pregnant women (where the fetus has an Rh-positive father) are at potential risk for alloimmunisation and erythroblastosis. Risk factors for maternal sensitisation to RhD antigen include: history of an Rh-positive fetus to an Rh-negative mother; invasive fetal procedures; fetomaternal haemorrhage; placental trauma; spontaneous, threatened, or induced abortion; omission (or inadequate dosing) of appropriate Rh immunoprophylaxis following a potentially immunising obstetric event in a previous or current pregnancy; and multiparity.

Accurate maternal history taking is an important step in evaluating potential risk of sensitisation or fetal anaemia in a current pregnancy. Inquiry should begin with questioning about previous pregnancies, paternal phenotype (if known), history of blood transfusion, administration of Rh immunoprophylaxis, and obstetric and neonatal outcome of all pregnancies.

Although the primary maternal immune response to sensitisation by the D antigen is usually weak, it may be greatly enhanced when a secondary immune response is generated by antigenic challenge in a subsequent pregnancy. Hence, the risk for fetal anaemia and immune fetal hydrops (abnormal accumulation of fluid in 2 or more fetal compartments) increases with increasing parity.[2] [26] [31] When hydrops has occurred in a previous pregnancy, it is likely to occur again, and at an earlier gestational age. Once hydrops or a stillbirth has occurred due to anti-D antibodies from Rh incompatibility, the estimated chance of intrauterine death of a subsequent RhD-positive fetus is 90% if untreated.[32]

Laboratory investigations

Blood type and antibody screening

At the first antenatal visit, all women are screened for ABO blood group, Rh type, and the presence of red blood cell (RBC) antibodies.[23] [33] Repeated RhD-antibody testing for all unsensitised RhD-negative women is also recommended at 24-28 weeks' gestation, unless the biological father is known to be RhD-negative.[33] A positive red blood cell antibody screen in an Rh-negative mother demands further investigation, including identification of the antibody and measurement of the titre.

An identifiable Rh antibody screen in an Rh-negative mother should prompt paternal phenotyping and genotyping (if paternity is certain). A father with Rh-positive blood may be homozygous or heterozygous for the D antigen. If the latter, the risk of transmission of the RhD gene (and hence the risk of Rh incompatibility) to the fetus is 50%, compared with 100% if he is homozygous. In the case of a heterozygous RhD-positive, or unknown, paternal genotype, fetal Rh type is determined by genetic testing of amniotic fluid cells or it can be estimated using cell-free fetal DNA in the maternal circulation, which may be helpful in mothers who refuse amniocentesis.[34] [35]

In sensitised patients the maternal serum antibody titre is a guide to disease severity. The American College of Obstetricians and Gynecologists states that a critical titre (titre associated with a significant risk for severe haemolytic disease of the fetus and newborn, and hydrops) is considered to be between 1:8 and 1:32 in most centres.[34] If the initial antibody titre is 1:8 or less, the patient may be monitored

with titre assessment every 4 weeks.[34] However, serial titres are not adequate for monitoring fetal status when the mother has had a previously affected fetus or neonate.[34]

Assessing fetomaternal haemorrhage

A rosette test can be used to rule out significant fetomaternal haemorrhage. If results are positive, a Kleihauer-Betke (acid elution) test or flow cytometry can measure the amount of fetal blood in the maternal circulation. Such assessments may be carried out in a variety of circumstances, including in unsensitised Rh-negative mothers carrying an RhD-positive fetus (or when fetal RhD status is unknown) following birth; sensitising events occurring after 20 weeks' gestation; or events potentially associated with placental trauma and disruption of the fetomaternal interface (e.g., placental abruption, blunt trauma to the abdomen, cordocentesis, placenta praevia with bleeding).[23][29] [36]

Fetal ultrasound and blood sampling

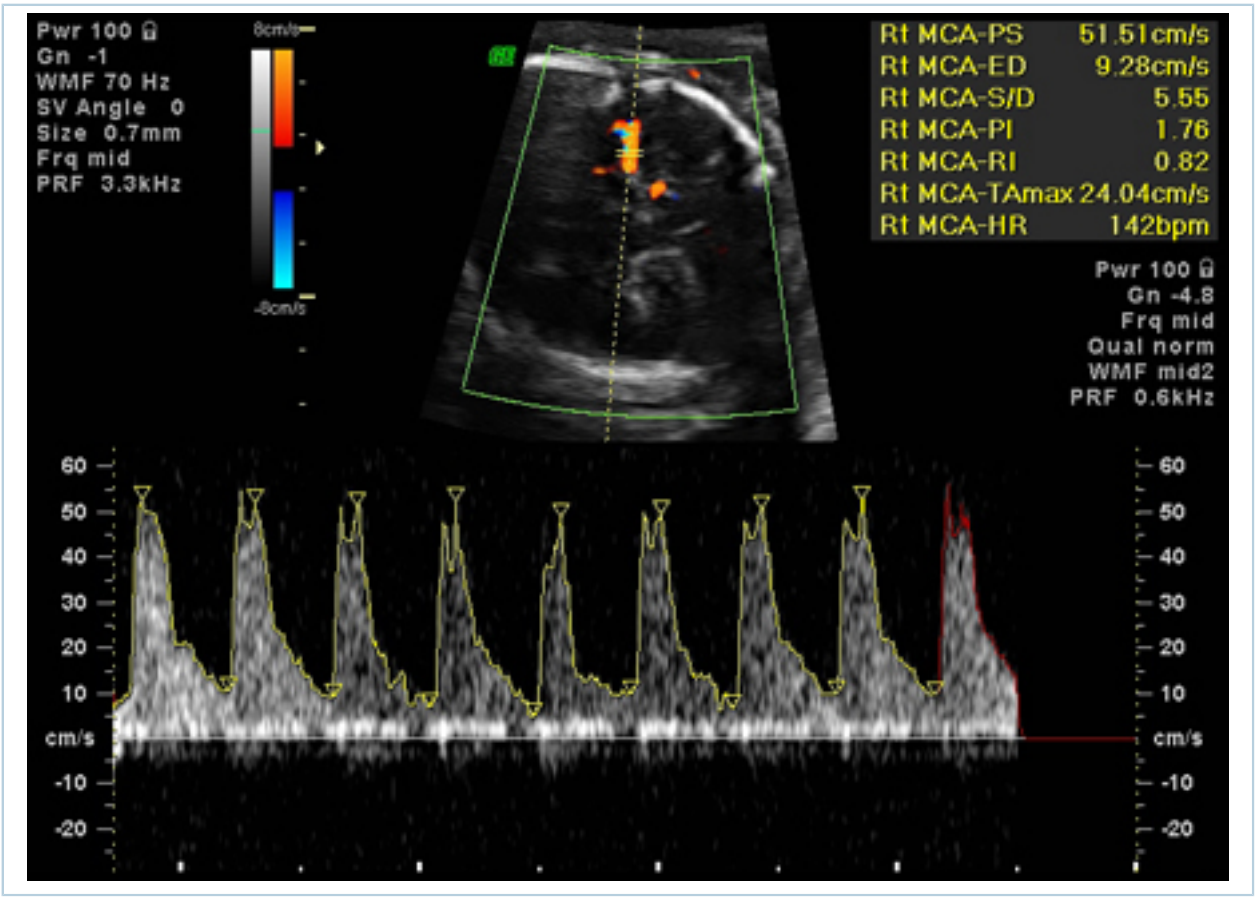
Fetal anaemia due to Rh incompatibility can be diagnosed by measuring peak systolic velocity in the middle cerebral artery (MCA). The prediction of moderate to severe anaemia by Doppler ultrasound has a sensitivity of 100% and false-positive rate of 12%.[31] [37] Elevated blood flow velocity for gestational age should prompt percutaneous umbilical blood sampling (if anaemia is strongly suspected).

Fetal blood sampling through umbilical cord venepuncture (cordocentesis) or the intrahepatic vein allows direct measurement of the fetal haemoglobin and haematocrit.

Definitive information on the severity of anaemia will direct appropriate and life-saving fetal therapy through intrauterine fetal transfusion.[38]

Ultrasound examination of the fetus at risk for Rh incompatibility may reveal subcutaneous oedema, ascites, pleural effusion, or pericardial effusion, all of which are consistent with severe fetal anaemia in an affected fetus.[39]

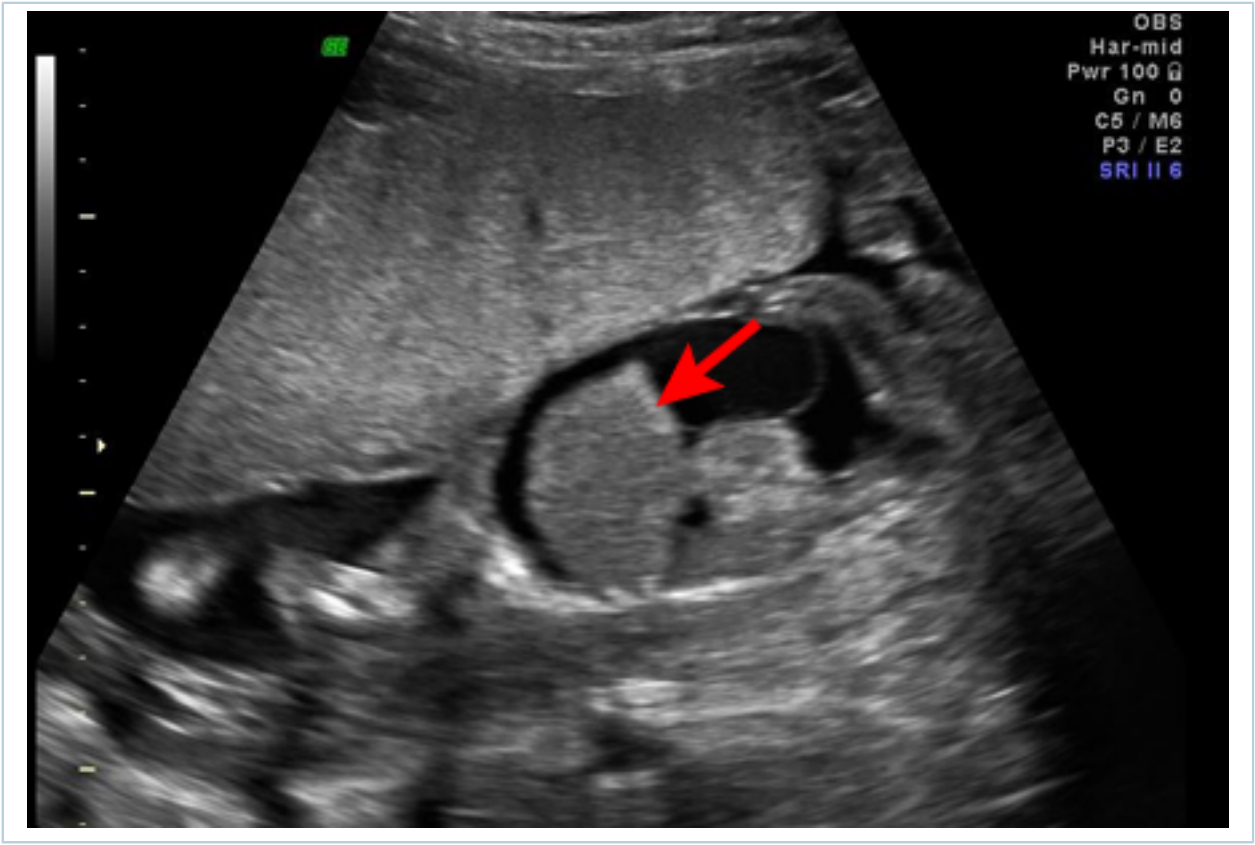
Non-invasive screening for fetal anaemia with Doppler ultrasound has supplanted serial amniocentesis for spectrophotometry in developed countries, but may not be available in all other regions. Where used, spectral analysis of amniotic fluid at optical density 450 nanometres (AOD450) measures the level of bilirubin as an indirect indicator of fetal haemolysis. Liley proposed a management scheme involving three zones based on gestational age between 27 and 42 weeks. When used to monitor fetal disease, serial procedures are undertaken at 10-day to 2-week intervals and continued until delivery.[16] Queenan and co-workers proposed a modified AOD450 curve between 14 weeks and 40 weeks. The Queenan curve has shown better predictive value than the Liley curve in severe anaemia.[30]



Increased velocity in the middle cerebral artery consistent with severe fetal anaemia

The Ottawa Hospital; used with consent of the patient

DIAGNOSIS



Fetal hydrops, with ascites and hepatomegaly (arrow) diagnosed on antenatal ultrasound

The Ottawa Hospital; used with consent of the patient

History and exam

Key diagnostic factors

presence of risk factors (common)

- Strong risk factors for maternal sensitisation to RhD antigen include: history of delivery of an Rh-positive fetus to an Rh-negative mother; fetomaternal haemorrhage; invasive fetal procedures; placental trauma; abortion (threatened, spontaneous, or induced); omission (or inadequate dosing) of appropriate Rh immunoprophylaxis following a potentially immunising obstetric event in a previous or current pregnancy; and multiparity.

Risk factors

Strong

history of an RhD-positive fetus in an RhD-negative mother

- RhD antigen is highly immunogenic. Only RhD-positive fetuses, from RhD-positive fathers, sensitise their RhD-negative mothers to produce anti-D antibodies.

fetomaternal haemorrhage

- Fetomaternal haemorrhage (FMH) is common and detectable in 65% of pregnancies either antenatally or in the early postnatal period.[17] RhD antigen is 50 times more immunogenic than other Rh antigens. Sensitisation of an RhD-negative mother with as little as 0.1 mL of RhD-positive fetal red blood cells (RBCs) may elicit a primary immune response.[23]

invasive fetal procedures

- Small amounts of FMH (>0.1 mL) are potentially immunising and occur in 2% of patients undergoing amniocentesis.[23] [24] The incidence of FMH at the time of chorionic villus sampling is about 14%.[25] Other invasive procedures, such as cordocentesis, can also cause FMH.

placental trauma

- Placental trauma of varying degrees may lead to sensitising FMH.

abortion

- An episode of threatened, spontaneous, or induced abortion can sensitise RhD-negative women, but the risk of RhD alloimmunisation is very low with pregnancy loss before 12 weeks' gestation.[27]

multiparity

- Although the primary maternal immune response to sensitisation by the D antigen is usually weak, it may be greatly enhanced when a secondary immune response is generated by antigenic challenge in a subsequent pregnancy. Hence, the risk for fetal anaemia and hydrops increases with increasing parity.[2] [26] [31]

omission of Rh immunoprophylaxis

- Omission (or inadequate dosing) of appropriate Rh immunoprophylaxis following potentially sensitising obstetric events, such as unrecognised FMH, in a previous or current pregnancy can lead to maternal sensitisation to the D antigen.

Weak

external cephalic version

- A meta-analysis of 17 studies found FMH (as detected by Kleihauer-Betke test) in 1% of women after external cephalic version.[22]

molar pregnancy

- Risk of RhD alloimmunisation is low in complete molar pregnancy because of absent or incomplete vascularisation of villi and absence of D antigen. Conversely, a partial mole should be viewed as a risk factor for sensitisation.[23][26] [29]

ectopic pregnancy

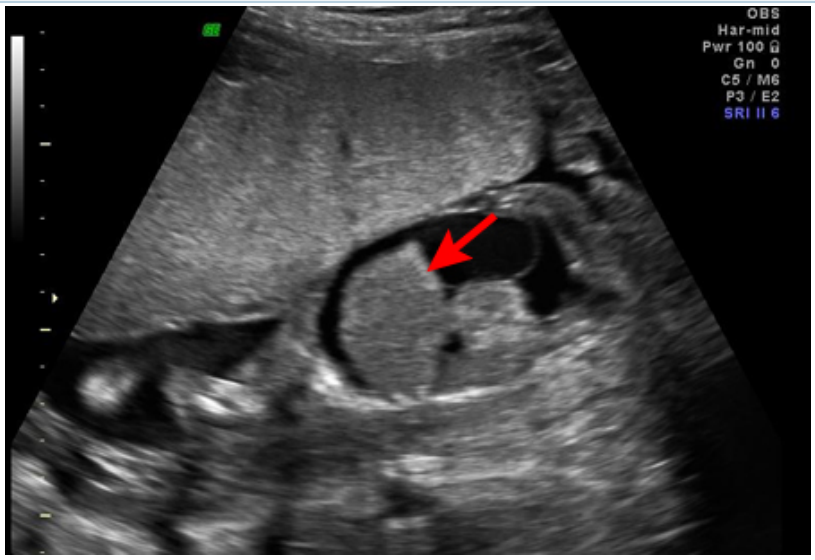
- Alloimmunisation has been reported after ectopic pregnancy, and 24% of patients with ruptured ectopic pregnancy have fetal RBCs detectable in the maternal circulation.[28]

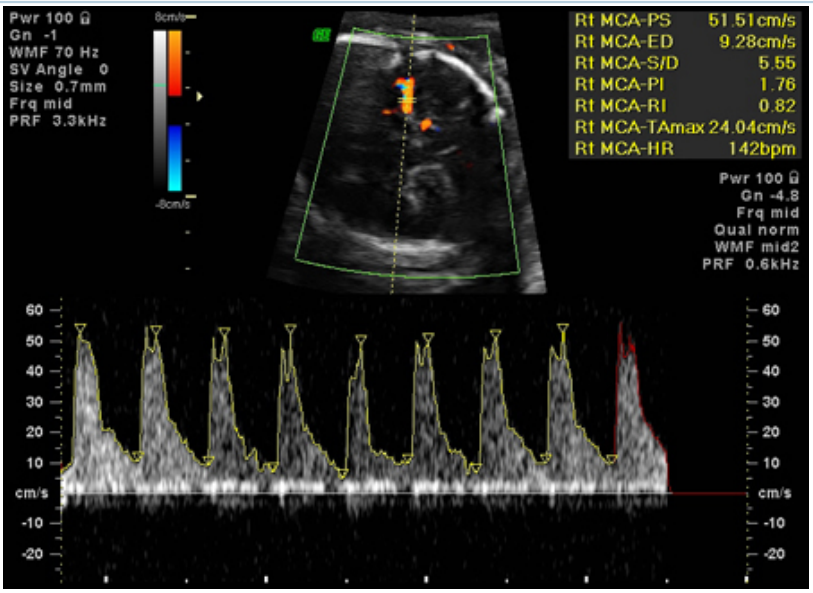
Investigations

1st test to order

Test	Result
maternal blood type • All Rh-negative pregnant women are at potential risk for alloimmunisation and erythroblastosis.	**Rh-negative**
maternal serum Rh antibody screen • Positive red blood cell antibody screen must prompt further investigation for possible alloimmunisation due to Rh antibodies.[16]	**positive screen**

Other tests to consider

Test	Result
maternal serum antibody titre • As methods vary between laboratories performing this test, each should report the titre below which severe fetal Rh incompatibility is unlikely and above which further investigations and monitoring are indicated.[38] • The maternal serum antibody titre is a guide to disease severity. The American College of Obstetricians and Gynecologists states that a critical titre (titre associated with a significant risk for severe haemolytic disease of the fetus and newborn, and hydrops) is considered to be between 1:8 and 1:32 in most centres.[34] If the initial antibody titre is 1:8 or less, the patient may be monitored with titre assessment every 4 weeks.[34] However, serial titres are not adequate for monitoring fetal status when the mother has had a previously affected fetus or neonate.[34]	**critical titre: between 1:8 and 1:32 (may vary among laboratories)**
paternal blood type • An Rh-positive partner of an Rh-negative mother creates blood group incompatibility in the fetus.	**Rh-positive**
paternal zygosity • Heterozygosity denotes a 50% risk of the offspring having an Rh-negative blood type and no risk of Rh incompatibility. Homozygosity denotes a 100% chance of an Rh-positive fetus, at risk of Rh incompatibility. Zygosity is determined by assay of plasma DNA in the case of RhD; serological testing of paternal red cells can be used for analysis of other red cell antigen systems.	**homozygous or heterozygous**
fetal ultrasound • Fluid in serous cavities of the fetus is easily detected with ultrasonography.[32] [37] [39] [40] • These findings are consistent with severe fetal anaemia in an affected fetus.[39]  *Fetal hydrops, with ascites and hepatomegaly (arrow) diagnosed on antenatal ultrasound* *The Ottawa Hospital; used with consent of the patient*	**may show subcutaneous oedema, ascites, pleural effusion, or pericardial effusion**

Test	Result
Doppler velocimetry of fetal middle cerebral artery (peak systolic velocity) • Measured Doppler sonography with estimation of peak systolic velocity in the fetal middle cerebral artery (MCA) can be used to predict moderate to severe anaemia in the fetus. MCA peak systolic velocity is increased in fetuses with significant anaemia. Elevated blood flow velocity for gestational age should prompt percutaneous umbilical blood sampling (if anaemia is strongly suspected).[37]  *Increased velocity in the middle cerebral artery consistent with severe fetal anaemia* *The Ottawa Hospital; used with consent of the patient*	**≥1.5 MoM**
fetal blood typing (from amniocentesis or maternal circulation) • If the father is heterozygous RhD-positive, or paternity is uncertain, the fetus' RhD type is determined by genetic testing of amniotic fluid cells or it can be estimated using cell-free fetal DNA in the maternal circulation.[35]	**Rh type**
direct assessment of fetal anaemia • Through umbilical cord venepuncture (cordocentesis) or the intrahepatic vein. • If fetal haemoglobin is within 20 g/L (2 g/dL) (i.e., 2 standard deviations) of gestational age norms and direct antiglobulin test is positive, the fetus is only mildly affected. Haemoglobin deficit of 20-70 g/L (2-7 g/dL) suggests moderate anaemia. Fetal anaemia is severe with haemoglobin deficits >70 g/L (>7 g/dL).	**fetal haemoglobin and haematocrit**
rosette test • A rosette test can be used to rule out significant fetomaternal haemorrhage.	**may be positive**
Kleihauer-Betke test/flow cytometry • Can measure the amount of fetal blood in the maternal circulation.	**variable**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Non-immune fetal hydrops	• Hydrops fetalis consists of generalised subcutaneous oedema and fluid collections in some or all serous cavities. • Placental calcification, oligohydramnios, and intrauterine growth restrictions may be associated with congenital infections.[40] [41]	• Maternal serum antibodies are negative in non-immune fetal hydrops. There are more than 80 causes of fetal hydrops. • Non-immune hydrops carries a high rate of infant mortality, and in many patients (17%) its cause remains indeterminate after diagnostic work-up.[39]
Parvovirus infection	• History of environmental exposure to parvovirus may arouse suspicion of possible infection in asymptomatic people. • Symptoms include maternal fever, myalgia, coryza, headache, nausea, and erythematous, maculopapular exanthema on the trunk and limbs. Arthropathy and arthritis are also common in women and adolescents. • Progressive fetal anaemia, due to preferential destruction of immature red blood cells (RBCs) by the virus, leads to hydrops and intrauterine fetal death.[31] [42]	• Viral-specific IgM appears about 10 to 12 days after infection. Fetal infection is confirmed by analysing amniotic fluid, cord blood, or serous fluid for viral DNA or RNA by polymerase chain reaction.[42]
Non-RhD haemolytic disease	• Usually transfusion-induced. The mechanism for fetal anaemia is haemolysis and erythroid suppression. • Prior obstetric history does not reliably predict occurrence in subsequent pregnancy, and maternal antibody titre does not correlate with severity.[2] • Kell alloimmunisation is the most common non-RhD haemolytic disease, with an incidence of 0.1% to 0.2% in the obstetric population.[2]	• Serum antibodies can be detected in the maternal blood. Although the titre is not as reliable as in RhD disease, severe disease is unusual with titres <1:32, with the exception of anti-Kell antibodies where significant fetal disease can occur at much lower titres. • Middle cerebral artery (MCA) Doppler should be performed and has been shown to be reliable for fetal anaemia detection. • Fetal haemoglobin should be assessed by cordocentesis when non-invasive

Condition	Differentiating signs / symptoms	Differentiating tests
		testing (MCA Doppler) is abnormal.[2]
Placental chorioangioma	• May be present in up to 1% of pregnancies.[31] • Large placental masses of ≥5 cm may produce complications such as fetal anaemia, hydrops, and polyhydramnios, and poor perinatal outcome.[31]	• A solid placental mass is detected by standard 2-dimensional sonography, and colour Doppler sonography reveals a pulsatile mass. • Maternal serum alpha-fetoprotein may be high in association with a placental chorioangioma. Doppler velocimetry of the MCA may be consistent with fetal anaemia.[43]
Fetomaternal haemorrhage	• Severe, acute fetomaternal haemorrhage may be entirely asymptomatic or manifest as a reduction in perceived fetal movements by the mother. Clinical symptoms are usually non-specific.	• Peak systolic velocity on MCA Doppler may be increased. • Kleihauer-Betke test (persistence of fetal RBCs in maternal serum after denaturation by strong acid) or flow cytometry is also helpful.[31]
Twin-twin transfusion syndrome (TTTS)	• Develops in association with monochorionic twin placentation, usually between 15 and 26 weeks' gestation. It is found in 5.5% to 17.5% of all monochorionic pregnancies.[44]	• Ultrasound findings include polyhydramnios in one twin (recipient), and amniotic sac and oligohydramnios in the other (donor). • Growth of fetuses is usually discordant.[44] • Hydrops may develop in later stages of the disease, usually in the recipient co-twin. • Perinatal mortality may reach 80% to 100% when untreated.[44]
Twin anaemia-polycythemia sequence (TAPS)	• Develops in monochorionic twins and is characterised by a large intertwin haemoglobin difference without the abnormal amniotic fluid seen in TTTS. • Results mainly due to slow intertwin blood transfusion leading to anaemia for the donor and polycythemia for the recipient. • Can occur spontaneously (3% to 5%) or after laser	• Absence of ultrasound finding of twin oligohydramnios (donor) and polyhydramnios (recipient) sequence. • Peak systolic velocity on MCA Doppler: donor >1.5 MoM (anaemia); recipient <1.0 MoM (polycythemia).

Condition	Differentiating signs / symptoms	Differentiating tests
	surgery for TTTS (2% to 13%).[45]	

Screening

At the first antenatal visit, ABO blood type, RhD type, and red blood cell (RBC)-antibody screening is recommended for all pregnant women.[23] [33] Repeated RhD-antibody testing for all unsensitised RhD-negative women is also recommended at 24-28 weeks' gestation, unless the biological father is known to be RhD-negative.[33]

Approach

The prevention of RhD sensitisation in Rh-negative mothers carrying an Rh-positive fetus is the primary management objective. It involves immunoprophylaxis via the administration of anti-D immunoglobulin (also known as Rho(D) immune globulin in some countries) to at-risk women.

If sensitisation does occur, the window for primary prevention is effectively closed and Rh immunoprophylaxis is no longer appropriate. Actions then involve fetal and maternal surveillance for, and management of, fetal anaemia or hydrops.

Prevention of RhD sensitisation

Immunoprophylaxis with anti-D immunoglobulin is highly effective in preventing sensitisation of Rh-negative mothers carrying an Rh-positive fetus.[23][26] [46] It has been instrumental in the dramatic reduction in death from Rh incompatibility. Anti-D immunoglobulin is a blood product containing a high titre of antibodies to Rh antigens of red blood cells. Its precise mechanism of action is unknown, but it may work by neutralising Rh-positive fetal red blood cells in the maternal blood, thus reducing the risk of sensitisation. Administration is efficacious by either the intramuscular or intravenous route.[47] Anti-Rh antibodies persist for more than 3 months after one dose.

A prerequisite for immunoprophylaxis is knowledge of the maternal rhesus status.[46] All pregnant women should be tested at the time of the first antenatal visit for RhD type, and screened for the presence of anti-D antibodies, to identify unsensitised RhD-negative patients who are potential candidates for immunoprophylaxis.[23] [46] Anti-D immunoglobulin is not given to an RhD-negative mother who is already sensitised to the RhD antigen.

Eligible candidates should receive routine ante- and postnatal administration of anti-D immunoglobulin, as described below. In addition, the risk of sensitisation can be reduced by administering anti-D immunoglobulin to women in situations in which fetomaternal haemorrhage (FMH) is likely, such as miscarriage, chorionic villus sampling, and amniocentesis.[7] Multiple clinical guidelines describing RhD sensitisation prevention strategies have been published, including those from the American College of Obstetricians and Gynecologists, and the International Federation of Gynecology and Obstetrics/ International Confederation of Midwives.[23] [46]

Routine postnatal administration of anti-D immunoglobulin

RhD sensitisation occurs in approximately 16% of pregnancies among RhD-negative women.[46] Postnatal administration of anti-D immunoglobulin reduces this risk to approximately 1.5%, and is the most effective intervention to prevent Rh incompatibility in subsequent pregnancies.[23] [46]

Following birth, newborns from RhD-negative women should have their Rh factor determined from umbilical-cord blood.[46] If the infant is confirmed to be RhD-positive, all RhD-negative women who are not known to be sensitised should receive anti-D immunoglobulin (intravenously or intramuscularly) within 72 hours of delivery.[23][29][46]

Guidelines vary on the dose of anti-D immunoglobulin that should be administered, and can depend on the size of the FMH, the brand of anti-D immunoglobulin used, and affordability.[46] A prophylactic dose of 1500 IU (equivalent to 300 micrograms) of anti-D immunoglobulin is commonly given in high-income countries and can prevent RhD sensitisation after exposure to up to 30 mL of RhD-positive fetal whole blood or 15 mL of fetal red cells.[23] [46] [48] On rare occasions, delivery-associated FMH may be greater

than 30 mL. Circumstances such as traumatic deliveries, caesarean sections, manual removal of the placenta, delivery of twins, and unexplained hydrops fetalis are more likely to be associated with a large FMH. Accordingly, several guidelines, including those from the American College of Obstetricians and Gynecologists, and from the British Society for Haematology, recommend that RhD-negative women who give birth to RhD-positive infants should undergo additional testing to assess the volume of FMH and guide the amount of anti-D immunoglobulin required to prevent sensitisation.[23][36] [49] However, at no time should anti-D immunoglobulin treatment be delayed pending the results of quantitative FMH testing.[50]

If anti-D immunoglobulin is not given within 72 hours of delivery, it should be given as soon as the need is recognised, for up to 28 days after delivery.[29]

Routine antenatal administration of anti-D immunoglobulin

Building on the efficacy of postnatal anti-D immunoglobulin administration, the risk of RhD sensitisation in Rh-negative women carrying an Rh-positive baby has been shown to be further reduced (to approximately 0.5%) by the introduction of routine antenatal administration.[46] [51]

Routine antenatal antibody screening should be obtained at 28 weeks of gestation before administration of anti-D immunoglobulin (to identify women who have become sensitised before 28 weeks of gestation).[23] [29][36] [52] If anti-D antibodies are identified, it should be determined whether this presence is immune-mediated or passive (e.g., as a result of previous anti-D immunoglobulin treatment). If RhD antibodies are passive, then the woman should continue to be offered prophylaxis with anti-D immunoglobulin; however, if they are present because of sensitisation, prophylaxis is not beneficial, and management should proceed in accordance with protocols for RhD-sensitised pregnancies.[23]

Prophylactic antenatal anti-D immunoglobulin should be offered to unsensitised RhD-negative women, whether the fetal blood type is unknown or known to be Rh-positive.[23] [29] The American College of Obstetricians and Gynecologists recommends that a single dose be offered at 28 weeks of gestation, while other guidelines recommend either a single dose at around 28 weeks, or two doses at around 28 and 34 weeks of gestation.[23] [29][36][46]

Non-invasive estimation of fetal Rh status is now possible via the analysis of cell-free DNA in maternal plasma, and this method may be acceptable for sensitised patients who refuse amniocentesis.[35] Some countries recommend employing this technique in the first trimester, to allow targeted antenatal RhD immunoprophylaxis (i.e., only where the fetus is RhD-positive); however, the American College of Obstetricians and Gynecologists does not recommend the routine use of this approach on the grounds of cost-effectiveness.[23] [46] When paternity is certain, rhesus testing of the baby's father may be offered as a means of determining fetal RhD status.[29] [35]

Routine antenatal anti-D immunoglobulin prophylaxis should be administered regardless of, and in addition to, any anti-D immunoglobulin that may have been given for a potentially sensitising event (see below).[36] In the past, it has been recommended that a second dose of anti-D immunoglobulin should be administered to women who have not given birth at 40 weeks; however, the current guidelines suggest that this is generally not required, provided that the antenatal injection was given no earlier than 28 weeks' gestation.[23] [29]

Administration of anti-D immunoglobulin following potentially sensitising events

In RhD-negative, previously unsensitised women, a variety of events associated with potential placental trauma or disruption of the fetomaternal interface can lead to sensitising FMH during pregnancy. Anti-D immunoglobulin can help minimise the risk of such sensitisation, and if indicated, should be administered as soon as possible after the event, ideally within 72 hours.[29] [36] If anti-D immunoglobulin is not given within 72 hours, it should be given as soon as the need is recognised, for up to 28 days after the potentially sensitising event.[29] For sensitising events occurring after 20 weeks of pregnancy, the magnitude of FMH should be assessed, and further doses of anti-D immunoglobulin administered if required.[36] [50]

Miscarriage/abortion and intrauterine fetal death

Guidelines for the administration of anti-D immunoglobulin following miscarriage/abortion vary and local protocols should be followed.[23][29] [36] [46] [50] [53] The American College of Obstetricians and Gynecologists states that in the case of spontaneous first-trimester miscarriage or abortion in RhD-negative women, the risk of sensitisation is very low so routine Rh testing and Rh immunoprophylaxis is not recommended. However, Rh testing and administration of anti-D immunoglobulin may be considered on an individual basis, according to patient preferences.[23] [27] It recommends that anti-D immunoglobulin should be given to unsensitised RhD-negative women who have a pregnancy termination (either medical or surgical); or who experience fetal death in the second or third trimester.[23] [27]

Guidelines from the International Federation of Gynecology and Obstetrics/International Confederation of Midwives note that because an intrauterine fetal death may have been caused by a large FMH, it may be useful to perform a Kleihauer–Betke test, to determine the size of the haemorrhage, and thus the dose of anti-D immunoglobulin needed.[46]

Ectopic pregnancy

Several guidelines recommend the administration of anti-D immunoglobulin for all cases of ectopic pregnancy in unsensitised RhD-negative women.[23][29] [46] However, in the UK, National Institute for Health and Care Excellence (NICE) guidelines recommend that anti-D immunoglobulin should only be administered to Rh-negative women who have surgical management of an ectopic pregnancy (and not those who have solely medical management).[53]

Molar pregnancy

In a complete molar pregnancy, sensitisation to RhD should not occur, due to the absence of fetal organ development. However, the situation is different in a partial molar pregnancy. Because differentiating between the forms of molar pregnancy may be difficult, it is generally advised to administer anti-D immunoglobulin to all unsensitised RhD-negative women with a molar pregnancy.[23] [46]

Invasive procedures (e.g., chorionic villus sampling, amniocentesis)

Most countries recommend administration of anti-D immunoglobulin following invasive diagnostic procedures, such as chorionic villus sampling or amniocentesis, in unsensitised RhD-negative women when the fetuses could be RhD-positive.[23][29] [36] [46]

Bleeding and abdominal trauma in pregnancy

Anti-D immunoglobulin is recommended for RhD-negative women who experience antenatal haemorrhage after 20 weeks of gestation; some guidelines also suggest anti-D immunoglobulin should be considered in certain cases of bleeding earlier in gestation.[23][36] [46]

Anti-D immunoglobulin should be administered to RhD-negative women who have experienced abdominal trauma.[23][29] [36] [46]

Quantitative testing for FMH may be considered following events potentially associated with placental trauma and disruption of the fetomaternal interface (e.g., placental abruption, blunt trauma to the abdomen, cordocentesis, placenta praevia with bleeding).[29] There is a substantial risk of FMH over 30 mL with such events.[29]

External cephalic version in breech presentation

Some guidelines recommend administration of anti-D immunoglobulin for unsensitised RhD-negative patients following external cephalic version.[23] [29] [36] Quantitative testing for FMH may also be considered.[29]

Verbal or written consent must be obtained prior to administration of anti-D immunoglobulin.

Management following RhD sensitisation

If antibody screening identifies anti-D antibodies in an RhD-negative pregnant woman, and assessments conclude that their presence is active, not passive, the patient should be considered sensitised, and specialist obstetric advice should be sought.[50] Rh immunoprophylaxis is no longer given.[34] Fortunately, initial sensitisation in a first affected pregnancy is often mild.

The initial management of an RhD-sensitised pregnancy involves the determination of the paternal rhesus status. If paternity is certain, and the father is RhD-negative, no further assessment/intervention is necessary. All children from a homozygous RhD-positive father, and 50% from a heterozygous RhD-positive father, will be RhD-positive.[34] In the case of a heterozygous RhD-positive, or unknown, paternal genotype, the fetal antigen type should be assessed (by amniocentesis or non-invasive analysis of maternal blood).[34] In the case of an RhD-positive fetus, management involves fetal and maternal surveillance for signs of fetal anaemia and hydrops.

Quantitation of maternal antibody titre is performed serially to document worsening disease and identify the need for additional fetal testing and/or treatment. The American College of Obstetricians and Gynecologists states that a critical titre (titre associated with a significant risk for severe haemolytic disease of the fetus and newborn, and hydrops) is considered to be between 1:8 and 1:32 in most centres.[34] If the initial antibody titre is 1:8 or less, the patient may be monitored with titre assessment every 4 weeks.[34] However, serial titres are not adequate for monitoring fetal status when the mother has had a previously affected fetus or neonate.[34] In the UK, the Royal College of Obstetricians and Gynaecologists recommends anti-D antibodies should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery, and referral to a fetal medicine specialist should occur if there are rising antibody levels, if the level reaches the specific threshold of >4 IU/mL, or if ultrasound features are suggestive of fetal anaemia.[52]

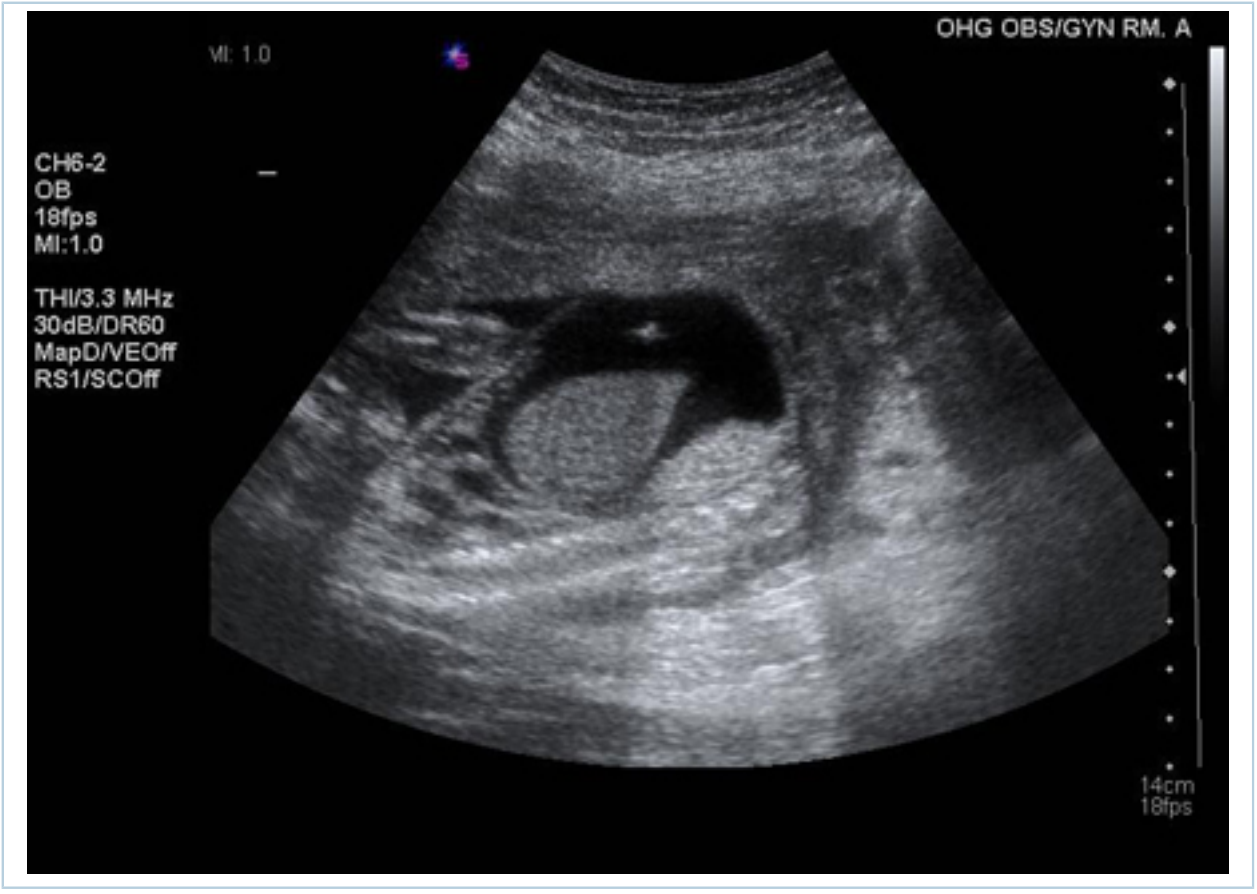
In a centre with trained personnel and when the fetus is at an appropriate gestational age, Doppler measurement of peak systolic velocity in the fetal middle cerebral artery is an appropriate non-invasive means to monitor pregnancies complicated by RhD sensitisation.[34] Fetal ultrasound assessment is also employed.

Most cases of rhesus sensitisation causing serious haemolytic disease in the fetus are the result of incompatibility with respect to the D antigen.[34] However, over 30 antigenic variants have been identified, and care of patients with sensitisation to non-RhD antigens that are known to cause haemolytic disease should be the same as that for patients with D sensitisation.[34] A possible exception is Kell sensitisation.[34]

Fetal therapy

The goal of fetal therapy is to correct severe anaemia, ameliorate tissue hypoxia, prevent (or reverse) fetal hydrops, and avoid fetal death.

If fetal blood is Rh-negative, or if middle cerebral artery blood flow or amniotic bilirubin levels remain normal in an Rh-positive fetus, the pregnancy can continue to term untreated. If fetal blood is Rh-positive or of unknown Rh status, and middle cerebral artery flow or amniotic bilirubin levels are elevated, suggesting fetal anaemia, the fetus can be given intravascular intrauterine blood transfusions by a specialist at an institution equipped to care for high-risk pregnancies.



Intraperitoneal transfusion; the echogenic needle tip is visualised in the pocket of ascites

The Ottawa Hospital; used with consent of the patient

Neonatal therapy

Neonates with erythroblastosis are immediately evaluated by a paediatrician to determine the need for exchange transfusion, phototherapy, or intravenous immunoglobulin (IVIG). IVIG is used in some clinical practice as it has been shown to reduce the need for exchange transfusion in neonates with proven haemolytic disease due to Rh and/or ABO incompatibility and to decrease the duration of hospitalisation

and phototherapy.[54] [55] However, there is an overall lack of evidence to support its use for the treatment of alloimmune haemolytic disease.[56] [57] [Evidence C]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial (summary)		
unsensitised RhD-negative mother		
	1st	**anti-D immunoglobulin**
sensitising event: miscarriage/abortion and intrauterine fetal death	**plus**	**additional anti-D immunoglobulin**
sensitising event: ectopic pregnancy	**plus**	**additional anti-D immunoglobulin**
sensitising event: molar pregnancy	**plus**	**additional anti-D immunoglobulin**
sensitising event: invasive procedures (e.g., chorionic villus sampling, amniocentesis)	**plus**	**additional anti-D immunoglobulin**
sensitising event: bleeding/abdominal trauma in pregnancy	**plus**	**additional anti-D immunoglobulin**
sensitising event: external cephalic version in breech presentation	**plus**	**additional anti-D immunoglobulin**
sensitised RhD-negative mother		
	1st	**seek specialist obstetric advice**

Acute (summary)		
neonate with erythroblastosis		
	1st	**paediatric evaluation**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

unsensitised RhD-negative mother

unsensitised RhD-negative mother — **1st** — **anti-D immunoglobulin**

Primary options

» anti-D immunoglobulin: consult specialist for guidance on dose

» Routine antenatal administration: anti-D immunoglobulin (also known as Rho(D) immune globulin in some countries) administered whether fetal blood type is unknown, or known to be RhD-positive. Single dose at 28 weeks' gestation (either intravenously or intramuscularly).[23] Some guidelines recommend a single dose at around 28 weeks, or two doses at around 28 and 34 weeks of gestation.[29] [36] [46]

» Routine postnatal administration: anti-D immunoglobulin administered (either intravenously or intramuscularly) in women who have given birth to Rh-positive infants within 72 hours of delivery.[23][29] [46] The size of fetomaternal haemorrhage should be assessed, and further doses of anti-D immunoglobulin administered if required.[23] [36]

» The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

sensitising event: miscarriage/abortion and intrauterine fetal death — **plus** — **additional anti-D immunoglobulin**

Treatment recommended for ALL patients in selected patient group

Primary options

» anti-D immunoglobulin: consult specialist for guidance on dose

» Additional anti-D immunoglobulin administration should not be given routinely following spontaneous miscarriage or abortion in the first trimester.[23] However, it may be considered on an individual basis, according to patient preferences.[23] [27]

» Anti-D immunoglobulin administration is recommended following pregnancy termination (either medical or surgical); or fetal death in the second or third trimester.[23] [27]

Initial

» Dose should be given within 72 hours of occurrence.[29] [36] The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

» For sensitising events occurring after 20 weeks of pregnancy, size of fetomaternal haemorrhage should be assessed, and further doses of anti-D immunoglobulin administered if required.[36] [50]

» Guidelines for anti-D immunoglobulin administration vary; follow local protocols.

sensitising event: ectopic pregnancy **plus** **additional anti-D immunoglobulin**

Treatment recommended for ALL patients in selected patient group

Primary options

» anti-D immunoglobulin: consult specialist for guidance on dose

» Additional anti-D immunoglobulin administration is recommended following all cases of ectopic pregnancy.[23] UK guidelines recommend that anti-D immunoglobulin should only be administered to Rh-negative women who have surgical management of an ectopic pregnancy (and not those who have solely medical management).[53]

» Dose should be given within 72 hours of identification.[23] [29] [36] The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

» Guidelines for anti-D immunoglobulin administration vary; follow local protocols.

sensitising event: molar pregnancy **plus** **additional anti-D immunoglobulin**

Treatment recommended for ALL patients in selected patient group

Primary options

» anti-D immunoglobulin: consult specialist for guidance on dose

» Additional anti-D immunoglobulin is advised to be administered in all molar pregnancies (due to the difficulty in differentiating between complete and partial forms).[23] [46]

» Dose should be given within 72 hours of identification.[29] [36] The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

Initial

sensitising event: invasive procedures (e.g., chorionic villus sampling, amniocentesis) **plus** **additional anti-D immunoglobulin**

Treatment recommended for ALL patients in selected patient group

Primary options

» anti-D immunoglobulin: consult specialist for guidance on dose

» Additional anti-D immunoglobulin administration is recommended following invasive diagnostic procedures such as chorionic villus sampling or amniocentesis.[23]

» Dose should be given within 72 hours of occurrence.[29] [36] The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

» If carried out after 20 weeks of pregnancy, size of fetomaternal haemorrhage should be assessed, and further doses of anti-D immunoglobulin administered if required.[36] [50]

sensitising event: bleeding/abdominal trauma in pregnancy **plus** **additional anti-D immunoglobulin**

Treatment recommended for ALL patients in selected patient group

Primary options

» anti-D immunoglobulin: consult specialist for guidance on dose

» Additional anti-D immunoglobulin is recommended for antenatal haemorrhage after 20 weeks of gestation, and abdominal trauma.[23]

» Dose should be given within 72 hours of occurrence.[29] [36] The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

» Consider quantitative testing for fetomaternal haemorrhage following events occurring after 20 weeks, or those potentially associated with placental trauma and disruption of the fetomaternal interface (e.g., placental abruption, blunt trauma to the abdomen, cordocentesis, placenta praevia with bleeding).[29] Administer further doses of anti-D immunoglobulin if required.[36]

sensitising event: external cephalic version in breech presentation **plus** **additional anti-D immunoglobulin**

Treatment recommended for ALL patients in selected patient group

Primary options

Initial

» anti-D immunoglobulin: consult specialist for guidance on dose

» Additional anti-D immunoglobulin administration is recommended following external cephalic version.[23] Quantitative testing for fetomaternal haemorrhage may also be considered.[29]

» Dose should be given within 72 hours of occurrence.[29] [36] The dose can vary depending on local guidelines, and factors such as brand of anti-D immunoglobulin.

sensitised RhD-negative mother

1st **seek specialist obstetric advice**

» If antibody screening identifies anti-D antibodies in an RhD-negative pregnant woman, and assessments conclude that their presence is active, not passive, the patient should be considered sensitised, and specialist obstetric advice should be sought.[50] Rh immunoprophylaxis is no longer given.[34]

» The initial management of an RhD-sensitised pregnancy involves the determination of the paternal rhesus status. If paternity is certain, and the father is RhD-negative, no further assessment/intervention is necessary. All children from a homozygous RhD-positive father will be RhD-positive, and there is a 50% risk of children from a heterozygous RhD-positive father being RhD-positive.[34] In the case of a heterozygous RhD-positive, or unknown, paternal genotype, the fetal antigen type should be assessed (by genetic testing of amniotic fluid cells or using cell-free fetal DNA in the maternal circulation).[34] [35] In the case of an RhD-positive fetus, management involves fetal and maternal surveillance for signs of fetal anaemia and hydrops.

» Quantitation of maternal antibody titre is performed serially to document worsening disease and identify the need for additional fetal testing and/or treatment. The American College of Obstetricians and Gynecologists states that a critical titre (titre associated with a significant risk for severe haemolytic disease of the fetus and newborn, and hydrops) is considered to be between 1:8 and 1:32 in most centres.[34] If the initial antibody titre is 1:8 or less, the patient may be monitored with titre assessment every 4 weeks.[34] However, serial titres are not adequate for monitoring fetal status when the mother has had a previously affected fetus or

Initial

neonate.[34] In the UK, the Royal College of Obstetricians and Gynaecologists recommends anti-D antibodies should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery, and referral to a fetal medicine specialist should occur if there are rising antibody levels, if the level reaches the specific threshold of >4 IU/mL, or if ultrasound features are suggestive of fetal anaemia.[52]

» In a centre with trained personnel and when the fetus is at an appropriate gestational age, Doppler measurement of peak systolic velocity in the fetal middle cerebral artery is an appropriate non-invasive means to monitor pregnancies complicated by RhD sensitisation.[34] Fetal ultrasound assessment is also employed.

» The goal of fetal therapy is to correct severe anaemia, ameliorate tissue hypoxia, prevent (or reverse) fetal hydrops, and avoid fetal death.

» If fetal middle cerebral artery flow or amniotic bilirubin levels are elevated, suggesting fetal anaemia, the fetus can be given intravascular intrauterine blood transfusions by a specialist at an institution equipped to care for high-risk pregnancies.

Acute

neonate with erythroblastosis

1st **paediatric evaluation**

Primary options

» normal immunoglobulin human: consult specialist for guidance on dose

» Neonates with erythroblastosis are immediately evaluated by a paediatrician to determine the need for exchange transfusion, phototherapy, or intravenous immunoglobulin.

MANAGEMENT

Emerging

Nipocalimab

Nipocalimab is a next-generation Fc receptor inhibitor, inhibiting immunoglobulin G (IgG) transport across the placenta (including the transfer of anti-red cell alloantibodies). A multicentre phase 2 study is ongoing to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of nipocalimab in pregnant women at high risk for early onset severe haemolytic disease of the fetus and newborn.[58] Nipocalimab has been granted rare paediatric disease designation and orphan drug designation by the US Food and Drug Administration for the prevention of haemolytic disease of the fetus and newborn.

Maternal therapy with plasmapheresis and/or intravenous immunoglobulin (IVIG)

Limited data, including isolated case reports, have supported the use of maternal plasmapheresis and/or IVIG in severe cases of maternal alloimmunisation in early gestation to reduce maternal antibody load and temporise, until a time in gestational age when intravascular fetal transfusion can be safely accomplished (i.e., >20 weeks). Limited reports of direct fetal treatment with IVIG suggest a possible role for this approach in selected patients.[59] [60] [61]

Patient discussions

Mothers should be counselled regarding the importance of fetal movement as a screening tool for fetal health and of decreased fetal movement as a symptom of developing fetal hydrops.

FOLLOW UP

Monitoring

Monitoring

Patients should be instructed about the need for monitoring the neonate and infant for signs and symptoms of anaemia. Infants affected by Rh incompatibility, even those successfully treated in utero, may develop late anaemia commencing 1 week to 3 months after birth, due to the continued presence of circulating antibody-coated fetal red blood cells that continue to be haemolysed. The importance of neonatal follow-up cannot be overemphasised, with assessments of the infant's haemoglobin once or twice a week until 3 months of life.[63]

Complications

Complications	Timeframe	Likelihood
hyperbilirubinaemia and kernicterus	**short term**	**high**
Encephalopathy, athetoid cerebral palsy, and/or sensorineural deafness may result from deposition of bilirubin into the basal ganglia. Postnatal treatment consists of intensive phototherapy and exchange transfusions to reduce bilirubin levels and prevent kernicterus.		
transfusion-related fetal bradycardia	**short term**	**low**
The most common complication of intrauterine transfusion is fetal bradycardia during transfusion (8%).[65] Fetal bradycardia and vasospasm are more frequent when accidental intra-arterial transfusion is given. Immediate interruption of the transfusion is therapeutic in most cases.		
transfusion-related neurodevelopmental abnormalities	**long term**	**low**
Although short-term neurological outcome is normal in >90% of infants, neurodevelopmental abnormalities have been reported in a few studies with small patient numbers.[63] In one study, 4.8% of the children treated by intrauterine transfusion developed neurodevelopmental impairment. Fetal hydrops was the strongest predictor for impaired outcome.[66]		
fetal and neonatal hydrops	**variable**	**high**
Hydrops fetalis is defined as abnormal accumulation of fluid in two or more fetal compartments. It is a major fetal complication in RhD disease that will develop when a haemoglobin deficit of 70 g/L (7 g/dL) is exceeded. Hydrops fetalis is diagnosed with ultrasound. Intrauterine fetal transfusion is life-saving and can reverse fetal hydrops. Cardiac decompensation is often seen in hydrops.[63] Perinatal mortality in fetal hydrops is 50%.[64]		
neonatal anaemia	**variable**	**high**
Characterised by reduced reticulocyte count and low serum erythropoietin levels. Diagnosed when haemoglobin falls <8 g/dL and is treated with transfusion. Erythropoietin has been used to prevent anaemia and reduce transfusions. Iron supplementation is not recommended.[63]		

Prognosis

Without immunoprophylaxis, haemolytic disease of the newborn recurs in 88% of pregnancies where the fetus is Rh-positive.[62]

Diagnostic guidelines

United Kingdom

High-throughput non-invasive prenatal testing for fetal RHD genotype (https://www.nice.org.uk/guidance/dg25)

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Treatment guidelines

United Kingdom

Ectopic pregnancy and miscarriage: diagnosis and initial management (https://www.nice.org.uk/guidance/ng126)

Published by: National Institute for Health and Care Excellence **Last published:** 2023

Blood transfusions in obstetrics (Green-top guideline no. 47) (https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines)

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2015

The management of women with red cell antibodies during pregnancy (Green-top guideline no. 65) (https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines)

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2014

BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn (https://b-s-h.org.uk/guidelines/?category=Transfusion&fromdate=&todate=)

Published by: British Committee for Standards in Haematology **Last published:** 2014 (updated 2023)

Routine antenatal anti-D prophylaxis for women who are rhesus D negative (https://www.nice.org.uk/guidance/TA156)

Published by: National Institute for Health and Care Excellence **Last published:** 2008

International

FIGO/ICM guidelines for preventing Rhesus disease: a call to action (https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.13459)

Published by: International Federation of Gynecology and Obstetrics; International Confederation of Midwives; Worldwide Initiative for Rhesus Disease Eradication **Last published:** 2021

North America

ACOG clinical practice update: paternal and fetal genotyping in the management of alloimmunization in pregnancy (https://www.acog.org/clinical)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2024

ACOG clinical practice update: Rh D immune globulin administration after abortion of pregnancy loss at less than 12 weeks of gestation (https://www.acog.org/clinical)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2024

Prevention of Rh alloimmunisation (https://www.jogc.com/article/S1701-2163(17)31111-8/fulltext)

Published by: Society of Obstetricians and Gynaecologists of Canada **Last published:** 2018

ACOG practice bulletin no. 192: management of alloimmunization during pregnancy (https://www.acog.org/clinical)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2018 (reaffirmed 2024)

ACOG practice bulletin no. 181: prevention of Rh D alloimmunization (https://www.acog.org/clinical)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2017 (reaffirmed 2024)

Red blood cell transfusions in newborn infants (https://www.cps.ca/en/documents/authors-auteurs/fetus-and-newborn-committee)

Published by: Canadian Paediatric Society **Last published:** 2014 (reaffirmed 2020)

Oceania

Prophylactic use of RhD immunoglobulin in pregnancy care (https://www.blood.gov.au/anti-d-0)

Published by: Royal Australian and New Zealand College of Obstetricians and Gynaecologists; National Blood Authority, Australia **Last published:** 2021

EVIDENCE TABLES

Evidence tables

What are the benefits and harms of immunoglobulin for neonates with alloimmune haemolytic disease/jaundice?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.2095/full)

Evidence C *

Confidence in the evidence is very low or low where GRADE has been performed and the intervention may be more effective/beneficial than the comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Newborn infants with alloimmune haemolytic disease
Intervention: Intravenous immunoglobulin (IVIG)
Comparison: Placebo or no treatment

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Use of exchange transfusion	Favours intervention	Very Low
Exchange transfusions per infant	Favours intervention	Very low
Use of top-up transfusion (in first week)	No statistically significant difference	Low
Use of top-up transfusion (after first week)	No statistically significant difference	Very low
Top-up transfusions per infant (in first week and after first week)	No statistically significant difference	GRADE assessment not performed for this outcome
Maximum total serum bilirubin	Favours intervention	Very low
Duration of phototherapy	Favours intervention	GRADE assessment not performed for this outcome
Longer-term neurological outcomes (1 to > 2 years)	See note [a]	GRADE assessment not performed for this outcome
Adverse effects	See note [b]	GRADE assessment not performed for this outcome

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Neonatal mortality	-	None of the studies identified by the review assessed this outcome

Note
The Cochrane review which underpins this Cochrane Clinical Answer (CCA) stated that the methods of only two of the nine included studies were robust enough to guide routine clinical practice, and that the quality of the evidence as assessed by GRADE was all low to very low. Therefore, they concluded that there is insufficient evidence to support the routine use of IVIG in infants with alloimmune haemolytic disease.

[a] Results reported narratively; two RCTs (204 infants) reported no cases of kernicterus, deafness or cerebral palsy, while a third RCT (80 infants) reported that neurodevelopmental outcome at aged ≥ 2 years was the same in those treated with IVIG and those treated with placebo.

[b] Results reported narratively; no adverse effects were reported in the IVIG group (9 RCTs; 658 infants). Sixteen infants across 6 RCTs were reported to have hypoglycaemia, hypocalcaemia, sepsis (with or without brain abscess), and inspissated bile syndrome, due to exchange transfusion.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

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Images

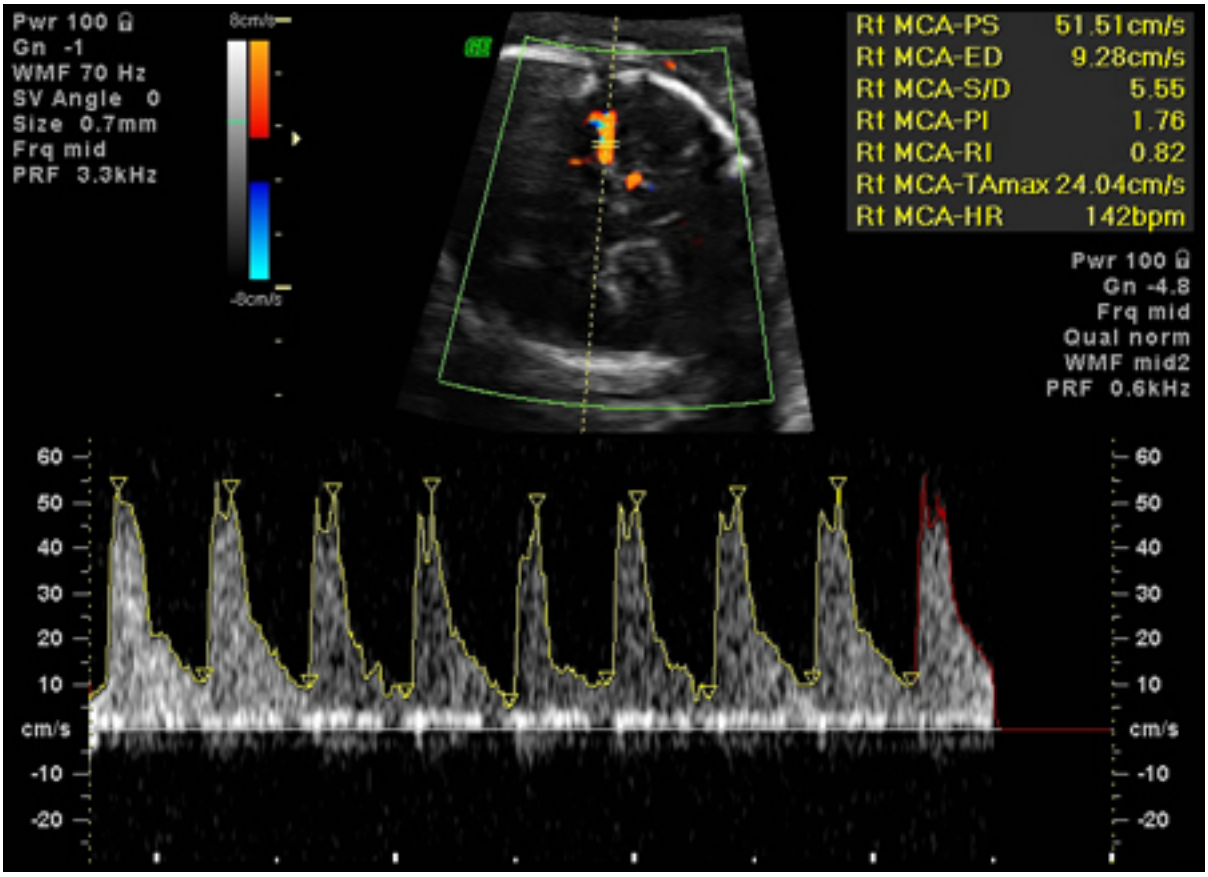

Figure 1: Increased velocity in the middle cerebral artery consistent with severe fetal anaemia

The Ottawa Hospital; used with consent of the patient

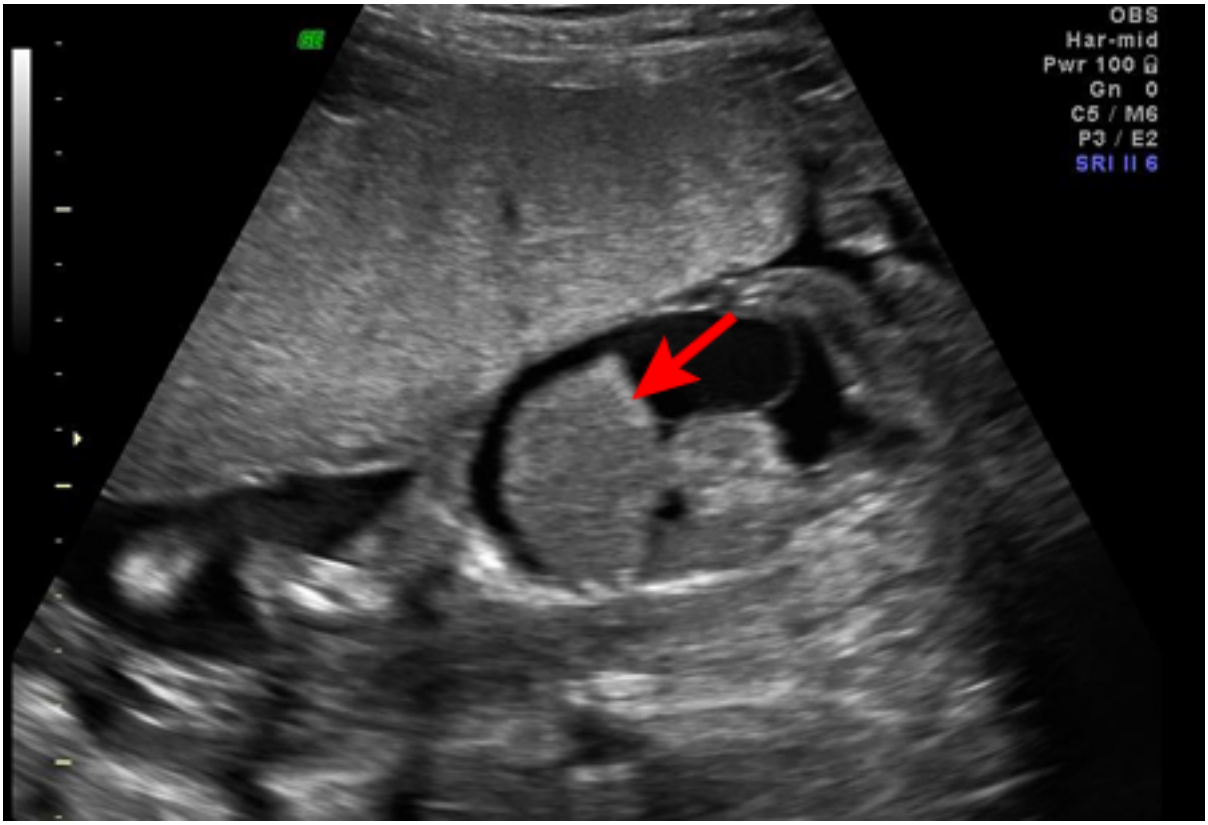

Figure 2: Fetal hydrops, with ascites and hepatomegaly (arrow) diagnosed on antenatal ultrasound

The Ottawa Hospital; used with consent of the patient

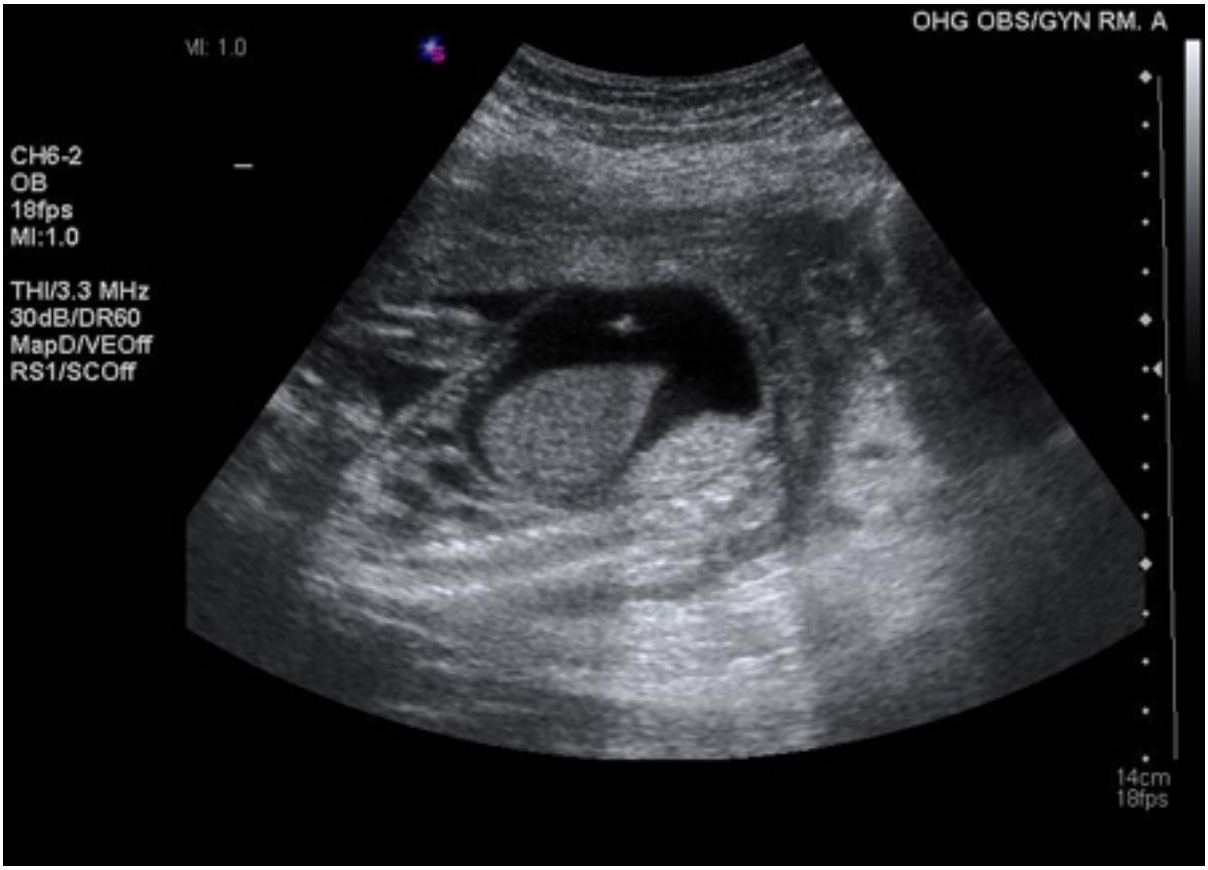

Figure 3: Intraperitoneal transfusion; the echogenic needle tip is visualised in the pocket of ascites

The Ottawa Hospital; used with consent of the patient

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Figure 1 – BMJ Best Practice Numeral Style

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