Congenital Disorders

Background information on Rhesus D Haemolytic Disease of the newborn and the impact of interventions

This document gives a brief overview about the condition, its epidemiology and specific interventions that may reduce its burden.

What is Rhesus D Haemolytic Disease of the newborn?

Haemolytic disease of the newborn is a potentially life-threatening disorder in the fetus or newborn. The risk of occurrence is increased in those pregnancies where the maternal and fetal blood groups (ABO, Rhesus (Rh) or Kell systems) are incompatible. Maternal and fetal blood group incompatibility can lead to the development of an alloimmune condition in the fetus. This usually occurs when a woman becomes sensitized to particular antigens present on red blood cells and produces IgG antibodies that may attack red blood cells in fetal circulation. Primary sensitisation can occur as a result of feto-maternal haemorrhage during pregnancy (e.g. during birth or as a result of invasive procedures) or inadvertently as a result of therapeutic blood transfusion (e.g. where blood typing to check compatibility has not been performed). Primary sensitisation has no adverse effects on health for the mother and in most cases does not affect the pregnancy. However, exposure to the same antigens in subsequent pregnancies leads to a rapid immune response (secondary sensitisation) which can result in miscarriage, stillbirth or haemolytic disease depending on the strength of the immune response.

Most of this document deals with rhesus haemolytic disease (RHD). The condition can range from mild to severe, with some cases presenting with no symptoms and others resulting in death. RhD incompatibility resulting in neonatal jaundice can lead to kernicterus and brain damage if not treated promptly; risk of developing cerebral palsy is also associated with RhD incompatibility.

What are the main risk factors?

The Rh blood group system consists of several antigens; however, the D antigen is most commonly associated with RHD and affects RhD positive infants born to RhD negative mothers. Other antigens in this system associated with RHD include Rhc, RhC, RhE and Rhe.

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Risk of RHD occurs when a RhD negative woman becomes sensitized to particular antigens present on fetal red blood cells during pregnancy. Primary sensitisation can occur as a result of feto-maternal haemorrhage, such as during birth or as a result of blood transfusion. However, not all RhD negative women who are exposed to RhD-positive blood become sensitised. This is influenced by a number of factors including the volume of fetal blood entering the mother's circulation, the mother's immune response and the fetus' blood type. The risk of primary sensitisation is less if the mother and fetus are ABO-incompatible (risk of sensitisation 2% as opposed to 16% for RhD)[1]. The risk of sensitisation is usually greatest in the first pregnancy and reduces with each subsequent pregnancy; however, once sensitisation has occurred it is not reversible. The risk of disease increases with the number of Rh positive pregnancies, with further pregnancies tending to cause worsening disease.

Global epidemiology

Population prevalence of blood groups

Ethnic groups vary in terms of the population frequencies of different blood groups[2]. For example, the RhD negative phenotype is more common in Caucasian populations (15%), and less frequent in those of African (approximately 5%) and East Asian ancestry (0.3%).

Incidence of RHD

The incidence of RHD is influenced by a number of factors, such as the frequency of RhD negativity in the population, number of births and access to anti-D prophylaxis. With respect to RhD, the low prevalence of the negative phenotype in some populations means that there are fewer women at risk of sensitisation. However, these women are also at higher risk of having a RhD positive partner, as this is the more common phenotype in the population. The risk of a RhD-positive fetus is further determined by paternal heterozygosity. Of individuals who are Rh positive, 45% are homozygous (CDe/CDe), and 55% are heterozygous (CDe/cde) for the *RhD* gene[1].

Clinical outcomes

Mortality, disability and quality of life

Prenatal anti-D prophylaxis for all Rh- women has been shown to be effective at reducing incidence of sensitisation and subsequently RHD. Outcomes in neonates affected by RHD can vary; those with mild disease can be treated effectively by phototherapy and have normal development. The outcomes in those with more severe disease depend on the time-point at which diagnosis was achieved and treatment initiated, as well as the quality of on-going care. Severe cases can present *in utero* and failure to initiate early treatment can result in perinatal mortality. However even those that survive or are treated early may be affected with impaired neurodevelopment (of varying degrees) or severe brain damage.

[1] Pilgrim H, Lloyd-Jones M, Rees A. Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation. *Health Technol Assess* 2009; 13(10):iii, ix-iii,103.
[2] Moise KJ. Fetal anemia due to non-Rhesus-D red-cell alloimmunization. *Semin Fetal Neonatal Med* 2008; 13(4):207-214.

Reducing prevalence, morbidity and mortality

Reducing birth prevalence depends on identifying at risk mothers and providing information on risk and on options available for reducing it (such as anti-D prophylaxis). Figure 1 illustrates the determinants and interventions for RHD as they relate to key stages in life. The main specific interventions are briefly discussed below.

Interventions before pregnancy

Blood typing of women of reproductive age or those planning a pregnancy and awareness raising can help inform people of their risks and possible mechanisms through which sensitisation can occur. In addition, knowledge of previous sensitisation events in RhD negative women can help with management of the pregnancy (e.g. monitoring maternal antibody titres).

Interventions during pregnancy

These involve either prenatal anti-D prophylaxis (administration of anti-D immunoglobulins, which act by destroying RhD positive bloods cells in circulation) for women who have not been sensitised or appropriate management of the pregnancy in those that have. Testing for anti-D can be done, for example at prenatal booking, 28 and 36 weeks.

The dosage and timing of prophylaxis is dependent on the preparation of anti-D that is used (e.g. intravenous or intramuscular) and its purpose (e.g. prior to or after a sensitising event). Routine prenatal prophylaxis is usually given prenatally at several time points, however, treatment is also indicated after other primary sensitising events such as abortion, miscarriage, amniocentesis, ectopic pregnancy and abdominal trauma. Interventions during pregnancy in those women who have become sensitised include monitoring maternal antibody titres and assessment of the fetus for signs of RHD. Severe cases of RHD can present *in utero* with anaemia, hydrops and intrauterine death. Intrauterine transfusion (IUT) can be used to treat *in utero* cases, with overall survival potentially as high as 86-90%. However, survival will depend on the severity of the condition and timeliness and effectiveness of IUT.

Interventions after birth

Diagnosis shortly after birth allows appropriate care to be planned and put in place, leading to increased survival and reduced disability. Mild cases of RHD present with mild jaundice that can be treated with phototherapy. Blood transfusion and exchange transfusion may be required in severe cases with significant anaemia and persistent hyperbilirubinaemia. If left untreated, RHD can lead to permanent brain damage, development of kernicterus and death in 70% of cases.

Cost-effectiveness of interventions

The cost-effectiveness will depend largely on the care pathway that is chosen, Figure 2 outlines some of the various options for a screening and prophylaxis programme. The cost-effectiveness when evaluated from an UK NHS perspective suggests that routine prenatal anti-D prophylaxis given to all RhD negative women is likely to be cost-effective at a threshold of around £30,000 per QALY gained. However, prior to adoption of prenatal anti-D prophylaxis, consideration must be given to the cost of prophylaxis as well as the cost of care for women who become sensitised and the subsequent care of affected infants as well as the local supply of anti-D. In the UK, the costs of anti-D prophylaxis per vial can vary from

£27.00-£313.50 depending on the preparation and does not include the cost of administration.

Issues of cost-effectiveness are quite specific to each country as costs can vary tremendously and are dependent on patient numbers. For cost-effectiveness cut-off points for different regions of the world, go to the following website http://www.who.int/choice/costs/CER_levels/en/index.html, and for costs for specific items by region and county, go to http://www.who.int/choice/costs/en/.

What are the main ethical legal and social issues (ELSI) to consider?

Providing safe and effective care

Reducing the incidence of rhesus haemolytic disease in the newborn requires a screening programme to identify those women at risk as well as the availability of prenatal anti-D prophylaxis. The provision of a screening programme and the offer of prophylaxis may be constrained by limited resources especially as anti-D prophylaxis requires the use of blood products and in some countries it might be difficult to ensure a reliable and safe source anti-D. This combined with the cost of therapy, may pose difficult questions for health services: how should screening strategies be implemented? Where resources are limited (such as the availability of anti-D supplies) how are resources to be distributed? Who should bear the cost of providing screening, services and treatment? These problems may be exacerbated in countries where the prevalence of the RhD negative phenotype is low and therefore the burden of disease is not perceived to be high.

Providing appropriate support for those with disabilities

Those with severe RHD disease may be very disabled if treatment is not prompt or fully effective; therefore there is a need to provide appropriate social support for affected individuals.

KEY REFERENCES

Pilgrim H, Lloyd-Jones M, Rees A. Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation. *Health Technol Assess* 2009; 13(10):iii, ix-iii,103.

Smits-Wintjens VE, Walther FJ, Lopriore E. Rhesus haemolytic disease of the newborn: Postnatal management, associated morbidity and long-term outcome. *Semin Fetal Neonatal Med*. 2008; 13(4):265-71.

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RELATED TOPICS

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Health services

Figure 1: Needs assessment flowchart for haemolytic disease

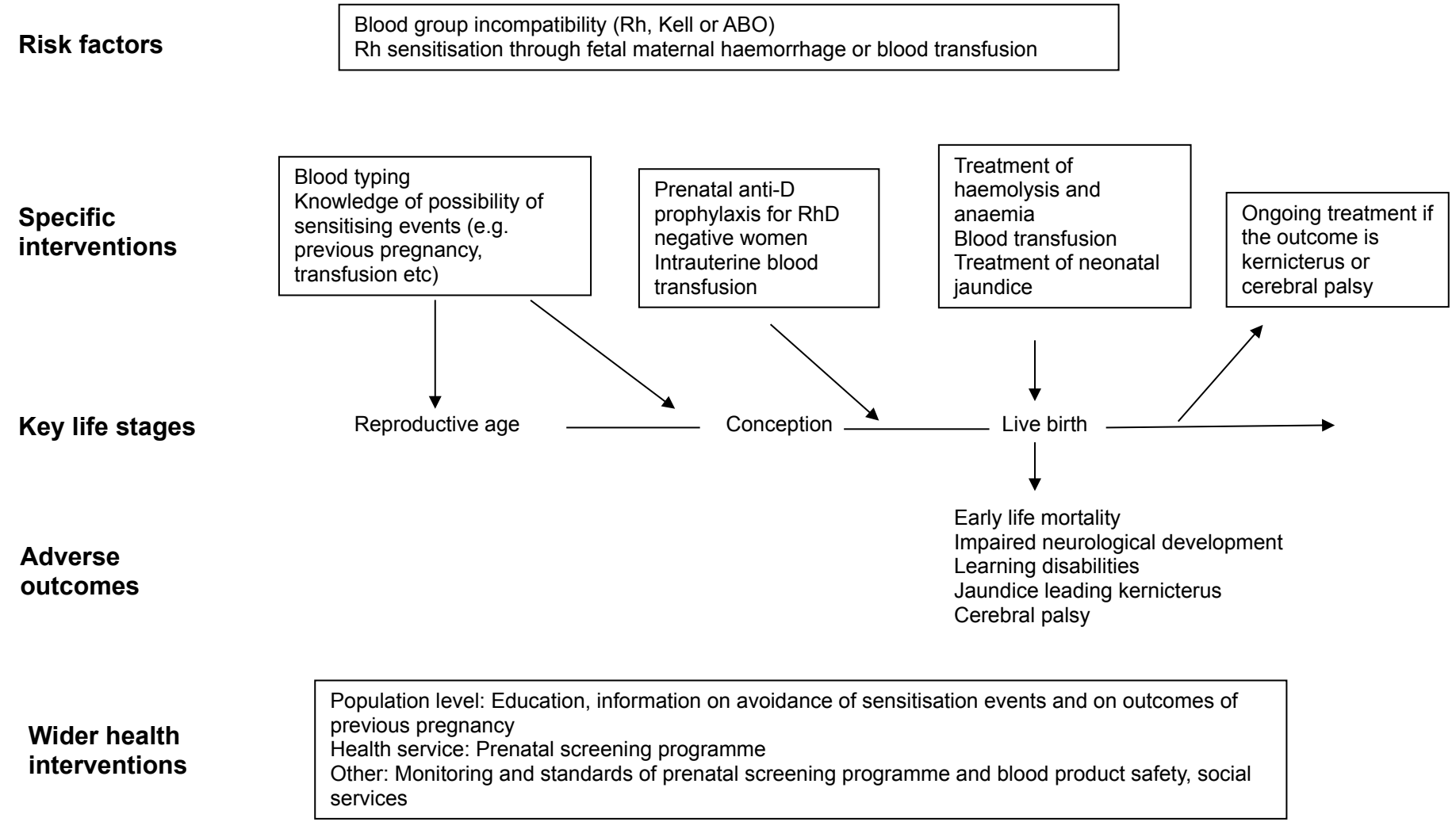

Figure 2: Optional screening care pathways