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IV. Antenatal prophylaxis in the prevention of Rh hemolytic disease of the fetus and newborn (HDN)

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Rh haemolytic disease of the fetus and newborn (HDN) is a condition in which the lifespan of the infant's red cells is shortened by the binding of specific IgG Rh antibodies produced by the mother, which transfer across the placenta. The disease begins in intra-uterine life and shows a wide spectrum of severity. Not all D-positive infants born to mothers with anti-D are affected by HDN. Some infants are only mildly affected and the hemolytic process is most severe after birth; however, jaundice and anemia become more severe at birth. More severely affected infants, if not treated with exchange transfusion, develop profound hyperbilirubinaemia which impregnates the basal ganglia causing *kernicterus* with signs of brain damage leading to death within a week of birth in 70% of cases; those who survive have permanent brain damage characterized by choreoathetosis and spasticity and, in milder cases, by high-frequency deafness. The most severe manifestation of HDN is profound anaemia, developing *in utero* as early as the 18th week of gestation and leading to *hydrops fetalis* with generalized edema, ascites, hepatosplenomegaly, erythroblastosis and a high mortality.

Treatment

In the antenatal period, severely affected fetuses can be transfused with Rh D-negative blood intraperitoneally or, preferably, intravascularly by fetoscopy from the 18th - 20th week of gestation and onwards. Fetal blood sampling is not without risk; even in experienced hands the risk of fetal loss is 1-2%, fetal mortality after each intrauterine transfusion is about 5% and the risk of transplacental haemorrhage (TPH) is much higher, with stimulation of maternal antibody levels. Premature delivery at 30 - 32 weeks is advocated by some. In the postnatal period, if HDN is manifest, exchange transfusion with D-negative blood removes anti-D coated cells which have a short survival time and also removes the bilirubin present in the plasma, thus preventing *kernicterus*. Phototherapy is indicated for mildly affected infants.

RhD immunization is due mainly to transplacental hemorrhage (TPH) from the fetus to the mother which occurs in over 50% of cases at delivery. About 1-3% of women have significant spontaneous TPH in the 3rd trimester. The chance of TPH during pregnancy is increased in entopic pregnancy and with obstetric interventions. In approximately 1% of D-negative women who deliver a first D-positive child, anti-D is detectable at the end of pregnancy. Anti-D is detectable 6 m post-partum in 7-9% of D-negative women with a D positive child and in a further 9% at delivery of the second D-positive infant (17% altogether of primary RhD immunization caused by one pregnancy).

Antenatal assessment of severity

All pregnant women should be grouped for ABO and D at least twice: at the first visit and at delivery. The sera should be tested for alloantibodies at the first visit and if found positive, followed-up regularly. In women with significant levels of anti-D, amniocentesis will only help in the diagnosis of severe HDN from the 28th week of gestation onwards to estimate the amount of bile pigment in the amniotic fluid. Ultrasonography also helps from the 18th week onwards and is becoming increasingly more useful with better definition; but measuring the Hb and PCV in a fetal blood sample (FBS) is the best method to assess reliably the severity of hemolytic disease *in utero* in those cases where the maternal anti-D is very strong or when there is a previous history of HDN.

Undiminished D-negative women should be re-tested at 28 weeks when, if the anti-D screen is negative, antenatal prophylaxis should be considered. All women should have their serum re-tested at delivery and if D-negative, undiminished and carrying a D-positive child should be given RhD immunoglobulin (see below). If the D group of the infant is unknown, and the RhD-negative mother is unimmunised, anti-D Ig should still be given.

Prevention of RhD immunization

RhD immunization which would otherwise follow pregnancy can be prevented by the administration to the mother of 20 mg (micrograms), equivalent to 100 i.u., anti-D immunoglobulin per ml of D-positive red cells in the maternal

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circulation. Nevertheless, failures of immunoprophylaxis do occur and the main causes are: 1) insufficient dose of anti-D Ig to cover a transplacental hemorrhage (TPH); 2) anti-D Ig given too late, i.e. after primary immunization has occurred; 3) anti-D Ig not given after pregnancy. However, it is mainly forgotten after abortion; the risk of RhD immunization by abortion increases with gestation, being about 1.5 - 2% after spontaneous abortion and considerably higher (4% - 5%) after therapeutic abortion or, 4) anti-D Ig not given after other potentially sensitizing episodes during pregnancy such as trauma, amniocentesis, versions, chronic villus sampling (CVS), etc.

The standard dose of anti-D for postpartum injection is 100 mg (500 i.u.), given i.m., in the UK and a few other countries and 250 - 300 mg elsewhere. The UK dose covers TPHs up to 4 - 5ml red cells (about 10 ml blood); this embraces about 99% of all TPHs. Larger TPHs can be identified by methods to detect fetal cells in maternal blood, and should be covered by additional anti-D Ig.

In women undergoing termination of pregnancy up to 20 weeks' gestation, 50 mg (250iu) anti-D Ig should be given; from 20 weeks onwards the dose should be the same as for women at term.

The postpartum injection of anti-D Ig is effective in most cases, as TPH occurs mainly during delivery. Nevertheless, appropriately administered postnatal prophylaxis has a minimum failure rate of 1.6% at the end of a second D-positive pregnancy, mostly due to "silent" FMH during pregnancy. In fact, RhD immunization during pregnancy would account for one seventh of Rh-negative women who will become immunized by an RhD-positive pregnancy in the absence of any kind of immunoprophylaxis.

Despite the absence of properly controlled randomized trials, there is highly suggestive evidence, from clinical trials, that if current guidelines on postnatal and post abortion prophylaxis are followed strictly, the administration of anti-D immunoglobulin during pregnancy, at 28 and 34 weeks gestation, suppresses primary RhD immunization in most women in whom it would otherwise occur. In one large Canadian series, antenatal prophylaxis reduced the incidence of RhD immunization from 1.8% to 0.1% and, in a UK trial in Yorkshire, from 0.9% to 0.16%.

Rh immunoprophylaxis has significantly reduced the incidence of RhD immunisation in pregnant women (e.g. from 1 in 238 in 1974 to 1 in 963 in 1988 in one series). It is expected that when anti-D Ig is given post-delivery to all previously unimmunised RhD-negative women, the incidence of anti-D in pregnancy will be about 1 in 2000, because postnatal prophylaxis is about 90% effective. Strict adherence to current guidelines, especially following potentially sensitizing events during pregnancy will reduce the incidence further. Routine antenatal prophylaxis would be expected to reduce the frequency of RhD immunisation in pregnant women to 1 in 10,000 or less.

Opponents to Rh antenatal propylaxis have raised the following arguments: a) the incidence of maternal Rh immunization is considered to be low when current guidelines are followed; b) the procedure is not cost-effective; c) there is a risk to fetuses and to mothers exposed to Rh immunoglobulin; d) it is not justified to give so many RhD negative pregnant women carrying D-negative fetuses a treatment they do not require.

On the other hand, there are powerful arguments advocating the use of routine antenatal prophylaxis as soon as possible: a) experience from several groups in Canada and Europe has shown that the incidence of maternal immunisation during pregnancy is not low, i.e. the order of 1.2 – 2%. When compliance with routine postnatal prophylaxis is high, Rh immunisation during the third trimester is by far the major cause (18-86%) of residual Rh immunisation. Hence, Rh HDN is still a healthcare issue. Stillbirths and infant mortality due to Rh HDN are of the order of 50 cases per year in the UK, albeit under-reported. Such deaths are preventable; b) antenatal prophylaxis is clinically effective since it reduces residual Rh immunisation from 1.5-2% to approximately 0.2%; c) the procedure is cost effective since it reduces the workload derived from RhD maternal immunization and its associated fetal/neonatal morbidity and mortality. Immunized mothers need to be followed up serologically and clinically by specialized obstetricians with the added costs of ultrasonography, amniocentesis and ultimately fetal blood sampling and intrauterine transfusions. Affected infants may need neonatal intensive care and exchange transfusions. In Canada, in 1988, the cost or preventing one case of maternal Rh immunization was $ 3,281, comparing favourably with the cost of treating a fetus/infant severely affected by HDN. Cost effectiveness is partly influenced by the dose of anti-D Ig and it is proposed that in the UK two doses of 100 mg each are used at 28 and 34 weeks for all unimmunized RhD – negative mothers, despite the knowledge that programmes of a single dose of 300 mg restricted to primigravidae are less costly, but perhaps not as effective as 2 doses. The Edinburgh Consensus Conference concluded that the cost per life year saved compares favourably with other NHS interventions; d) Antenatal prophylaxis has been shown to be safe for the fetus and mother. It is known that the level of anti-D Ig administered to the mother is too low to cause haemolysis or any harm to the fetus, even when the high 300 mg dose is given. The procedure has been used in Canada and many other countries, including some areas in the UK, with no untoward effects to mother or fetus. Anti-D Ig for i.m. use, manufactured according to GMP has never been known to transmit bloodborne viruses such as HBV, HCV or HIV. Experimental data has shown that the theoritical risk of transmission of prion diseases by intravenous or intracerebral injection of a

fractionated blood product such as anti-D Ig is insignificant or considerably lower than the risk of prion transmission by blood transfusion. If vCJD proves to be transmissible by blood transfusion, fetuses and infants affected by HDN and requiring blood transfusion will be at risk of acquiring vCJD; e) There is no worldwide shortage of supply of anti-D Ig and the fractionated product can be subjected to viral inactivation; f) the evidence *a priori* that approximately 2% of mothers become immunised during pregnancy and the knowledge that this can be prevented by antenatal prophylaxis make it unnecessary to conduct a considerably large and expensive randomized clinical trial. This was the advise given by Sir Richard Doyle to UK professionals in the late 70's and the opinion of the American College of Obstetricians when they recommended the introduction of antenatal prophylaxis in the USA over 20 years ago.