Executive summary

Health Council of the Netherlands. Pregnancy immunisation by red blood cells. The Hague: Health Council of the Netherlands, 2009; publication no. 2009/04.

This advisory report concerns pregnancy immunisation by red blood cells – the phenomenon whereby women form so-called irregular erythrocyte antibodies (IEA) against foreign blood cells (erythrocytes). In addition to pregnancy, blood transfusion can cause IEA formation. The distinction between antibodies targeting the Rhesus D antigen (D-IEA) and antibodies targeting other erythrocyte antigens (Non-D-IEA) may also be made.

IEA can lead to severe illness in the unborn or newborn child, namely haemolytic disease of the foetus and newborn (HDFN). Over the past several years, methods have been developed to prevent the formation of IEA and to detect already formed IEA. Dutch research conducted as part of the Identification and Prevention of Pregnancy Immunisation (Opsporing en Preventie Zwangerschapsimmunisatie, OPZI) project has contributed significantly to these developments.

This advisory report addresses the following: screening for non-D-IEA, options for changing transfusion policies for young girls and women of childbearing age in order to reduce the formation of non-D-IEA, prophylaxis to prevent the formation of D-IEA and ways to ensure this treatment is only given to women who may benefit from it.

Screening for non-D irregular erythrocyte antibodies

In the 18-month OPZI project, all pregnant women in the Netherlands were tested for non-D-IEA during week twelve of their pregnancy and the occurrence of HDFN. Severe HDFN, requiring intra-uterine transfusion or exchange transfusion during the first week after birth, occurred in 21 pregnancies (3.7 percent of pregnancies with clinically relevant non-D-IEA; 0.007 percent of all pregnancies). The HDFN was caused by, in order of decreasing incidence, antibodies targeting the Kell antigen (K-IEA), the rhesus-c antigen (c-IEA), the rhesus-E antigen (E-IEA) or other specific antibodies.

The committee feels the potential health gains of this screening programme are significant: per 100,000 pregnant women screened, four to six cases of foetal death or brain damage are expected to be prevented. The cost per prevented case of prenatal death or perinatal disease with permanent consequences is 500,000 euros, an amount well within generally accepted limits. The committee believes this screening programme meets the generally accepted criteria for responsible screening programmes. It therefore recommends pregnant women be screened for non-D-IEA during week 12 of the pregnancy.

The test for non-D-IEA is performed in all pregnant women in the Netherlands, and follow-up testing is performed in all women testing positive for non-D-IEA. The OPZI project outlines alternative scenarios in which not all women are screened, or follow-up testing is only performed in a specific subset of all non-D-IEA positive women. Regarding these scenarios, the committee recommends the following: it advises selective screening only for those women who have been pregnant before or have received a blood transfusion in the past. The committee also recommends selective follow-up screening for women that have tested positive for c-IEA, E-IEA or K-IEA. For follow-up testing for c-IEA, E-IEA of K-IEA, the committee recommends typing the biological father of the – unborn – child for the specific antigen in question. If the father is homozygous for the antigen, then the child is a carrier and further testing is required. If the father is negative for the antigen, no further follow-up is required. If the father is heterozygous, the committee recommends prenatal testing of the mother's blood to determine whether the child is carrying the antigen in question. If the child tests positive, further follow-up tests are required – this is not necessary if the child tests negative. In the event c-IEA or E-IEA is present, follow-up testing may initially be restricted to laboratory testing. Only if these tests show an increased risk of HDFN does the committee recommend clinical follow-up. For K-IEA, the committee recommends both laboratory and clinical testing in all

cases – these antibodies have the potential to cause HDFN in extremely low concentrations. When women test positive for another non-D-IEA that may cause severe HDFN it is recommended that the father is typed for the antigen in question. If the father is positive the woman should be re-tested once. Due to the risk of HDFN caused by late formation of c-IEA in particular, the committee's final recommendation is to test all pregnant women for the presence of the c-antigen during week 12 of the pregnancy, and to repeat the test for c-IEA in all c-negative women during week 30.

Transfusion policies for young girls and women of childbearing age

The results of screening for non-D-IEA show that a significant percentage of HDFN is caused by c-IEA, E-IEA or K-IEA. A study showed past blood transfusions to be a risk factor for the development of these IEA. The committee therefore recommends giving young girls and women of childbearing age requiring blood transfusions erythrocytes that are compatible in terms of antigens c, E and K. The committee finds the cost-effectiveness calculations for the introduction of compatible blood transfusions to be convincing.

Antenatal prophylaxis

A programme to prevent D-IEA formation has been in place in the Netherlands for about 40 years. For this postnatal anti-D immunoprophylaxis (postnatal prophylaxis), the D-antigen status of children born to D-negative mothers is determined immediately after delivery. Mothers of D-positive children are given anti-D immunoglobulin (anti-D-Ig) in order to prevent the formation of D-IEA, thereby reducing the chances of HDFN occurring during a subsequent pregnancy.

Despite postnatal prophylaxis, however, HDFN still occurs, albeit less frequently than it used to. One of the reasons for this is that the formation of D-IEA can already take place during pregnancy. In order to combat the occurrence of HDFN caused by this early D-IEA formation, antenatal prophylaxis was introduced alongside postnatal prophylaxis in 1998. In this programme, D-negative pregnant women are given anti-D-Ig during pregnancy (at around week 30 of the pregnancy, in the Netherlands). The effects of antenatal prophylaxis were examined within the framework of the OPZI-project.

Antenatal prophylaxis causes a statistically significant decrease in the incidence of pregnancy immunisation against the rhesus-D antigen. The percentage of women in whom HDFN occurred was also lower in the group receiving ante-

natal prophylaxis compared to the control group, but the difference was not statistically significant. The committee is faced with a dilemma: the OPZI-project shows that the introduction of antenatal prophylaxis has met the expectations as far as immunization is concerned. The effect on HDFN is less outspoken, although antenatal prophylaxis does result in a decrease in HDFN which the committee finds clinically relevant. The committee would like stronger evidence for the prevention of HDFN by antenatal prophylaxis, but believes the likelihood of such data, preferably from randomised research, becoming available is essentially none. The committee therefore recommends antenatal prophylaxis be continued.

Prenatal D-typing

Under the current programme, all D-negative pregnant women receive antenatal prophylaxis, while only D-negative women pregnant with a D-positive child benefit from it. Women pregnant with a D-negative child do not form any D-IEA, due to the lack of rhesus-D antigen on the child's erythrocytes. In the Netherlands, this amounts to forty percent of pregnant D-negative women, or about 16,000 per year. The discovery that genetic material from the unborn child can be detected in the mother's blood now allows the determination of the child's rhesus-D status before birth (so-called prenatal D-typing), thereby restricting antenatal prophylaxis to D-negative women pregnant with D-positive children.

The committee feels prenatal D-typing can be used to limit antenatal prophylaxis to those women who may benefit from it, namely D-negative women pregnant with D-positive children. The committee feels this has two advantages: D-negative women pregnant with D-negative children are not unnecessarily exposed to a blood product, and less anti-D-Ig is used. This may allow the use of anti-D-Ig sourced exclusively from unpaid (Dutch) donors. The committee supports this position. The committee therefore recommends adding prenatal D-typing to the programme.

Three of the four studies of prenatal D-typing published to date report discrepancies in test results, in which prenatal D-typing indicated a D-negative child, but postnatal D-typing showed the child to be D-positive. These discrepancies were caused by logistical problems during the screening process. If the decision is made to implement prenatal D-typing, the committee recommends the logistical reliability of the test be further studied. In the committee's opinion, this would best be achieved by maintaining – for an agreed-upon study period – postnatal D-typing for D-negative pregnant women with prenatal D-typing tests indi-

cating they are carrying a D-negative child. If the study shows prenatal D-typing is logistically reliable, postnatal D-typing will no longer be required.