Prenatal testing of the fetal rhesus factor: Test is reliable, but benefit is unclear

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If the blood of a pregnant woman is rhesus-negative (Rh-negative) and the blood of the foetus is rhesus-positive (Rh-positive), the woman may develop antibodies, which can cause severe harm to subsequent children in particular. In order to prevent this effect called sensitization, all Rh-negative pregnant women in Germany currently receive a prophylaxis. A new type of test using a blood sample of the pregnant woman can determine the child's rhesus factor already before birth, however. Provided the test is sufficiently reliable, many women might not need the prophylaxis. Currently, the blood of the newborn baby is tested directly after birth.

The German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined whether the management of prophylaxis based on this test has advantages or disadvantages for the children or for the expectant mothers. The final results are now available. According to the findings, there are no studies to answer this question. The reliability of the new test is as high as the reliability of the conventional test used after birth, however.

Risk particularly in subsequent pregnancies

The rhesus factor is an inherited characteristic of the red blood cells (erythrocytes). It acts as an antigen, i.e. Rh-negative people can produce antibodies against foreign Rh-positive blood cells in their blood. This can cause severe, even fatal incompatibility reactions. The rhesus factor

therefore plays an important role in blood transfusion and pregnancy.

During pregnancy, and particularly during birth, the blood of an Rh-positive child can enter the bloodstream of the Rh-negative mother. This causes the production of antibodies in a process called sensitization. These antibodies can enter the child's bloodstream, causing anaemia, cardiac failure, brain damage, or even death of the foetus.

However, not the foetus of the current pregnancy, but Rh-positive children in subsequent pregnancies are the ones who carry the greatest risk. The reason is that these children are subject to the defence reaction of their mother's blood at a very early stage of the pregnancy.

Standard prophylaxis for all rhesus-negative pregnant women

All Rh-negative pregnant women in Germany currently receive a standard dose of anti-D immunoglobulin. These antibodies are used to prevent sensitization by catching erythrocytes that reach the mother's bloodstream from the foetal bloodstream already before birth. Human anti-D immunoglobulin from sensitized donors is used for this prophylaxis.

After birth, the infant's rhesus factor is determined using a blood sample of the infant (postnatal testing). If the blood of the newborn is Rh-positive, the mother receives another anti-D prophylaxis.

Mother's blood contains information on the foetal rhesus factor

Now a test has become available to determine the foetal rhesus factor already before birth. This is a non-invasive procedure, in which the

foetus is not touched. Instead, the test analyses so-called cell-free foetal DNA circulating in the maternal plasma.

In principle, this allows limiting prenatal anti-D prophylaxis only to those Rh-negative pregnant women whose foetus is Rh-positive according to the prenatal test. Currently, about 15 per cent of all pregnant women receive the prophylaxis, corresponding to about 110 000 pregnant women per year. Implementing the new test could reduce this number to about 60 000.

Studies cannot answer the research question of the commission

The Federal Joint Committee (G-BA), which is also responsible for the German "maternity guidelines", therefore wanted to know from IQWiG whether the introduction of the new test can have health advantages or disadvantages for children or mothers, e.g. increasing the occurrence of haemolytic anaemia or decreasing the occurrence of side effects of the prophylaxis.

The IQWiG researchers found out that there are currently no studies that allow drawing precise conclusions on the effects the introduction of the new test might have.

Both tests equally reliable

However, there are studies that provide information on how reliable the prenatal test is in determining the child's rhesus factor. The reliability is comparatively high, which is referred to as "high diagnostic accuracy": The test correctly identifies 99.9 per cent of all Rh-positive foetuses (sensitivity) and 99.1 per cent of all Rh-negative foetuses (specificity). This means that 0.1 per cent of pregnant women who would require anti-

D prophylaxis before birth would not receive this prophylaxis if this decision was based on the test result. Hence, the prenatal test is as reliable as testing after birth.

Balancing possible advantages and disadvantages

The new test allows using the anti-D prophylaxis when it is needed and spare some pregnant women from unnecessary prenatal prophylaxis. It is unclear whether these pregnant women have an advantage, however, because reliable data on possible side effects of the prophylaxis are missing.

The risk that false test results might lead to additional sensitizations is considered low, despite the lack of sufficient data. On the one hand, the test can be rated as very reliable. On the other, the risk is low that sensitization occurs already during pregnancy.

In its report, the Institute did not address the question which effects it might have at the level of the German health care system if a large number of unnecessary anti-D prophylaxis are avoided. General aspects of importance are not only the financing of this prophylaxis, but also its acquisition and ethical aspects, however, because male donors are sensitized with a blood product to produce the vaccine. The number of donors worldwide is limited, and Germany has to import the preparations.

Prenatal test suitable to replace postnatal test

If the prenatal test was to replace the postnatal test, this would increase neither the rate of prophylaxis that is falsely withheld nor the rate of haemolytic anaemia to a measurable extent. This is because both tests are equivalent. It is recommended, however, to evaluate the procedure

first and particularly to test how high the sensitivity of the new prenatal test actually is under the health care conditions in Germany. Only after this evaluation, a safe decision could be made whether postnatal testing is in fact dispensable. Responsible authorities in Denmark and the Netherlands, where only prenatal testing is used nowadays, also had arranged for prior evaluation.

More information: www.iqwig.de/en/projects-resul … sitization.7579.html

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