Summary

The Rhesus NIPT allows you the freedom to decide whether you prefer general Rh prophylaxis in your pregnancy, or targeted prophylaxis **only for an RhD-positive fetus** after non-invasive fetal blood grouping. Both options are **equivalent** for the safety of your unborn child.

Rhesus NIPT

- **Possible from GA 11+0**
- **Sensitivity: 99.93%** [3]
- **Specificity: 99.61%** [3]
- **Turn-around time: approx. 7 days**

References

[1] Prof. Dr. med. Tobias J. Legler, Anti-D-Prophylaxe bei RhD-negativen Frauen - Hämotherapie www.drk-haemotherapie.de

[2] Institute for Quality and Efficiency in Health Care, www.iqwig.de/projekte/d16-01.html

[3] Legler TJ et al, Arch Gynecol Obstet 2021 Apr 9. doi: 10.1007/s00404-021-06055-1

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Rhesus NIPT

Determination of the fetal Rhesus factor from maternal blood

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Dear Expectant Mother,

You may already know your blood type, for example if you are a blood donor. Your blood type is also determined as a part of maternity care at the beginning of your pregnancy to determine if you have the blood group factor RhD-negative ("Rhesus-negative"). About **17% of all women are RhD-negative.**

If you are RhD-negative, the following information will be of interest to you.

Rhesus factor and anti-D

The blood group factor RhD (aka Rhesus factor D) is one of many known blood group factors. RhD, however, is highly immunogenic, which means that carriers of the RhD-negative factor often form antibodies against RhD when they come into contact with red blood cells (erythrocytes) that have the RhD blood group factor.

During pregnancy and childbirth, small amounts of erythrocytes in the fetus can enter the maternal bloodstream. If the fetus has the blood group factor RhD-positive and the mother is RhD-negative, the mother may be "sensitized" or "immunized". The antibodies formed against Rhesus factor D are called "anti-D".

RhD-positive red blood cells can trigger the formation of anti-D in RhD-negative people.

Rh prophylaxis

Because anti-D can cause haemolytic disease* in the fetus, rhesus prophylaxis was introduced at the end of the 1960s. In this treatment, a small dose of anti-D, such as Rhophylac 300, is administered to the mother. This breaks down any of the fetus' erythrocytes that may enter the mother's blood stream, thus preventing the mother from being immunized against the fetus' RhD factor. At birth, a newborn's blood group is determined from the umbilical cord blood. If the newborn is RhD-positive, Rh prophylaxis is administered to an RhD-negative mother.

According to maternal care guidelines in the past , Rh prophylaxis has been administered to all RhD-negative pregnant women in the **28th – 30th week of pregnancy**, independent of the rhesus status of the unborn child. **Rh prophylaxis is therefore administered to some pregnant women without actually being medically necessary. This affects around 40% of RhD-negative pregnant women.**

* Anti-D used to be a common cause of haemolytic disease. The unborn child receives a large amount of antibodies from the mother through the placenta. This will protect the newborn from infection. In the case of anti-D, however, this means that the fetus' erythrocytes are broken down more quickly. This leads to fetal anemia, which in the worst case can lead to the death of the unborn child.

In less severe cases, babies can be born with an increased incidence of neonatal jaundice, although this usually responds well to treatment.

It is important to discover if the mother will form anti-D and other blood group antibodies during pregnancy. Two antibody screening tests are therefore usually carried out during pregnancy, one in early pregnancy and another between the 24th and 27th weeks of pregnancy. Other, mostly harmless antibodies will also give a positive test in addition to anti-D, so the vast majority of pregnancies proceed normally even if the antibody test is positive.

Why should rhesus prophylaxis be used only when needed?

The Rh prophylaxis treatment is very safe. Even so, pregnant women occasionally express concern since Rh prophylaxis is a blood product. It is produced from the blood of donors who have previously immunized themselves against the Rhesus-D factor. Although anti-D immunoglobin is an exceptionally infection-proof blood product, transmission of infection cannot be ruled out for all batches and for all pathogens. Human anti-D immunoglobin can also rarely (frequency between 1:1000 and 1:10,000) cause hypersensitivity reactions[1].

Targeted Rh prophylaxis after fetal blood group testing protects just as well as the treatment of all RhD-negative pregnant women.

Non-invasive determination of the fetal Rh factor

It has recently become possible to non-invasively test the unborn child's (fetal) Rh factor from the mother's blood. Similar to other tests for non-invasive prenatal diagnostics (e.g. the Harmony® Test), cell-free fetal DNA in the pregnant woman's blood is used to examine the fetal *RHD* gene by using a method called PCR. Statistically, about 40% of the children of RhD-negative women are also RhD-negative; therefore, **an RhD-positive fetus can be expected in 60% of the tests.** On average, **non-invasive fetal blood group testing can avoid unnecessary Rh prophylaxis** treatment in approximately 40% of the subsequent pregnancies.

With the determination of the fetal Rh factor, Rh prophylaxis only needs to be administered to those pregnant woman who are actually expecting an RhD-positive child.

The non-invasive testing has no effect on the unborn child as blood is only taken from the mother. It should be emphasized that there are no health implications for an individual whether they are RhD-positive or RhD-negative, except for in the case of maternal/fetal Rh incompatibility as described previously.

Likewise, the purpose of Rh prophylaxis is to avoid mother-fetus Rhesus immunizations. Administrating Rh prophylaxis only for pregnant women expecting an RhD-positive child works as well as the administration of Rh prophylaxis for all pregnant women[2].

Test Reliability

As with other medical tests, Rhesus NIPT non-invasive fetal blood group testing can produce so-called "**false positive**" and "**false negative**" results.

False positive findings are possible due to "silent alleles", which are **genes without a real function**. In such cases, although the fetus was actually RhD-negative, the test results would mean that Rh prophylaxis would be given unnecessarily. This occurs in approx. 0.4%[3] of cases. **Without the use of non-invasive fetal blood group testing, however, Rh prophylaxis would have been given anyway.**

False negative results are possible, due to factors such as **insufficient cell-free fetal DNA** in the mother's blood. Since the amount of cell-free fetal DNA increases as the pregnancy progresses, it is recommended that the Rhesus NIPT is carried out only after the 19th week of pregnancy. If another non-invasive prenatal test is performed (e.g. the Harmony® Test), and the fetal fraction of the blood is determined to be at least 4%, the fetal Rh status can also be determined from the 12th week of pregnancy.

Overall, the false negative rate is approximately 1 out of 2000 tests. In this case, a required prenatal Rh prophylaxis would not be administered. Given the generally low immunization risk during pregnancy (no more than 1-2% risk per pregnancy with an RhD-positive fetus), this proportion of false negative results is considered acceptable.

In the opinion of the german „Institute for Quality and Efficiency in Health Care" (IQWiG), the standard administration of Rh prophylaxis and targeted prophylaxis after testing with Rhesus NIPT give equivalent protective effects, because false negative results are also occasionally found in blood testing during childbirth[2].