ANAEMIAS IN PREGNANCY: DIAGNOSIS AND PREVENTION

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I. Physiological and haematological changes during pregnancy

Pregnancy induces physiological changes that often confuse the diagnosis of several haematological disorders and the assessment of their treatment. This is especially true for anaemia.

A number of marked haematological changes are induced by pregnancy. One of the most significant changes is that of blood volume expansion by a mean of 50 percent. Plasma volume increases disproportionately compared with red cell mass, resulting in physiological decrease in haematocrit. During this time, iron requirement for mother and fetus average nearly 1.000 mg.

I. Increase in plasma volume

During pregnancy there is an increase about 50% of plasma volume, which reaches its maximum by week 32 of gestation. This is accompanied by a similar increase of the cardiac output. These changes:

- Increase blood supply to the uterus
- Increase the excretory capacity of the kidneys
- Help dissipate heat produced by the elevate metabolic rate during pregnancy
- Protect the fetus against impaired placental perfusion as a result of aortal caval compression by the gravid uterus.

2. Red blood cells

The mother's red cell mass increases by 18–25% during pregnancy. This occurs more slowly than the increase in plasma volume. The discrepancy between the rates of increase in plasma volume and red cell mass results in a physiological reduction in the haemoglobin concentration during pregnancy. Normal or elevated haemoglobin during pregnancy may be a sign of pre-eclampsia in which plasma volume is reduced.

3. Iron metabolism

The mother's iron requirement is increased during the last two trimesters of pregnancy because of the demand of the fetus and the increase of the maternal red cell mass. Up to 80% of the increased requirements occur in the last trimester. The total iron requirement over the whole pregnancy is approximately 1.300 mg.

II. Anaemia in pregnancy

I. Definition of anaemia

A precise definition of anaemia in women is complicated by normal differences in the concentration of haemoglobin between women and men, between white and black women, between women who are pregnant and those who are not, and between pregnant women who receive iron supplement and those who do not. Anaemia in non-pregnant women is defined as haemoglobin concentration less than 12 g/dL and less than 10 g/dL during pregnancy or the puerper-

ium. The haemoglobin concentration is lower in the second trimester; early in pregnancy and again near term, the haemoglobin level of most healthy women with iron stores is 11 g/dL or higher. Anaemia in pregnancy, as defined by WHO, is a haemoglobin concentration of less than 11 g/dL in the first and third trimesters. In the second trimester a fall of 0,5 g/dL due to increased plasma volume is allowed and a cut-off value of 10,5 g/dL is used.

2. Frequency of anaemia

Acute blood loss and chronic anaemia in pregnancy are major causes of maternal morbidity and mortality worldwide.

The frequency of anaemia during pregnancy varies considerably, depending primarily upon whether supplemental iron is taken during pregnancy. There is a reported observation that haemoglobin levels averaged 12,7 g/dL among women who received supplemental iron compared with 11,2 g/dL for women who did not.

3. Effects of anaemia on pregnancy

Anaemia in pregnancy increases the likelihood of fetal growth retardation, premature birth and fetal loss. Its effects on maternal and perinatal morbidity and mortality can be avoided by effective prevention and treatment, taking early corrective measures and thus reducing the need for transfusion if obstetric haemorrhage occurs.

4. Etiology of anaemia

The causes of anaemia during pregnancy are the same as those encountered in non-pregnant women. Any anaemia common to childbearing age women may complicate pregnancy. A classification based primarily on etiology and including most of the common causes of anaemia is shown on *table 1*:

Table 1. Causes of anaemia during pregnancy

Acquired anaemia	Hereditary anaemia
Iron-deficiency anaemia	Thalassaemias
Anaemia caused by acute blood loss	Sickle-cell haemoglobinopathies
Anaemia of infection or malignancy	Other haemoglobinopathies
Megaloblastic anaemia	Hereditary haemolytic anaemia
Acquired haemolytic anaemia	
Aplastic or hypoplastic anaemia	

Although laboratory error as a cause of apparent anaemia has not been included, the results from clinical laboratories may sometimes be inaccurate. A common source of error during pregnancy stems from the rapid erythrocyte sedimentation rate, which is induced by hyperfibrinogenemia of normal pregnancy. If the specimen of blood is not mixed immediately before sampling, the results will likely be inaccurate. Most automated devices used currently have constant mixing features that obviate this problem.

5. Acquired anaemias

5.I. Iron-deficiency anaemia

The two most common causes of anaemia during pregnancy and the puerperium are iron-deficiency and acute blood loss. Not infrequently the two are intimately related, because excessive blood loss with its concomitant loss of haemoglobin iron and exhaustion of iron stores in one pregnancy can be an important cause of iron-deficiency anaemia in the next pregnancy.

The absolutely prevalent importance of iron-deficiency anaemia in preg-

nancy and puerperium needs to be underlined, as well as the ease of its recognition and the economy of its treatment.

The iron requirements of pregnancy are considerable. In a typical gestation with a single fetus, the maternal needs of iron induced by pregnancy averages close to 800 mg, about 300 mg for the fetus and placenta and about 500 mg, if available, for maternal haemoglobin expansion. Approximately 200 mg more are shed through the gut, urine and skin. This total amount, 1.000 mg, exceeds considerably the iron store of most women. Unless the difference between the amount of stored iron available to the mother and iron requirements of normal pregnancy cited above is compensated for by absorption of iron from the gastrointestinal tract, iron-deficiency anaemia develops.

Because the amount of iron diverted to the fetus from an iron-deficient mother is not much different from the amount normally transferred, the newborn infant of a severely anaemic mother does not suffer from iron-deficiency anaemia. Iron stores in the infant are influenced much more when the cord is clamped.

Maternal iron-deficiency anaemia is associated with lower scores on tests of motor and mental development in infancy.

Diagnosis

Classical morphological evidence of iron-deficiency anaemia -erythrocyte hypochromia and microcytosis- is less prominent in the pregnant woman compared with the non-pregnant woman with the same haemoglobin concentration. Moderate iron-deficiency anaemia during pregnancy, for example, a haemoglobin concentration of 9 g/dL is not accompanied by obvious morphological changes in erythrocytes. With this degree of anaemia from iron-deficiency serum ferritin levels are lower than normal, and there is non-stainable bone marrow iron. The serum iron-binding capacity is elevated, but by itself is of little diagnostic value, because it is also elevated in normal pregnancy in the absence of iron-deficiency. Moderate normoblastic hyperplasia of the bone marrow also is found to be similar to the normal pregnancy. Thus, iron-deficiency anaemia during pregnancy is the consequence primarily of expansion of plasma volume without normal expansion of maternal haemoglobin mass.

Treatment

The objectives of treatment are correction of the deficit in haemoglobin mass and eventually restitution of iron stores. Both of these objectives can be accomplished with orally administration of iron compounds (ferrous sulfate, fumarate or gluconate) that provide a daily dose of 180–200 mg of elemental iron. Iron treatment should continue for at least another two or three months to build up iron stores to about 200-300 mg, which is equivalent to a serum ferritin of 30 mg/L. Folic acid may be given along with the iron as a safeguard against folate deficiency in a daily dose of 2 mg folate.

5.2. Anaemia from acute blood loss

Anaemia resulting from recent haemorrhage is more likely to be evident during puerperium. Both abruptio placentae and placenta previa may be sources of serious blood loss and anaemia before as well as after the delivery. Earlier in pregnancy, anaemia caused by acute blood loss is common in instances of abortion, ectopic pregnancy, and hydatiform molla.

Treatment

Massive haemorrhage demands immediate blood replacement with whole blood or packed red cells and volume expanders in amounts that restore and maintain adequate perfusion of vital organs. Even though the amount of blood replaced commonly does not completely repair the haemoglobin deficit created by the haemorrhage, the residual anaemia should be treated with iron.

5.3 Anaemia of infection or malignancy

- HIV infection - if a patient has anaemia with leucopenia, thrombocytopenia, lymphadenopathy and oral candidiasis, the possibility of HIV infection must be considered.
- Malaria - haemolysis due to malaria is an important cause of severe anaemia in pregnancy. Where malaria is suspected in a pregnant woman, early diagnosis and treatment is essential to minimize the risk of maternal morbidity and mortality and the need for transfusion. Chloroquine, quinine and sulfadoxine-pyrimethamine combination are considered safe in all three trimesters of pregnancy.

5.4. Megaloblastic anaemia

Megaloblastic anaemias are a family of haematological disorders whose characteristic blood and bone marrow abnormalities are caused by impaired DNA synthesis. The prevalence of megaloblastic anaemia during pregnancy varies considerably throughout the world.

- Folic acid deficiency - it usually is found in women who do not consume fresh leafy vegetables or foods with high contents of animal proteins. In some instances high ethanol ingestion either is the cause or contributes to its development. Women with megaloblastic anaemia may develop troublesome nausea, vomiting, and anorexia during pregnancy.

  Treatment

  The treatment of pregnancy-induced megaloblastic anaemia should include folic acid, a nutritious diet and iron. As little as 1 mg of folic acid administrated orally once daily produces a striking haematological response.

- Vitamin B_{12} deficiency

  Megaloblastic anaemia caused by vitamin B_{12} deficiency during pregnancy is exceedingly rare. It is due to malabsorption or to dietary deficiency.

5.5. Acquired haemolytic anaemia

Autoimmune haemolysis is an uncommon condition mediated by the patient's own immunological mechanisms. The cause of aberrant antibody production is unknown. Anaemia due to these factors may be due to warm-active or cold-active antibodies, or a combination. These syndromes also may be classified as primary (idiopathic) and secondary autoimmune haemolysis, caused by underlying disease or other factors. With autoimmune haemolytic anaemia, typically both the direct and indirect antiglobulin tests are positive. Haemolysis and the positive antiglobulin tests may be consequence of either IgM or IgG anti-erythrocyte antibodies. Spherocytes and reticulocytes are characteristic of the peripheral blood smear.

Women with haemolytic anaemia sometimes demonstrate marked acceleration of haemolysis during pregnancy. Glucocorticoids usually are effective as in non-pregnant state and treatment with prednisone, 1 mg/Kg per day, or its equivalent.

6. Hereditary anaemias

6.1. Sickle-cell disease

Anaemia is usually severe and may be exacerbated by acute sequestration of sickle-cells in spleen or, more commonly, by aplastic crisis that occurs when bone marrow red cells production slows down during acute infections. Folate deficiency is common in sickle-cell disease because red cell production is increased. Because the body does not excrete iron and reutilize the iron from the red cells, iron-deficiency in patients with sickle-cell anaemia is no more common than in the general population.

The avoidance or early treatment of infections and administration of folate are important in the management of sickle-cell disease in pregnancy.

6.2. Thalassaemia

The genetically determined haemoglobinopathies that are classified as thalassaemias are characterized by an impaired production rate of one or more of the peptide chains that are normal components of globin. The abnormal synthesis rates may results in ineffective erythropoiesis, haemolysis and varying degrees of anaemia. The different forms of thalassaemias are classified according to the globin chain which is deficient in amount compared to its partner chain. The two major forms of thalassaemias involve either impaired production of alpha-peptide chains causing α-thalassaemia, or beta-chain to cause β-thalassaemia.

- ***α-thalassaemia:*** because there are two α-globin genes, the genetics of α-thalassaemia is more complicated than β-thalassaemia. For each syndrome, a close correlation has been established between clinical severity and the degree of impairment of α-globin chains. There are two major phenotypes. The deletion of all four α-globin chains characterizes homozygous α-thalassaemia.
  The fetus dies either in utero or very soon after birth and demonstrates the typical clinical features of non-immune hydrops fetalis. The compound heterozygous state of α^0 and α^+ results in the deletion of three or four genes, leaving only one functional α-globin gene per diploid genome. The disease is characterized by haemolytic anaemia of varying severity and, in some patients, disease severity is similar to β-thalassaemia. Anaemia in these women usually is worsened during pregnancy. A deletion of two genes results clinically in α-thalassaemia minor, which is characterized by minimal to moderate hypochromic microcytic anaemia. Women with α-thalassaemia minor appear to tolerate pregnancy quite well. The single gene deletion (-α/αα) is the silent carrier state. No clinical abnormality is evident in the individual with a single gene deletion.

  Diagnosis
  Diagnosis of α-thalassaemia minor, as well as α-thalassaemia major in the fetus, can be accomplished by DNA analysis using molecular techniques.

- ***β-thalassaemias*** are the consequence of impaired production of β-globin chains. This basic defects lead to the panorama of pathology that characterized homozygous thalassaemia, so-called
  β-thalassaemia major or Cooley anaemia. With heterozygous β-thalassaemia minor, hypochromia, microcytosis, and slide to moderate anaemia develop without the intense haemolysis in the homozygous state. In the typical case of thalassaemia major, the neonate is healthy in birth, but as the haemoglobin F levels fall, the infant becomes severely anaemic

and fails to thrive. If children are entered into an adequate transfusion programme, they develop normally until the end of the first decade when effects of iron loading become apparent. Those female who do survive beyond childhood are usually sterile if they are not treated in accordance with the last modern practice in this respect. β-thalassaemia minor is characterized with mild anaemia and hypochromic and microcytic cells. The haemoglobin concentration typically is 8 to10 g/dL. There is usually pregnancy-induced augmentation of erythropoiesis. There is no specific therapy for β-thalassaemia minor during pregnancy. Most often the outcomes for the mother and fetus are satisfactory.

The diagnostic recognition of heterozygous β-thalassaemia may be occasionally made difficult, during pregnancy, by slight modification of some haematological parameters (microcytosis, HbA_2 level), suggesting to repeat a confirmatory diagnostic investigation some time after delivery.

7. Prevention and management of chronic anaemia in pregnancy

The prevention of anaemia and the needs for transfusion during pregnancy can be reduced by:

- Prevention and management of nutritional anaemia.
- Adequate antenatal care.

7.1. Prevention of nutritional anaemia in pregnancy

The following measures are important in preventing nutritional anaemia in pregnant women:

1. Education about nutrition, food preparation and breast-feeding.
2. The provision of adequate maternal and child health care.
3. Access to family planning information, education and service.

7.2. Dietary sources of iron

Iron-deficiency is mainly due to inadequate nutrition. There are two types of dietary iron:

- Haem iron, which is well absorbed and is contained in foods of animal origin.
- Non-haem iron, which is poorly absorbed and is contained in foods of plant origin.

  The absorption of non-haem iron requires the presence of vitamin C in the diet.

7.3. Prophylactic administration of haematinics

Prophylactic administration of haematinics is strongly indicated in countries where iron and folate deficiency is common. The optimum daily doses to prevent anaemia in pregnant women are:

- 120 mg elemental iron: e.g. 200 mg tablet of ferrous sulfate.
- 500 μg folate.

8. Transfusion

It is important to remember that transfusion does not treat the cause of anaemia or correct the non-haematological effects of iron-deficiency.

The decision to transfuse blood must not be based on patient's haemoglobin

concentration alone, but also on her clinical needs, including stage of pregnancy and clinical conditions.

III. Haemolytic Disease of the Newborn (HDN)

Destruction of fetal red cells resulting from maternal alloimmunisation still remains a significant cause of neonatal mortality and brain damage as a result of Haemolytic Disease of the Newborn (HDN). Such infants are often grossly edematous and are said to have hydrops fetalis. Clinical management of these cases entails a series of laboratory-based and obstetric investigation that can predict the severity of fetal anaemia and indicate where in utero transfusion would be life-saving.

I. Causes of alloimmune fetal anaemia

Potentially any paternally inherited antigen that is carried on the surface of fetal red cells, which traffic between fetal and maternal circulation, can prompt a maternal immune response. If this response is of sufficient magnitude, maternal antibodies can cross the placenta and cause destruction of the fetal cell that initially caused the alloimmunization.

Obviously in women who have been transfused there is a greater chance that the first child will have a HDN. In some 0,5% to 1% of transfused women, a blood group antibody will be formed and may cause HDN if the fetus red cells carry the antigen against which it is directed.

In the past, relatively small volumes of blood from one person were injected into others in a practice known as heterohaemotherapy (it was believed that immunity to disease could be passively transferred). Cases of immunization and later, HDN, followed this practice. There are documented cases in which the use of syringes, that have become contaminated with blood (for the injection of illegal drugs: "blood brotherhood" rituals) and the exchange of blood (for "emotional gratification" purposes) have resulted in immunization and subsequently in HDN.

The transfer of IgG antibody from mother to fetus is a normal physiological event and is essential in regard to antibodies other than those directed against red cells. Mechanisms of immunoglobulin synthesis are not fully developed at birth, so those transferred maternal antibodies are necessary for protection against various infections for the first few weeks of the infant's life.

The mechanism of in vivo red cell clearance, when a blood group antibody causes HDN, is the extravascular one. Indeed HDN can be thought of as a form of warm antibody-induced haemolytic anaemia, albeit one caused by an alloantibody not an autoantibody. That is to say, in HDN antibody is made in the mother and red cell destruction occurs in the fetus.

Antibodies to blood group antigens that cause fetal anaemia

Despite the introduction of immunoprophylaxis programmes, Rh D incompatibility still remains the major cause of HDN. The D antigen is the most immunogenic protein structures that arise from the surface of the erythrocyte, and this is most likely due to the fact that D-negative individuals completely lack this protein. All other antibodies of the Rh system should be considered to be capable of causing HDN, but only c antibody often causes severe HDN. HDN due to anti-C, -E, -e is rare and the outcome seldom severe. Recently more attention has been paid to anti-G. These antibodies react with red cells expressing D and/or C, thus it may be mistaken for anti-D; it may also be present together with anti-D or -C. Other Rh system antibodies that have been reported to have caused serious HDN are -ce (-f), -CE, -Hr0 (Rh17).

Among the antibodies outside the Rh system responsible for HDN is anti-K from the Kell system. The HDN caused by anti-K is often very severe. Its patogenesis differs from that due to anti-D, mainly because anti-K destroys not only peripheral red cells but also suppresses erytropoesis through the immune destruction of early erythroid progenitors in the fetal liver. For this reason the prediction of the severity of HDN is more difficult than that caused by anti-D. The correlation between the anti-K titre and the severity of disease is lower, lower concentration of amniotic bilirubin and lower hyperbiliru- binemia in babies with anaemia, reduced reticulocytosis and erythroblastosis, lower predictive value of cellular functional assays.

ABO incompatibility and immunization to D antigen

Levine first noticed that immunization to D in D- women who deliver D+ infants is less common when the fetal red cells are incompatible with an ABO system antibody in the mother's plasma than when they are compatible. Other authors confirmed this observation. It was reasoned that the protective effect of ABO incompatibility was related to the rate of clearance of the fetal red cells from the maternal circulation. When group A D+ red cells enter the circulation of a group O D- woman, those cells are rapidly destroyed by women anti-A. Thus they comprise a single immunogenic challenge. When group O D+ fetal red cells enter the circulation of a group O D- woman, whose serum does not contain anti-D, they survive normally. A few cells are removed from the woman's circulation each day as they reach the end of their normal life-span. Thus the entry of a volume of group O D+ fetal red cells into the circulation of the group O D- women will result in a series of small immunizing doses (as a few cells are removed each day) over a period of months. A series of small immunizing dose is more likely to initiate antibody production than is a single dose.

2. Diagnosis of HDN

2.I. Laboratory methods

Routine serological methods

For many years it has been routine practice to perform immunohaematological tests during pregnancy to predict the risk of HDN. Although the methodology and quality of serological testing have improved significantly, the ability of these tests to predict haemolytic disease with certainty is far from perfect. Such tests will always be considered supplementary to obstetric monitoring.

- ABO and Rh D group
  The ABO and Rh D group of all pregnant women should be determined as early as possible during each pregnancy, when they first attend for antenatal care.

- Blood groups antibody detection
  At the first antenatal visit mother's serum should also be screened for any IgG antibodies to red cells, which can cause HDN or could cause problems in obtaining compatible blood in the event of obstetric haemorrhage. If no antibodies are detected, although the risk of occurrence of D alloimmunisation between the first trimester visit and 28 weeks' gestation is quite low (on the order of 18%), the pregnant woman should have a further antibody check at 28-30 weeks gestation.

– Quantification of antibodies
  Once detected, the ability of an antibody to cause HDN is generally estimated by antibody quantification. Serial testing (at least once monthly) provides useful information regarding the antibody trend through pregnancy. Rising levels may be indicative of HDN developing in the fetus, but not confirm the blood group of the fetus or the severity of haemolysis.

– Detection of fetal red cells in the maternal circulation
  There are many different methods in use for the detection of a larger than usual fetal to maternal haemorrhage (FMH). Once of the earliest method used to detect fetal red cells in maternal circulation was described by Kleihauer and Betke. The rosette test, the test with fluorescein-labeled antibodies, the enzyme-linked antiglobulin test and other tests are used nowadays for evaluation of the feto-maternal haemorrhage.

Functional cellular assays

Serological tests indicate whether an antibody is of clinical importance, but they do not predict its functional activity. Immune destruction is a complex process, in which the interaction between sensitized erythrocytes and cells of the mononuclear system (monocytes, lymphocytes via their Fc gamma-receptors), plays an important role, although the mechanisms of in vivo immune red cell destruction are far from clear. Presently there are three functional assays: the monocytes monolayer assay (MMA), antibody-dependent cellular cytotoxicity (ADCC) assay, and the chemiluminescence test (CLT).

Fetal genotyping

With recent advances in molecular biology, DNA amplification, and the cloning of RH and KEL genes, it has been possible to establish the fetal blood groups from chorionic villi or from amniocytes. These tests are of great value to predict or exclude fetal haemolytic disease, when a woman has a high antibody level at the beginning of pregnancy and the partner is heterozygous for the corresponding blood groups. However, because of the invasive means by which such samples are obtained, these approaches increase the risk of future sensitizing of the mother. The demonstration of free fetal DNA in maternal plasma by the end of 90-ties raised a new possibility. Using maternal plasma and real time PCR with its automation opened the possibility for examining a large number of samples.

2.2. Obstetric monitoring

Amniocentesis

The level of bilirubin in the amniotic fluid gives an indirect assessment of the severity of fetal haemolysis.

Ultrasound examination

Ultrasound examinations are of limited use in predicting moderately severe HDN. Measurement of the liver and spleen size, polyhydramnios, and enlargement of the heart has been used to diagnose the prehydropic changes.

Fetal Doppler ultra-sonography

Ultra-sonography is a non-invasive method that can be used to study fetal haemodynamics and show physical indications of developing anaemia before hydrops develops.

Fetal blood sampling

The best method to assess haemolytic disease is the direct determination of fetal haemoglobin, haematocrit, and blood groups by testing a blood sample obtained by cordocentesis. This procedure is not without risk even in experienced hands; the risk of fetal loss is 1 %–2 %. Furthermore, there is a risk of feto-maternal haemorrhage and the problem of boosting the antibody level as well as stimulating the development of new antibodies.

3. Prevention of HDN

TThe administration of prophylactic of anti-D will remain the single most critical clinical intervention to prevent HDN, caused by anti-D antibodies (Rhesus disease). The development of fetal anaemia is most often caused by the failure of anti-D prophylaxis, either by non-administration, at insufficient dose or unrecognized fetal leak late in pregnancy.

Approaches to prevention of Rhesus disease include:

- Postpartum administration of anti-Rh D immunoglobulin to those Rh D-negative women who give birth to a Rh D-positive fetus.
- Selective administration of Rh D immunoglobulin antenatally to cover procedures or accidents.
- Routine antenatal prophylaxis.

Postpartum prophylaxis

Postpartum prophylaxis is the most common approach to the prevention of Rhesus disease. The immunization to D of Rh D-negative mother following delivery of Rh D-positive child can be prevented in 98% to 99% of women providing a suitable quantity of anti-D immunoglobulin. Although 20 μg (100 IU) of anti-D per 1 mL of D+ fetal red cells appears to be sufficient to prevent immunization to D, it has been suggested that 25 μg (125 IU) / 1 mL D+ fetal red cells could be used to provide a safety margin. At least 100 μg (500 IU) dose of anti-Rh D immunoglobulin should be administered to an Rh D-negative mother within 72 hours of delivery if the fetus is Rh D-positive. A dose of 100 μg of anti-Rh D immunoglobulin gives protection for up to 4 mL of fetal red cells. If the Kleihauer or other test is performed and shows more than 4 mL of fetal red cells in the maternal circulation, further anti-Rh D immunoglobulin must be given. It must be noted that other dosages (300, 250 and 200 μg) are suggested by different guidelines (as the American one) and are in use in different countries, depending mostly on medical traditions and on local availability of different commercial preparations.

Selective prophylaxis

If any sensitizing event (procedures during pregnancy, abortion, antepartum haemorrhage etc) occurs during the antenatal period, 50 μg (250 UI) of anti-Rh D immunoglobulin should be administered up to 20 gestation weeks. It is recommended, for all events after 20 weeks, the application of 100 μg (500 UI) anti-D immunoglobulin, followed by a test to identify FMH greater than 4 mL red cells. Additional anti-D immunoglobulin should be given as required.

Antenatal prophylaxis

Since not all cases of feto-maternal haemorrhage are detected during pregnancy, there is still a risk (estimated as 1%) that maternal sensitization to Rh D-positive red cells may occur. For this reason, some countries now recommend that all pregnant women who are Rh D-negative should receive routine anti-Rh D proph-

ylaxis (reducing sensitization to 0,2% or less), being the extent of the practice of course also depending on different availability of financial resources.

Use of monoclonal anti-D for prophylaxis

Monoclonal antibodies are now being developed for use as prophylactic anti-D, and novel anti-D antibodies have been engineered that do not react with immune system effector cells, in the hope that such antibodies can be used to "block" Rh haemolytic disease of the newborn. Additionally those therapeutic reagents are decreasing the potential risk of transmission of human blood-borne infectious agents.

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