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Prevention Of Erythrocytic Alloimmunization: Review Of The Literature

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***Abstract**: The current dissemination of systematic prophylaxis in the third trimester is still incomplete despite professional recommendations (poor adaptation of doses, poor patient information, forgetfulness); it is therefore important to further improve information for pregnant women (1). It is a frequent pathology whose diagnosis is easily made thanks to biological assays. Management can now be anticipated and follow-up must be adapted. The prognosis has improved considerably today thanks to advances in research, non-invasive fetal blood group genotyping, Doppler velocimetry of the middle cerebral artery, fetal transfusion and intensive phototherapy.*

Keywords: Alloimmunization, Prevention.

INTRODUCTION :

It is due to the synthesis of alloantibodies in response to the transplacental passage of fetal red blood cells in the maternal circulation. These maternal antibodies cross the placenta into the fetal circulation, the antigenic target being blood group antigens.
The immune complexes formed lead to erythrocyte hemolysis, the consequences of which will depend on the type of antigen involved, the extent of immunization and the gestational age.
In general, the quantity of antibodies produced during the primary immunization is insufficient to have harmful consequences on the current pregnancy;
upon re-contact with the antigen (subsequent pregnancy with an incompatible fetus), reactivation of the immunization may lead to massive production of antibodies that will cross the placental barrier and cause significant lysis of fetal red blood cells.
This AIFME can then be responsible for a fetal anemia leading in its major form to fetoplacental hydrops and then death in utero.
At birth, the newborn is at risk of anemia and hyperbilirubinemia. If this hyperbilirubinemia is severe (> 200 mg/l), kernicterus may occur due to toxicity of free bilirubin on the basal ganglia.
Prematurity of medical indication also often complicates these pregnancies.

EPIDEMIOLOGY :

It has decreased considerably since the introduction in 1970 of systematic injections of anti-D immunoglobulin in rhesus-negative women during pregnancy and after delivery;
However, it remains the leading cause of fetal anemia.
The number of pregnancies in France is approximately 1-1.1 million per year. Approximately 15% of the French population is RhD-negative, so the number of RhD-negative women who become pregnant each year can be estimated at 150,000-165,000.
Because the frequency of the RhD gene is 0.6% in the French population, the annual number of RhD-negative women with RhD-positive fetuses would be about 90,000 (75,000 beyond 28 SA).
RhD alloimmunization concerns about one woman out of 100, and it is estimated that a severe form of hemolytic disease in the fetus and newborn is likely to occur in 10% of these patients, or less than 100 cases per year in France [1, 2]. And represents 0.9/1000 in Europe and 1.3/1000 in the USA and Canada.

PHYSIOPATHOLOGY :

is defined by the attachment to the fetal red blood cell of maternal alloantibodies transmitted in utero directed against blood group antigens of paternal origin.
The development of immunization involves:

- a contact between a blood group antigen and the organism that does not possess it;
- a reaction of the organism with production of antibodies specific to the unknown blood group antigen target;
- and the formation of immune complexes resulting in tissue immunohemolysis.
- It occurs in women of RhD-negative erythrocyte phenotype who are pregnant with a fetus of RhD-positive erythrocyte phenotype.

Maternal anti-RhD immunoglobulin G (IgG) antibodies cross the placenta into the fetal circulation, and may be responsible for fetal and neonatal hemolytic disease.
The essential etiology, apart from transfusion, is the passage of fetal blood into the maternal circulation or fetomaternal hemorrhage. This can occur in high-risk situations (metrorrhagia, abdominal trauma, invasive ovarian sampling, etc.), but also occultly, particularly in the third trimester of pregnancy.

RhD-IFME is the most frequent and severe cause of symptomatic alloimmunization, accounting for 70% of cases detected at birth and 90% of those requiring in utero treatment.
Other AIFME are rare; severe fetal anemia can be seen with c and Kell systems, rarely with E system and exceptionally with other antibodies [3, 4].

CONSEQUENCES OF ALLOIMMUNIZATION
can lead to serious fetal and neonatal consequences.

- Fetal hemolysis leads to anemia: To compensate for this anemia, compensatory erythropoiesis occurs, leading to hepatomegaly, resulting in fetal hepatocyte suffering (by compression of hepatocytes and hepatic vessels).
- This hepatic suffering leads to a decrease in the synthesis of hepatic proteins, including albumin, causing a decrease in oncotic pressure.
- If the anemia is not corrected by in utero transfusion, myocardial activity will increase, leading to cardiac failure and then a state of fetal anasarca (ascites, pericardial effusion, subcutaneous edema, hydramnios...) and may lead to fetal death in utero (FIDU) (2,4).
- During pregnancy, bilirubin released during hemolysis is eliminated by the maternal liver.At birth, the newborn's liver is immature and free bilirubin is not properly conjugated.

In addition, persistent maternal antibodies in the circulation may require exchange transfusion to limit neonatal hemolysis(5).

IMMUNIZING CIRCUMSTANCES
Approximately one quarter of anti-D alloimmunizations occur after fetomaternal hemorrhage with no identifiable risk factor, especially in the third trimester, and are therefore likely to escape targeted prevention. Indeed, a "spontaneous" passage of fetal red blood cells into the maternal circulation occurs in 4% of cases in the first trimester, 12% in the second trimester and 45% in the third trimester [1].
The remaining three quarters occur in high-risk situations.

- **In the first trimester (moderate risk of fetal red blood cell passage)**
  - Any spontaneous miscarriage or threatened spontaneous miscarriage in the first trimester
  - Any termination of pregnancy (abortion or IMG), regardless of the term and method used
  - Molar pregnancy
  - Ectopic pregnancy (EP)
  - Metrorrhagia
  - Choriocentesis (chorionic villus biopsy), amniocentesis Embryonic reduction
  - Abdominal trauma
  - Cervical cerclage
- **In the second and third trimesters**
  - Significant risk of passage of fetal red blood cells
  - Medical termination of pregnancy
  - Late spontaneous miscarriage
  - Fetal death in utero (FIDU)
  - External maneuver version (EMV)
  - Abdominal or pelvic trauma (regardless of the term of the pregnancy)
  - Abdominal or pelvic surgery (any term of pregnancy)
  - Ovarian sampling: amniocentesis, cordocentesis, placentocentesis Delivery by any route
  - Moderate risk of passage of fetal red blood cells
  - Metrorrhagia
  - Cerclage of the uterine cervix
  - Threat of preterm delivery (PAD) requiring treatment

PREVENTION:
This prevention is only possible in the RhD. system is based on the 2005 recommendations for clinical practice (RPC) of the Collège national des gynécologues et obstétriciens franc ¸ais (CNGOF), the Centre national de référence en hémobiologie périnatale (CNRHP) and the Société française de médecine périnatale (SFMP).
The principle is based on the administration of anti-D immunoglobulins that will destroy RhD-positive red blood cells of fetal origin and thus eliminate them from the maternal circulation and prevent immunization.
mmunoglobulins are obtained from human plasma from donors who have voluntarily been immunized against the D antigen. This practice is currently prohibited in Europe and France is therefore totally dependent on the supply of plasma from North America.

This situation poses problems related to the fragility and cost of this supply and a theoretical risk of infectious safety [1].
In conventional pregnancy monitoring, a double RhD blood grouping and irregular agglutinin test (RAI) are mandatory in the first trimester of pregnancy in all women.

- If the woman is RhD-negative, information should be delivered on anti-D immunization: screening, follow-up, prevention.
- During this consultation, two attitudes are possible:
- determination of the spouse's rhesus group
- or, ideally, proposal to perform a polymerase chain reaction (PCR) on maternal blood as early as 11 to 12 SA to determine the fetal RHD genotype.
- The DNA present in the plasma of pregnant women includes 1-6% DNA of fetal origin in cell-free form (5); therefore, it is possible through a gene amplification technique, to determine the fetal sex genotype and the fetal RHD genotype
  (6 -7)
- If the woman is not immune to the D antigen, an IAT check should be performed during the sixth month of pregnancy, ideally between 26 and 28 weeks' gestation:
- if the spouse is RhD-negative and paternity is certain or if the fetus is RhD-negative: anti-D prophylaxis can be avoided;
- if the spouse is RhD positive or unknown and/or if the fetus is RhD positive: anti-D prophylaxis should be offered.
- The patient is informed and consent is required before any administration of anti-D immunoglobulin.
- Before any decision is made to administer anti-D immunoglobulin, the absence of anti-D immunization is ascertained by an IAT less than one week old.
- In emergency situations, the result should not be waited for before injection.

ROUTE OF ADMINISTRATION:

When the anti-D immunoglobulin galenic allows the intramuscular or intravenous route, the intravenous route is always preferred for postexposure prophylaxis.
The intravenous route is highly recommended when approaching the 72-hour window or in cases of maternal-fetal hemorrhage proven by a Kleihauer test.
When a new antenatal circumstance indicating targeted immunoprophylaxis occurs after an initial administration of anti-D, repeat prophylaxis may be withheld for a period of time that depends on the previously rec ue dose (9 weeks for 200 g, 12 weeks for 300 g). The effectiveness of immunoprophylaxis is based on :

- an appropriate dosage of anti-D
- injection of immunoglobulins within 72 hours after a potentially immunizing event, beyond which a benefit can be expected for up to 30 days.

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KLEIHAUER TEST:

Allows the detection of fetal red blood cells in the maternal circulation. It is the simplest diagnostic test to distinguish fetal red blood cells from maternal red blood cells. It is performed in situations where there is a risk of significant passage of fetal red blood cells into the maternal blood.
The main disadvantages of this test are that it is operator-dependent and subject to false positives related to the persistence of maternal HbF (e.g. heterozygous hemoglobinopathy).
The results of diagnostic tests are presented as a percentage most often (number of fetal red blood cells out of 10,000 maternal red blood cells).

IN THE FIRST TRIMESTER:

- There is no lower age limit for performing prevention. A single injection of 200 g of anti-D immunoglobulin is justified in all situations listed in the Table above.
- A Kleihauer test is not performed.

SECOND TRIMESTER:

- In circumstances that may result in significant passage of fetal red blood cells, anti-D immunoglobulin dosing is based on the Kleihauer test
- For all other circumstances, a single injection of 200 g is sufficient.

IN THE THIRD TRIMESTER:

- A routine injection of 300 g of anti-D gamma globulin should be offered to all RhD-negative women whose spouse is RhD positive or unknown or if the fetal RhD is positive.
- It is performed intramuscularly at 28 SA ± 1 week ;
- If the routine injection has not been performed at 28 weeks' amenorrhea (SA), the patient may be offered an injection :
  - of 300 µg between 28 and 32 SA,
  - of 200 µg after 32 SA.
- there is no need to subsequently repeat IARs (which will be positive) until 37 SA.
- It is recommended that a new IAT be performed in the last month to identify any immunization other than anti-D, mainly for transfusion purposes.

AT DELIVERY:

- The RhD phenotype of the newborn should be determined. Sampling can be performed on blood collected from the umbilical cord.
  - If the child is RhD positive, a Kleihauer test is performed on a maternal blood sample collected at least 30 minutes after delivery, and the mother is offered anti-D prophylaxis.
  - Dosage and route of administration are to be adjusted according to the Kleihauer test .
  - If immunoglobulin administration is missed in the first 72 hours, the injection can still be given beyond that, as soon as possible and up to 30 days after delivery.
  - If anti-D immune globulin is routinely injected into the mother at 28 SA, the Coombs test may be positive in the RhD-positive newborn (nearly 10% of cases). In the absence of associated symptoms (jaundice, anemia), no further investigation is required.

CANADIAN RECOMMENDATIONS: (8)

Prenatal:

300 g of anti-D Ig should routinely be given to any nonsensitized Rh-negative woman at 28 weeks' gestation, when the fetal blood type is unknown or has been determined to be Rh-positive.

Otherwise, 2 doses of 100-120 g (the latter being the smallest dose currently available in Canada) may be given: the first at 28 weeks and the second at 34 weeks (I-A).

All pregnant women should be typed and screened for alloantibodies (D-negative or D-positive) by indirect antiglobulin testing at the first prenatal visit and again at 28 weeks (III-C).

When paternity is definitely known, the father of the baby can be offered an Rh test if the pregnant woman is Rh-negative, to avoid unnecessary administration of blood products (III-C).

A woman with "weak D" (also called Du positive) should not receive anti-D (III-D).

A repeat prenatal dose of Rh immune globulin is usually not necessary at 40 weeks, provided the prenatal injection was not given before 28 weeks' gestation (III-C).

Postpartum:

300 g of anti-D Ig should be administered i.m. or i.v. within 72 hours of delivery to a nonsensitized Rh-negative woman who has given birth to an Rh-positive child.

Additional anti-D Ig may be required in cases of maternal-fetal hemorrhage (MFH) where fetal red cell loss exceeds 15 ml (approximately 30 ml of fetal blood).

Alternatively, 120 g of anti-D Ig can be given i.m. or i.v. within 72 hours of delivery, with appropriate testing and additional anti-D Ig given for FMH of more than 6 mL of fetal red blood cells (12 mL of fetal blood) (I-A).

If anti-D Ig is not given within 72 hours of delivery or other potentially sensitizing event, it should be given as soon as the need is recognized, up to 28 days after delivery or other potentially sensitizing event (III-B).

There is no good evidence to support the inclusion or exclusion of routine postpartum FMH surveillance testing, and the cost/benefit of such testing in at-risk Rh mothers has not been determined 34,35 (III-C).

Recommendations in immunizing circumstances at risk for FMH:

After spontaneous, threatened, or induced abortion during the first 12 weeks of gestation, nonsensitized D-negative women should be given a minimum of 120 g of anti-D Ig. After 12 weeks of gestation, 300 g should be administered (II-3B).

At the time of abortion, blood typing and antibody testing should be performed unless it was performed during pregnancy, in which case antibody testing need not be repeated (III-B).

In ectopic pregnancies, anti-D Ig should be administered to nonsensitized D-negative women at a minimum of 120 g before 12 weeks' gestation and 300 g after 12 weeks (III-B).

Anti-D Ig should be given to nonsensitized D-negative women following a molar pregnancy because of the possibility of the presence of partial mole. If a diagnosis of complete mole is certain, anti-D Ig can be omitted (III-B).

At the time of amniocentesis, 300 g of anti-D Ig should be administered to nonsensitized D-negative women (II-3B).

Following chorionic villus sampling, anti-D Ig should be administered to nonsensitized D-negative women. During the first 12 weeks of gestation, a minimum of 120 g of anti-D should be administered. After the 12th week, 300 g of anti-D should be administered (II-B).
After cordocentesis, 300 g of anti-D Ig should be administered to nonsensitized D-negative women (II-3B).
Quantitative testing for FMH may be considered following events that may be related to placental trauma and disruption of the fetomaternal interface (e.g., placental abruption, abdominal contusion, cordocentesis, placenta previa with bleeding). There is a significant risk of FMH greater than 30 mL in such incidents, especially in the case of abdominal contusion (III-B).
It is recommended that120 gor300 gof anti-D Ig be administered when performing tests to quantify FMH following situations that may be related to placental trauma and disruption of the fetal-maternal interface (e.g., placental abruption, external cephalic version, abdominal contusion, placenta previa with bleeding). If FMH exceeds the amount corresponding to the given dose (6 ml or 15 ml of fetal erythrocytes), an additional 10 μg of anti-D Ig should be administered for every 0.5 ml of fetal erythrocytes. There is a risk of excessive FMH, especially in cases of abdominal contusion 62 (III-B)

Conclusion

The current dissemination of systematic prophylaxis in the third trimester is still incomplete despite professional recommendations (poor adaptation of doses, poor patient information, forgetfulness); it is therefore important to further improve information for pregnant women (1).

It is a frequent pathology whose diagnosis is easily made thanks to biological assays. Management can now be anticipated and follow-up must be adapted.

The prognosis has improved considerably today thanks to advances in research, non-invasive fetal blood group genotyping, Doppler velocimetry of the middle cerebral artery, fetal transfusion and intensive phototherapy.

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