«APPROVING»
on the sitting of chair of obstetrics and
gynecology №1 of “UMSA”
(protocol № 1 from 28. 08.2020)

Acting manager of chair of obstetric and
gynecology №1
professor  A.M. Gromova

METHODOICAL POINTING
for the independent work of students for preparation to practical lesson

<table>
<thead>
<tr>
<th>Educational subject</th>
<th>Obstetric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modul №</td>
<td>2</td>
</tr>
<tr>
<td>Subject of lesson</td>
<td>Immunologic disorders in pregnancy</td>
</tr>
<tr>
<td>Course</td>
<td>V</td>
</tr>
<tr>
<td>faculty</td>
<td>Foreign students training faculty (medical)</td>
</tr>
</tbody>
</table>
Immunologic disorders in pregnancy

1. Relevance of the topic: abilities to diagnose Rh and other isoimmunization, hemolytic disease in obstetrics practice allows to prescribe adequate therapy to pregnant women, therefore decrease the amount of perinatal diseases and lethality.

2. Specific goals:

- To be able to diagnose the Rh and other isoimmunization in the obstetrics
- To prescribe the adequate treatment to the pregnant women
- To be able to diagnose the hemolytic disease of the infant and to prescribe the treatment of this pathology

3. The basic level of expertise, skills, abilities, required for learning the topic (interdisciplinary integration)

<table>
<thead>
<tr>
<th>Names of previous disciplines</th>
<th>Skills acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiology</td>
<td>Blood types</td>
</tr>
<tr>
<td></td>
<td>Blood transfusion technique</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>Physiology of the neonatal period</td>
</tr>
<tr>
<td></td>
<td>The hemolytic disease of the newborn.</td>
</tr>
<tr>
<td>Immunology</td>
<td>The mechanism and pathogenesis of the immune-conflict for the Rh-factor and group incompatibility</td>
</tr>
</tbody>
</table>

4. Tasks for independent work during preparation to the lesson and in the lesson.

4.1. A list of basic terms, parameters, characteristics that a student must learn during preparation to the lesson.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemolytic Disease of Newborn (HDN)</td>
<td>HDN is a disease conditioned by immunologic havoc because of the incompatibility of the maternal and fetal blood by erythrocytic antigens</td>
</tr>
<tr>
<td>2. Cordocentesis</td>
<td>collecting blood from the fetal umbilical cord through the anterior abdominal wall of the woman</td>
</tr>
<tr>
<td>3. Rhesus isoimmunization (Rh)</td>
<td>is an immunologic disorder that occurs in a pregnant, Rh-negative patient is carrying an Rh-positive fetus.</td>
</tr>
</tbody>
</table>
4.2. Theoretical questions for the lesson.

1. What changes are taking place in all systems of a pregnant woman?
2. What is the scheme for examining a pregnant woman?
3. How does the tactics of a pregnant woman depend on the titer of rhesus antibodies?
4. What are the pathogenesis of hemolytic disease of the newborn?
5. What are the principles of pregnancy management in antenatal clinics?

4.3. Practical activities (tasks) to be performed on the lesson

1. To estimate the titer of rhesus antibodies
2. To evaluate fetal cardiotocography
3. To make a plan of management of a pregnant women with Rh-isoimmunization

Topic content:

Immunologic disorders in pregnancy

Rhesus (Rh) isoimmunization is an immunologic disorder that occurs in a pregnant, Rh-negative patient is carrying an Rh-positive fetus. The immunologic system in the mother is stimulated to produce antibodies to the Rh antigen, which then crosses the placenta and destroys red blood cells.

Risk of Rh Sensitivization: mismatched blood transfusion (90 – 95 %), full-term delivery, ABO-compatible or incompatible (14 – 17 %), induced abortion (5 – 6 %), spontaneous abortion (3 – 4 %), amniocentesis (1 – 3 %), full-term pregnancy (1 – 2 %), ectopic pregnancy (< 1%).

Pathophysiology. The "Rh disease" results from the Rh negative mother becoming isoimmunized to an Rh antibody from the red cells of her first child.

1) The first Rh positive pregnancy will almost never be affected unless the mother has a previous blood transfusion with Rh positive blood;
2) Once immunized, the mother’s immune system responds by manufacturing anti Rh isoantibodies with the second pregnancy;
3) If the second pregnancy is one in which the fetus Rh is positive, the mother’s anti Rh isoantibodies are transferred to the fetus across the placenta.

Stages of hemolytic disease of infant severity:

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>I stage</th>
<th>II stage</th>
<th>III stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia, hemoglobin level in umbilical cord (g/L)</td>
<td>150</td>
<td>150–100</td>
<td>100</td>
</tr>
<tr>
<td>Jaundice, bilirubin level in umbilical cord (mkmol/L)</td>
<td>85.5</td>
<td>85.6–136.8</td>
<td>136.9</td>
</tr>
<tr>
<td>Edema</td>
<td>Subcutaneous edema</td>
<td>Edema of subcutaneous fat and</td>
<td>Hydrops fetalis</td>
</tr>
</tbody>
</table>
**Indications to exchange blood transfusion in infants:**

<table>
<thead>
<tr>
<th>Laboratory symptom</th>
<th>In term fetus</th>
<th>Preterm fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I day</td>
<td>Repeated</td>
</tr>
<tr>
<td>Indirect bilirubin. mkmoll/L</td>
<td>&gt; 68.42</td>
<td>300.7</td>
</tr>
<tr>
<td>Indirect bilirubin per hour, mkmoll/L</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>&lt; 150</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
</tr>
</tbody>
</table>

Critical indirect bilirubin level which damage the nervous ganglia and provoke kernicterus in in term fetus 307.8 – 342 mkmol/L in preterm fetus 153–205 mkmol/L.

**Diagnosis of isoimmunization:** basis of history – previous pregnancies abortions, ectopic pregnancy.

- Determination of the father’s Rh status;
- Maternal blood is tested for presence of variety of antibodies that may cause significant disturbances in fetus – "antibody screening test" "indirect" and "direct Coomb’s tests". Mild isoimmunization – antibody titer below 1:16. Rarely produced fetal hydrops do not usually cause any intervention in the pregnancy. The newborn may be anemic and hyperbilirubinemia may develop. Severe isoimmunization – titer of over 1:16 or greater is generally considered to be the critical point at which there is a sufficient risk of fetal jeopardy to warrant additional evaluation. The amniocentesis or percutaneous umbilical blood sampling (PUBS) should be done;
- Amniocentesis denotes the amount of blood destruction by estimating the amount of bilirubin pigments in the amniotic fluid;
- Percutaneous umbilical blood sampling (PUBS) under ultrasound guidance – fetal blood can be taken for hematocrit, hemoglobin, blood gases, pH, bilirubin levels;
- Amniotic fluid spectrophotometry – there is an excellent correlation between the amount of biliary pigment in the amniotic fluid and the fetal hematocrit beginning at 27 weeks gestation. Liley chart can be used – it is a spectrophotometric graph based on the correlation of cord blood hemoglobin concentrations at birth and the amniotic fluid change in optical density at 450nr;
- Ultrasonic detection – both the placenta and the fetal liver are enlarged with hydrops. Fetal hydrops is easily diagnosed by the characteristic appearance of one or more of the following: ascites, pleural effusion, pericardial effusion, skin edema.
Appearance of these factors during ultrasonic examination eliminates the need for diagnostic amniocentesis and necessitates the therapeutic intervention based on fetal gestational age;

- New techniques for evaluating fetal Rh Status 1) determination of fetal RhD blood type by DNA amplification using a single fetal nucleated erythrocyte isolated from maternal blood, 2) determination of fetal RhD genotype from amniotic fluid or chorionic villus cells using DNA amplification;

  Administration of Rh Immune Globulin (RhoGAM) prevents an active antibody response by the mother in most cases. Standard 300-mg dose of Rh immune globulin effectively neutralizes 15 ml of fetal red blood cells.

  **Indications** of RhoGAM administration man unsensitized Rh-negative patient (unless the father of the infant is known to be Rh-).

  - At approximately 28 weeks pregnancy – the risk of sensitization is reduced to 0.2 %;
  - Within 3 days (72 hours of delivery) days of delivery of an Rh-positive infant – the risk of subsequent sensitization decreases from approximately 15 % to 2 %;
  - At the time of amniocentesis;
  - After positive Kleihauer-Betke test – it allows to identify fetal cells in maternal circulation in cases of trauma or bleeding during pregnancy because of which feto-maternal hemorrhage has occurred;
  - After ectopic pregnancy, spontaneous or induced abortion – 50 mg of RhoGAM can be used to prevent sensitization.

**Pregnancy Isosensitization**

**1. Etiology and Pathogenesis**

Isosensitization is one of clinical forms of pregnancy immunopathologies, which arises at incompatibility of the mother’s and fetal organisms by various erythrocytic antigens and leads to severe consequences of embryogenesis and postnatal development.

Rh-isoimmunization is humoral immune response to the fetal erythrocytic antigens of Rh-group including Cc, Dd and Ee (Rh-alleles coded), with the penetration of the formed antibodies through the placenta, which causes extracellular hemolysis (opsonization of fetal erythrocytes with the woman’s antibodies and erythrocyte phagocytosis) and anemia and leads to fetal erythroblastosis.

Presently, more than ten isoserologic red blood systems are known. Five basic factors of the rhesus system are known: D, C, c, E, e (Fisher’s terminology), which might be marked Rho, Rh’, hr’, Rh”, hr” (Winner’s terminology). Rh-positive
erythrocytes contain D-factor (Rho-factor), and the so-called Rh-negative erythrocytes do not have it, though they surely have other Rh-system antigens.

Etiology of Rh-sensitization development: artificial abortions; spontaneous abortions; Rh-positive blood transfusion in anamnesis; extrauterine pregnancy; no specific prophylaxis of rhesus incompatibility after the previous pregnancy; rhesus incompatibility at previous pregnancy; erroneous transfusion of Rh-positive blood to a Rh-negative woman; “grandmother” theory (sensitization of a Rh-negative woman at birth conditioned by a contact with Rh-positive erythrocytes of her mother) – up to 20% of sensitization (reveals itself already at the first pregnancy); usage of one syringe by drug addicts

At erythrocytic antigens isosensitization hemolytic disease of fetus (HDF) or of newborn (HDN) may develop.

Isoimmunization risk is increased by: abruption of placenta; operative interventions (manual removal of afterbirth, cesarean section); viral infections (herpetic, cytomegalovirus); amniocentesis and chorion biopsy; mother’s trauma during pregnancy.

Rh-factor has evident antigenic properties, therefore even one Rh-positive blood transfusion to a Rh-negative woman, but the most frequently – pregnancy and delivery of Rh-positive fetuses lead to isoimmunization. Rh-immunization may arise at operative interventions (manual removal of afterbirth, cesarean section), after an artificial abortion, spontaneous abortion, extrauterine pregnancy. If fetal erythrocytes having D-antigen, absent in the mother, penetrate into the mother’s bloodstream during the first pregnancy, this leads first to the synthesis of Rh-antibodies of M immunoglobulins, which do not penetrate through the placenta, and then to G antibodies, which can penetrate through the placenta. During pregnancy, because of a small amount of fetal erythrocytes and because of active immunosuppressive mechanisms the primary immune response of the mother is reduced, but after childbirth in connection with a big amount of the child’s erythrocytes in the mother’s bloodstream, which have penetrated during delivery, and because of immunosuppression elimination active synthesis of Rh-antibodies takes place. For this very reason introduction of exogenous Rh-antibodies (anti-D-immunoglobulin)
in the course of 24 – 72 h after delivery or 24 – 48 h after abortion (D-antigens appear in the embryo at the beginning of the second month of gestation) is and effective method of reducing both Rh-sensitization and Rh-RDN frequency. In the countries, where such prevention is carried out, Rh-HDN frequency has reduced considerably, for instance, in GB – by 95 %.

<table>
<thead>
<tr>
<th>Rh (-) fetus</th>
<th>Rh (+) mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoting factors</td>
<td></td>
</tr>
<tr>
<td>Penetration of fetal erythrocytes into mother’s bloodstream</td>
<td></td>
</tr>
<tr>
<td>Synthesis of antibodies to fetal Ig M erythrocytes (do not penetrate through the placenta)</td>
<td></td>
</tr>
<tr>
<td>Synthesis of antibodies to fetal Ig G erythrocytes (easily penetrate through the placenta, are synthesized in 3 months)</td>
<td></td>
</tr>
<tr>
<td>Conjugation with fetal erythrocytes</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte destruction</td>
<td>Erythrocyte membrane damage</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Erythrocyte capture by liver, spleen and bone-marrow macrophages</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Erythrocyte death</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
</tbody>
</table>

2. Diagnostics in the Course of Pregnancy

Isosensitization detection:

Anamnasis data. Special attention is paid to obstetric anamnasis, a history of blood transfusions, their complications, information on the character and tolerance of prophylactic immunizations.

First of all, such inspection is conducted on:
- all pregnant women with Rh-negative blood, whose husbands have Rh-positive blood; the pregnant are inspected for isoantibodies presence when they are registered, at 20 weeks, and then every 4 weeks;
- all parturient women, whose children suffer from HDF;
- all women, who have given birth to dead children, children with universal edema, or children hemolytic disease signs.

**Evaluation of spouses’ blood antigenicity (Rh-factor, blood group)**

Detection of Rh-antibody titer (the size of Rh-antibody titer not always reflects the degree of rhesus incompatibility severity). Rh-antibody titer from 1:2 to 1:16 is detected as the one not threatening the development of the edematous form of HD. If the titer is 1:32 and more, the edematous form of HD is more frequent. Rh-antibody titer of 1:63 and more is expedient to be viewed as critical.

Conditions, when antibody titer loses its information value and control over the dynamics of pregnancy course by the data of amniotic fluid investigation is required:

- antibody titer is at the critical level and higher when detected for the first time;
- the titer reaches or exceeds the critical level at any pregnancy term;
- there is detected a considerable increase (for 2 and more dilutions) of the titer between any two consecutive tests, even if the highest index does not reach the critical level;
- any augmentation of antibody titer and ultrasound signs of HDF;
- stillbirth or birth of children with HD in anamnesis in combination with US signs of HD at this pregnancy.

Coombs’ test: if incomplete (blocking) antibodies are present, on the surface of erythrocytes of the examined patient there is observed the agglutination of erythrocytes at their incubation with antiglobulin serum (indirect Coombs’ test) or with dilutions of the patient’s serum in reaction with erythrocytes of a donor preliminarily sensitized with salines (direct test).

Rh-factor detection by fetal hemoglobin in the maternal blood flow

Antenatal diagnostics of haemolytic disease of fetus (HDF)

Noninvasive methods:

- antibody-dependent cell-mediated cytotoxicity assay – ADCQ;
- supersonic scanning (allows to diagnose HD signs from 20 weeks of pregnancy; is conducted once a month in the pregnant women of the risk group
of HDF development, after 30 weeks – twice a month). Ultrasound investigation is obligatory once a month till 30 weeks, twice a month – after 30 weeks, in case supersonic scanning shows signs of HDF – daily till delivery;

- cardiography (detects signs of chronic intrauterine fetal hypoxia and reduction of compensatory capacity of the fetoplacental complex);
- detection of fetoplacental complex hormones (increase of the level of placental lactogen; decrease of estradiol level; α-fetoprotein increase);
- dopplerometric investigation of the uteroplacentofetal blood flow;
- proteinogram of maternal blood (decrease of the level of albumins and γ-globulins and increase of the level of β-globulins in the course of pregnancy).

Invasive methods:

- transabdominal amniocentesis. Amniocentesis is conducted transabdominally in the presence of indications but not earlier than 26 weeks of gestation. The following parameters are detected: optical bilirubin density (at wave length of 450 nm), whole protein content (HDF – more than 3 g/L), glucose content (HDF – more than 1.5 g/L), creatinine concentration (HDF – less than 150 mmole/L), acid-base balance of the amniotic fluid, estradiol and placental lactogen concentration.

The mechanism of bilirubin concentration increase in the amniotic fluid is conditioned by bilirubin transudation through the Wharton’s jelly of the umbilical cord and bilirubin diffusion through the placenta.

- Cordocentesis (is conducted from 24 weeks of pregnancy) – collecting blood from the fetal umbilical cord through the anterior abdominal wall of the woman (is conducted in specialized medical institutions).

3. Pregnancy and Labor Management at Isosensitization

All pregnant women with Rh-negative blood can be divided into 3 dispensary groups:

1 – the group of nonsensitized pregnant women (antibodies are absent);
2 – the group of sensitized pregnant women threatened by Rh-incompatibility (there are antibodies but no HDF signs);
3 – pregnant women with detected Rh-incompatibility (antibodies + HDF signs).

General principles of management at the stage of antenatal clinic:

- detection of Rh-antibodies titers in the blood (when the woman is registered, at 20 weeks, then once in 4 weeks);
- blood analysis for the presence of group immune antibodies (in pregnant women with the O (I) blood group, and the husband with the A (II), B (III), AB (IV) blood group);
- referral of pregnant women to the hospital if antibody titer or HDF signs are detected by means of additional researches;
- conducting prophylaxis of Rh-sensitization in Rh-negative pregnant women in the absence of antibodies at the term of 28–32 weeks by means of introducing human anti-D-immunoglobulin.

<table>
<thead>
<tr>
<th>Rh affinity of the father</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh (-)</td>
<td>Rh (+)</td>
</tr>
<tr>
<td>Further tests are not needed, the woman is managed as a normal pregnant woman</td>
<td>Screening-test for antibodies presence at 24 and 28 weeks</td>
</tr>
<tr>
<td>The test for antibodies presence is negative</td>
<td>The test for antibodies presence is positive</td>
</tr>
<tr>
<td>Anti-D-immunoglobulin is introduced at 28 weeks of pregnancy</td>
<td>The test for antibodies presence is repeated every 2 weeks, and</td>
</tr>
<tr>
<td></td>
<td>The woman is managed as a patient with isosensitization</td>
</tr>
</tbody>
</table>
Management of the 2\textsuperscript{nd} group of pregnant women: the group of sensitized pregnant women threatened by Rh-incompatibility (there are antibodies but no HDF signs).

This group includes Rh (-) women:

1) pregnant women with Rh-antibodies detected;

2) pregnant women, whose sensitization factor may be detected by the data of compromised obstetric and posttransfusion history (spontaneous abortions, stillbirth, preterm delivery, hemotransfusions nonregistering Rh-factor, delivering children with HDF), in whome antibodies can not be detected.

Patients of this group have 5 courses of desensitizing therapy beginning from 12 weeks of pregnancy with an 8-week interval.

Management of the 3\textsuperscript{rd} group of patients – pregnant women with detected Rh-incompatibility (antibodies + HDF signs) – is carried out in a specialized obstetric hospital including:

Prophylaxis and treatment of fetoplacental insufficiency (FPI) (under the control of hormones: progesterone, prolactin, HGC, estradiol, estriol):

- aktovegin – 5.0 ml i.v. drop-by-drop in 200 ml of sodium chloride physiologic saline No. 10;
- dipiridamol – 4.0 ml i.v. drop-by-drop in 200 ml of sodium chloride physiologic saline No. 10;
- essentiale 5.0 + autoblood 5.0 i.v. 5 times, then 1 capsule 3 times No. 10;
- ATP 1.0 i.m. alternated with cocarboxylase 100 mg i.v. No. 10;
- folic acid 1 tablet 3 times with ferric sulphate 1 tablet 3 times a day;

beginning from the 35\textsuperscript{th} week – once a week

Repeated introduction of anti-D-immunoglobulin in the puerperal period

| Management of the 2\textsuperscript{nd} group of pregnant women: the group of sensitized pregnant women threatened by Rh-incompatibility (there are antibodies but no HDF signs). |
| This group includes Rh (-) women: |
| 1) pregnant women with Rh-antibodies detected; |
| 2) pregnant women, whose sensitization factor may be detected by the data of compromised obstetric and posttransfusion history (spontaneous abortions, stillbirth, preterm delivery, hemotransfusions nonregistering Rh-factor, delivering children with HDF), in whome antibodies can not be detected. |
| Patients of this group have 5 courses of desensitizing therapy beginning from 12 weeks of pregnancy with an 8-week interval. |
| Management of the 3\textsuperscript{rd} group of patients – pregnant women with detected Rh-incompatibility (antibodies + HDF signs) – is carried out in a specialized obstetric hospital including: |
| Prophylaxis and treatment of fetoplacental insufficiency (FPI) (under the control of hormones: progesterone, prolactin, HGC, estradiol, estriol): |
| - aktovegin – 5.0 ml i.v. drop-by-drop in 200 ml of sodium chloride physiologic saline No. 10; |
| - dipiridamol – 4.0 ml i.v. drop-by-drop in 200 ml of sodium chloride physiologic saline No. 10; |
| - essentiale 5.0 + autoblood 5.0 i.v. 5 times, then 1 capsule 3 times No. 10; |
| - ATP 1.0 i.m. alternated with cocarboxylase 100 mg i.v. No. 10; |
| - folic acid 1 tablet 3 times with ferric sulphate 1 tablet 3 times a day; |
• vitamin B$_{12}$ 100 i.m. and vitamin B$_{6}$ 5% – 1.0 i.m. alternated No. 10.

Rheocorrecting therapy:
• rheosorbilact 200.0 ml i.v. drop-by-drop No. 3 every other week;
• 5% glucose – 200.0 + curantyl 4.0 i.v. No. 5 every day.

**Invasive methods**

Intracuterine substituting blood transfusion (in specialized hospitals).

Indications:
1) considerable hematocrit decrease (lower than 25%);
2) hemoglobin decrease (less than 80 g/L).

**Delivery**

Indications to preterm delivery at Rh-incompatibility:
1. antibody titer equals or exceeds 1:64 (critical level);
2. titer increase at reanalysis by 4 times and more;
3. OPB 0.35–0.7 and higher; bilirubin concentration in the amniotic fluid 4.7–9.5 mg/L;
4. ultrasound signs of HD in the fetus;
5. stillbirth and delivering children with HD in the anamnesis.

The optimum delivery method for women with antibodies is delivery at the term of 38 weeks (sensitization presence is rather a contraindication than an indication to cesarean section).

If there are no antibodies and sensitization signs, preterm delivery is not indicated, but delivering an overmature fetus is inadmissible (the optimum delivery term is 39–40 weeks). Vaginal delivery is the most expedient.

1. Delivery by means of cesarean section:
   - severe HD at the term of 34–35 weeks, after preliminary prophylaxis of the syndrome of respiratory disorders (SRD) of fetus (by conventional regimens);
   - edematous HD at any term since bearing at full term leads to fetal death;
   - conducting a procedure of intrauterine substituting blood transfusion.

2. Delivery through the natural maternal passages: if the neck of uterus is mature and it is necessary to conduct preterm delivery, the optimum method is
amniotomy. If the neck of uterus is not mature, it is to be prepared with prostaglandins.

4. Rh-Sensitization Prophylaxis

Prophylaxis of sensitization by Rh-factor includes:
- maintenance of the first pregnancy of women with Rh-negative blood and delivery of a healthy child;
- blood transfusion subject to Rh-factor;
- conducting desensitizing therapy during pregnancy;
- carrying out specific prophylaxis Rh-sensitization by means of introducing anti-RhO (O)-immunoglobulin to Rh-negative women after detecting fetal Rh affinity; anti-Rh0 (D)-immunoglobulin is introduced once, i.m., in the dose of 300 micrograms in the course of the first 72 hours after delivery; the dose of anti-Rh0 (B)-immunoglobulin is to be increased to 600 micrograms after cesarean section, manual removal of afterbirth, placental presentation, premature detachment of normally located placenta;
- to prevent sensitization development immunoglobulin is to be introduced to women with Rh-negative blood after a spontaneous or artificial abortion during 48 hours.

Antenatal prophylaxis in pregnant women with Rh-negative blood but without Rh-sensitization (absence of antibodies in the maternal blood flow) is conducted in critical terms of gestation – 28 weeks (many authors also recommend at 34 weeks of gestation).

Human anti-Rh0(D)-immunoglobulin is used in Europe.
Postnatal usage – 200–300 micrograms AT in one dose i.m.
Antenatal prophylaxis (from 12 to 28 weeks) – from 120 to 300 micrograms AT in one dose i.m.

5. Hemolytic Disease of Newborn (HDN)

HDN is a disease conditioned by immunologic havoc because of the incompatibility of the maternal and fetal blood by erythrocytic antigens.

HDN classification foresees determination of: 1) havoc type (Rh-, ABO-, other systems); 2) time of onset (antenatal from; postnatal form); 3) clinical form (antenatal
(intrauterine fetal death with maceration, edematous (universal hydrops fetalis), anemic, edematous-anemic) and postnatal (edematous, icteric, anemic, mixed)); 4) severity degree at icteric and anemic forms (mild, moderate and severe); 5) period of the disease (acute, recovery, residual manifestations); 6) complications (bilirubin encephalopathy – nuclear icterus, other neurologic disorders; hemorrhagic syndrome or hydrops fetalis; injuries of the liver (toxic hepatitis, bile clotting syndrome), heart (parenchymatous myocarditis), kidneys, adrenal glands, metabolic disorders – hypoglycaemia, hemorrhagic syndrome); 7) concomitant diseases and background conditions (prematurity, intrauterine infections, asphyxia).

Symptoms allowing to suspect HDN:
1. Bilirubin level in the umbilical blood higher than 51.3 micromole/L.
2. Hemoglobin level after birth lower than 180 g/L and erythrocytes less than $4 \times 10^{12}$.
3. Hematocrit less than 0.4.
4. Enlarged liver, spleen.
5. Hourly bilirubin increase more than 6.8 micromole/L in mature children and 5.1 micromole/L in premature children.

Mild HDN is diagnosed at the presence of moderately pronounced clinico-laboratory or only laboratory signs in the child. Hemoglobin level in the umbilical blood during the first hours of life more than 140 g/L, indirect bilirubin (IB) in the umbilical blood less than 60 micromole/L; then – hourly bilirubin increase 3.5 – 4 micromole/h; hemoglobin more than 180 g/L; bilirubin level by 50 micromole/L and more lower than the critical level.

Moderate HDN – hyperbilirubinemia requiring substituting blood transfusion or hemosorption but not accompanied by bilirubin brain intoxication or development of other complications.

Severe HDN is indicated by severe anemia (hemoglobin less than 100 g/L) or icterus (hyperbilirubinemia more than 85 micromole/L) at birth, presence of symptoms of bilirubin injure of brain of any intensity, more than 2 substituting blood transfusions necessary, edematous form of the disease, bilirubin level less than 20
micromole/L than the critical level, hourly bilirubin increase more than 5 micromole/L, the presence of tonoclonic spasms.

Clinical presentation

Edematous form – the most severe manifestation of Rh-HDN.
Icteric HDN – the most frequently diagnosed form.
Bilirubin encephalopathy (BE) is rarely detected clinically during the first 36 hours of life, usually the first manifestations are diagnosed on the 3rd – 6th day of life.
Anemic HDN (declares itself at the end of the 1st week – at the beginning of the 2nd week) – the children are pale, flaccid, suck and gain weight badly.

HDN treatment is divided into conservative and surgical.
Presently, the basic method of HDN treatment is substituting blood transfusion (SBT).

Conservative therapy:

- infusion therapy: during the 1st day – 50 ml/kg, further – 20 ml/kg/day. Some authors recommend 60 – 100 ml/kg for mature children, 40 – 60 ml/kg for premature children. The volume of introduced liquid and the volume of feeding are calculated separately till the 4th day. The speed of liquid introduction is 2 drops a min. after each transfusion of 60 – 80 ml of liquid – diuretics;
- phototherapy.

Indications to phototherapy and SBT depending on the level of total bilirubin in blood serum:

- diuretics (mannitol 0.5–1 g/kg – binds indirect bilirubin, prevents its exit from the bloodstream and encephalopathy development);
- hemolysis reduction (infusion therapy + vitamin E 10 mg/kg/day – OD ml 5 % 3 times a day i.m.);
- bilirubin metabolism acceleration;
- efferent methods (low-volume membranous plasmapheresis);
- bile outflow increase (10 % sol. MgSO₄, allochol);
- metabolic therapy (cocarboxylase 8 mg/kg; inosine 0.3 – 0.5 ml; pipolphen, lipoic acid 0.3 – 0.5 ml; lipostabil 0.5 ml/kg);
cleansing enema.

Surgical therapy:

SBT is the most effective during the first 6–9 hours. It is indicated in the following cases:

- onset of the first signs of BE irrespective of total bilirubin level of the blood serum;
- inefficient phototherapy if bilirubin level exceeds the values indicated in the figures. A decision to conduct SBT should be preceded by carrying out intensive phototherapy.

The newborn is fed with donor milk since the mother’s milk contains Rh-antibodies or hemolysins.

**Self-control materials.**

**A. Assignments for self-control**

1. A 20-year-old woman just delivered a viable male neonate at 38 weeks of gestation after being a restrained passenger in a car accident. Upon arriving at the emergency department she was “cleared” by the trauma and orthopedic teams and sent to the labor and delivery floor. There she began having vaginal bleeding and then went into labor spontaneously. The estimated blood loss with delivery was 900 mL, and now she is stable. After obtaining her prenatal information you realize she is Rh negative and antibody D negative. The next step is:

A. Assess neonatal Rh antigen status  
B. perform a CBC  
C. transfuse packed red blood cells  
D. perform a Kleihauer–Betke test  
E. give additional Rh immune globulin

2. At a woman 28 y.o G2P2, delivered at the second labor a 3 400 g girl with anemia and icteric skin colour. Blood type at a woman B (III) Rh-, at the father of new-born B (III) Rh+, at new-born B(III) Rh+. What is the most credible diagnosis?

A. Rh-izooimmunization.  
B. conflict on an antigen A.  
C. conflict on an antigen In.  
D. conflict on an antigen AV.  
E. infection

3. A 28 year old woman had the second labour and born a girl with manifestations of anemia and progressing jaundice. The child’s weight was 3
400 g, the length was 52 cm. The woman’s blood group is B(III) Rh-, the father’s blood group is A(III) Rh+, the child’s blood group is B(III) Rh+. What is the cause of anemia?
A. rhesus incompatibility
B. antigen A incompatibility
C. antigen B incompatibility
D. antigen AB incompatibility
E. intrauterine infection

4. A primigravida is 22 years old. She has Rh(-), her husband has Rh(+). Antibodies to Rh weren’t found at 32 weeks of pregnancy. Redetermination of antibodies to Rh didn’t reveal them at 35 weeks of pregnancy as well. How often should the antibodies be determined hereafter?
A. once a week
B. once in two weeks
C. once in three weeks
D. monthly
E. there is no need in further checks

5. A 38-year-old G1P1 comes to see you for her first prenatal visit at 10 weeks gestational age. She had a previous term vaginal delivery without any complications. You detect fetal heart tones at this visit, and her uterine size is consistent with dates. You also draw her prenatal labs at this visit and tell her to follow up in 4 weeks for a return OB visit. Two weeks later, the results of the patient’s prenatal labs come back. Her blood type is A–, with an anti-D antibody titer of 1:4. Which of the following is the most appropriate next step in the management of this patient?
A. repeat the titer in 4 weeks
B. schedule an amniocentesis for amniotic fluid bilirubin at 16 weeks
C. repeat the titer at 28 weeks
D. schedule Percutaneous Umbilical Blood Sampling (PUBS) to determine fetal hematocrit at 20 weeks
E. schedule PUBS as soon as possible to determine fetal blood type

6. A 23-year-old G3P1011 at 6 weeks presents for routine prenatal care. She had a cesarean delivery 3 years ago for breech presentation after a failed external cephalic version. Her daughter is Rh-negative. She also had an elective termination of pregnancy 1 year ago. She is Rh-negative and is found to have a positive anti-D titer of 1:8 on routine prenatal labs. Failure to administer RhoGAM at which time is the most likely cause of her sensitization?
A. after elective termination
B. at the time of cesarean delivery
C. at the time of external cephalic version
D. within 3 days of delivering an Rh-negative fetus
E. at 28 weeks in the pregnancy for which she had a cesarean delivery

7. A 27-year-old G2P1 at 29 weeks gestational age, who is being followed for Rh isoimmunization presents for her OB visit. The fundal height is noted to be 33 cm.
An ultrasound reveals fetal ascites and a pericardial effusion. Which of the following can be another finding in fetal hydrops?
A. subcutaneous edema  
B. oligohydramnios  
C. hydrocephalus  
D. hydrenephrosis  
E. over-distended fetal bladder

8. The major factor allowing fetal erythrocytes to enter the maternal circulation is:
A. labor and delivery  
B. normal placental circulation  
C. spontaneous abortion  
D. premature rupture of membranes  
E. low level placental abruption

9. Pregnancies with severely affected Rh-immunised fetuses may be complicated by:
A. all of the above  
B. polyhydramnios  
C. fetal hydrops  
D. fetal cardiac failure  
E. fetal anemia

10. Human Rh immune globulin (RhoGAM):
A. attaches to the fetal Rh+ cells in the maternal circulation and obscures the antigen sites  
B. prevents the transfer of incompatible fetal cells to the mother  
C. prevents antibody production in the maternal hematopoietic system  
D. all of the above  
E. none of the above

B. SITUATIONAL TASKS

1. A 25 year old woman had the third labour and born a girl with manifestations of anemia and progressing jaundice. The child’s weight was 3 600 g, the length was 51 cm. The woman’s blood group is B (III) Rh-, the father’s blood group is A (III) Rh+, the child’s blood group is B (III) Rh+. What is the cause of anemia?

2. Patient with Rh negative type of blood on 16 week of pregnancy presents the history of isoimmunisation. Which test is the most informative in this case?
3. A child was born in time. On the second day at a child jaundice of skin and mucus membranes appeared. Indirect bilirubin is 136 mcmol/l. At a mother blood type 0[I]Rh-, at a child - A[II]Rh+. What is the mechanism of icterus?

4. Examination of Rh-negative pregnant woman at 32 weeks of gestation revealed a four-time rise of Rh-antibody titer within 2 weeks, the titer was 1:64. In the first two pregnancies the patient had experienced antenatal fetal death due to hemolytic disease. What is the optimal tactics of pregnancy management?

5. A woman with blood group B(III) Rh(+) gave birth to a full-term healthy boy. Examination on the 3rd day of the infant’s life shows him to have icteric tint to his skin. The child has no problems with suckling, sleep is nondisturbed. The abdomen is soft, the liver protrudes by 2 cm from under the costal margin. Complete blood count: hemoglobin - 200 g/L, erythrocytes - 5.5 1012/L, total bilirubin - 62 mcmol/L, indirect bilirubin - 52 mcmol/L. What condition can be suspected?
Literature.

Main:

Additional:

On-line resources
UMSA Academy website http://www.umsa.edu.ua/
Website of the Department of Obstetrics and Gynecology № 1 http://www.umsa.edu.ua/kafhome/kaf_akushgenikology_1/kaf_akushginecology.html
Videos UMSA library website https://biblumsa.blogspot.com/

Methodical guidelines have been drawn up by CMedS As. Professor Krutikova E. I.

name surname [signature]