MINISTRY OF HEALTH CARE OF UKRAINE
ODESA NATIONAL MEDICAL UNIVERSITY

Faculty: international

Department of Pediatrics

APPROVED

Vice-rector for scientific and pedagogical work

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METHODOLOGICAL RECOMMENDATION

FOR THE LECTURE

FROM EDUCATIONAL COMPONENT

Faculty: international Course 5

Educational component - "PEDIATRICS"

Topic 2: Hemolytic and hemorrhagic disease of the newborn

Approved:
Meeting of the Department of Pediatrics
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Head of the department _____ (Mykola ARYAYEV.)

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*Note.*In the case of publication of methodological developments as an independent printed work, the academic council of the faculty provides a recommendation for publication in the presence of two reviews, one of which is external — from a reviewer of another institution of higher education.

Lecture № 2

Topic: “Hemolytic and hemorrhagic disease of the newborn “

Relevance by topics: Hemorrhagic disease of newborn found in 0.25-0.5% of children. Prophylactic measures and treatment can help prevent complications that are life-threatening for the newborn. Mortality in case of low and untimely treatment of HHDN reaches 30%. Death is often caused by high acute blood loss or bleeding in the brain, less frequently - in the internal organs. The prognosis is favorable only in case of timely treatment of HHDN.

Target: To improve the knowledge of applicant in the care of newborn with hemolytic and hemorrhagic disease

Basic understanding: Erythroblastosis Fetalis, hemolytic disease, hemorrhagic disorders, vitamin K deficiency

Plan and organizational structure of the lecture:

1. Defining the learning goal. Providing positive motivation.
2. Definition, etiology, pathogenesis of hemolytic disease of the newborn (Erythroblastosis Fetalis)
3. Clinical manifestations and Laboratory data of hemolytic disease (HD) of the newborn
4. Diagnosis of hemolytic disease (HD) of the newborn
5. Treatment of hemolytic disease (HD) of the newborn
6. Other forms of hemolytic disease
7. Hemorrhagic disorder of the newborn
   7.1. Etiology and epidemiology vitamin K deficiency
   7.2. Pathophysiology, history, physical and Evaluation
8. Treatment

Content of lecture material (lecture text)

1. Defining the learning goal. Providing positive motivation.

Rh hemolytic disease is diagnosed in 0.6-0.8% of newborns, and Hemolytic and hemorrhagic disease of the newborn (HHDN) caused by AB0 incompatibility - 3-5% of newborns. Mortality in HHDN varies quite a large range, depending on the clinical form. Up to 10% of children suffers from cerebral palsy and infectious diseases, anemia, eczema and neuro dermatitis.

Hemorrhagic disease of newborn found in 0.25-0.5% of children. Prophylactic measures and treatment can help prevent complications that are life-threatening for the newborn. Mortality in case of low and untimely treatment of HHDN reaches 30%. Death is often caused by high acute blood loss or bleeding in the brain, less frequently - in the internal organs. The prognosis is favorable only in case of timely treatment of HHDN.

Content of lecture material.

2. Definition, etiology, pathogenesis of hemolytic disease of the newborn (Erythroblastosis Fetalis)

Erythroblastosis fetalis is caused by the transplacental passage of maternal antibody active against paternal RBC antigens of the infant and is characterized by an increased rate of RBC destruction. It is an important cause of anemia and jaundice in newborn infants despite the development of a method of preventing maternal isoimmunization by Rh antigens. Although more than 60 different RBC antigens are capable of eliciting an antibody response, significant disease is associated primarily with the D antigen of the Rh group and with incompatibility of ABO factors. Rarely, hemolytic disease may be caused by C or E antigens or by other RBC antigens such as C^W, C^X, D^U, K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. Anti-Lewis antibodies do not cause disease.

Hemolytic disease of the newborn caused by Rh incompatibility

The Rh antigenic determinants are genetically transmitted from each parent, determine the Rh type, and direct the production of a number of blood group factors (C, c, D, d, E, and e). Each factor can elicit a specific antibody response under suitable conditions; 90% are due to D antigen and the remainder to C or E.

Pathogenesis. Isoimmune hemolytic disease from D antigen is approximately three times more frequent among white persons than among blacks. When Rh-positive blood is infused into an Rh-negative woman through error or when small quantities (usually more than 1 mL) of Rh-positive fetal blood containing D antigen inherited from an Rh-positive father enter the maternal circulation during pregnancy, with spontaneous or induced abortion, or at delivery, antibody formation against D antigen may be induced in the unsensitized Rh-negative recipient mother. Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in IgM antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta and causes hemolytic manifestations.

Hemolytic disease rarely occurs during a first pregnancy because transfusion of Rh-positive fetal blood into an Rh-negative mother occurs near the time of delivery, too late for the mother to become sensitized and transmit antibody to her infant before delivery. The fact that 55% of Rh-positive fathers are heterozygous (D/d) and may have Rh-negative offspring and that fetal-to-maternal transfusion occurs in only 50% of pregnancies reduces the chance of sensitization, as does small family size, in which the opportunities for its reoccurrence are reduced. Finally, the capacity of Rh-negative women to form antibodies is variable, some producing low titers even after adequate antigenic challenge. Thus, the overall incidence of isoimmunization of Rh-negative mothers at risk is low, with antibody to D detected in less than 10% of those studied, even after five or more pregnancies; only about 5% ever have babies with hemolytic disease.

When the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh-positive cells from her circulation by her preexisting anti-A or anti-B, which are IgM antibodies and do not cross the placenta. Once a mother has been sensitized, her infant is likely to have hemolytic disease. The severity of Rh illness worsens with successive pregnancies. The possibility that the first affected infant after sensitization may represent the end of the mother's childbearing potential for Rh-positive infants argues urgently for the prevention of sensitization. The injection of anti-D gamma globulin (RhoGAM) into the mother immediately after the delivery of each Rh-positive infant has been a successful strategy to reduce Rh hemolytic disease (see later).

3. Clinical manifestations and Laboratory data of hemolytic disease (HD) of the newborn

A wide spectrum of hemolytic disease occurs in affected infants born to sensitized mothers, depending on the nature of the individual immune response. The severity of the disease may range from only laboratory evidence of mild hemolysis (15% of cases) to severe anemia with compensatory hyperplasia of erythropoietic tissue leading to massive enlargement of the liver and spleen. When the compensatory capacity of the hematopoietic system is exceeded, profound anemia occurs and results in pallor, signs of cardiac decompensation (cardiomegaly, respiratory distress), massive anasarca, and circulatory collapse. This clinical picture of excessive abnormal fluid in two or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), termed **hydrops fetalis,** frequently results in death in utero or shortly after birth. With the use of RhoGAM to prevent Rh sensitization, nonimmune (nonhemolytic) conditions have become

frequent causes of hydrops (Table 3). The severity of hydrops is related to the level of anemia and the degree of reduction in serum albumin (oncotic pressure), which is due in part to hepatic dysfunction. Alternatively, heart failure may increase right heart pressure, with the subsequent development of edema and ascites. Failure to initiate spontaneous effective ventilation because of pulmonary edema or bilateral pleural effusions results in birth asphyxia; after successful resuscitation, severe respiratory distress may develop. Petechiae, purpura, and thrombocytopenia may also be present in severe cases as a result of decreased platelet production or the presence of concurrent disseminated intravascular coagulation.

TABLE 3 -- Etiology of Hydrops Fetalis[*]

CATEGORY	DISORDERS	CATEGORY	DISORDERS
Anemia	Immune (Rh, Kell) hemolysis	Teratomas	Choriocarcinoma
	α-Thalassemia		Sacrococcygeal teratoma
	Red blood cell enzyme deficiencies (G6PD)	Tumors and storage diseases	Neuroblastoma
	Fetomaternal hemorrhage		Hepatoblastoma
	Donor in twin-to-twin transfusion		Gaucher disease
Cardiac dysrhythmias	Supraventricular tachycardia		Niemann-Pick disease
	Atrial flutter		Mucolipidosis
	Congenital heart block		GM_1 gangliosidosis
Structural heart lesions	Premature closure of foramen ovale		Mucopolysaccharidosis
	Tricuspid insufficiency	Chromosome abnormalities	Trisomy 13, 15, 16, 18, 21
	Hypoplastic left heart		XX/XY, 45XO
	Endocardial cushion defect		Partial duplication of chromosome 11, 15, 17,

CATEGORY	DISORDERS	CATEGORY	DISORDERS
			18
	Cardiomyopathy		Partial deletion of chromosome 13, 18
	Endocardial fibroelastosis		Triploidy
	Tuberous sclerosis with cardiac rhabdomyoma		Tetraploidy
	Pericardial teratoma	Bone diseases	Osteogenesis imperfecta
Vascular	Chorioangioma of placenta, chorionic vessels, or umbilical vessels		Asphyxiating thoracic dystrophy
	Umbilical artery aneurysm		Skeletal dysplasias
	Angiomyxoma of umbilical cord	Congenital infections	Cytomegalovirus
	True knot of umbilical cord		Parvovirus
	Hepatic hemangioma		Rubella
	Cerebral arteriovenous malformation (aneurysm of vein of Galen)		Toxoplasmosis
	Angiosteohypertrophy (Klippel-Trénaunay syndrome)		Syphilis
	Thrombosis of renal or umbilical vein or inferior vena cava		Leptospirosis
	Recipient in twin-to-twin transfusion		Chagas disease
Lymphatic	Lymphangiectasia	Others	Bowel obstruction with

CATEGORY	DISORDERS	CATEGORY	DISORDERS
			perforation and meconium peritonitis, volvulus
	Cystic hygroma		Hepatic fibrosis
	Chylothorax, chylous ascites		Beckwith-Wiedemann syndrome
	Noonan syndrome		Prune-belly syndrome
	Multiple pterygium syndrome		Congenital nephrosis
Central nervous system	Absent corpus callosum		Infant of a diabetic mother
	Encephalocele		Myotonic dystrophy
	Intracranial hemorrhage		Neu-Laxova syndrome
	Holoprosencephaly		Maternal therapy with indomethacin
Thoracic lesions	Cystic adenomatoid malformation of lung	Idiopathic	Multiple congenital anomaly syndromes
	Mediastinal teratoma		
	Diaphragmatic hernia		
	Sequestered lung		

Modified from Phibbs R: In Polin N, Fox W (eds): Fetal and Neonatal Physiology, 2nd ed. Philadelphia, WB Saunders, 1998.

G6PD, glucose-6-phosphate dehydrogenase.

* The incidence of nonimmune (nonhemolytic) hydrops fetalis is 1/2,000–⅓, 500 births.

Jaundice may be absent at birth because of placental clearance of lipid-soluble unconjugated bilirubin, but in severe cases, bilirubin pigments stain the amniotic fluid, cord, and vernix caseosa yellow. Jaundice is generally evident on the 1st day of life because the infant's bilirubin-conjugating and excretory systems are unable to cope with the load resulting from massive hemolysis. Indirect-reacting bilirubin therefore accumulates postnatally and may rapidly reach extremely high levels and

present a significant risk of bilirubin encephalopathy. The risk of kernicterus developing from hemolytic disease is greater than from comparable nonhemolytic hyperbilirubinemia, although the risk in an individual patient may be affected by other complications (anoxia, acidosis). Hypoglycemia occurs frequently in infants with severe isoimmune hemolytic disease and may be related to hyperinsulinism and hypertrophy of the pancreatic islet cells in these infants.Infants born after intrauterine transfusion for prenatally diagnosed erythroblastosis may be severely affected because the indications for transfusion are evidence of already severe disease in utero (hydrops, fetal anemia). Such infants usually have very high (but extremely variable) cord levels of bilirubin, which reflects the severity of the hemolysis and its effects on hepatic function. Infants treated with intra-umbilical vein transfusions in utero may also have a benign postnatal course if the anemia and hydrops resolve before birth. Anemia from continuing hemolysis may be masked by the previous intrauterine transfusion, and the clinical manifestations of erythroblastosis may be superimposed on various degrees of immaturity resulting from spontaneous or induced premature delivery.

Laboratory data. Before treatment, the direct Coombs test is usually positive, and anemia is generally present. The cord blood hemoglobin content varies and is usually proportional to the severity of the disease; with hydrops fetalis it may be as low as 3–4 g/dL. Alternatively, despite hemolysis, it may be within the normal range because of compensatory bone marrow and extramedullary hematopoiesis. The blood smear typically shows polychromasia and a marked increase in nucleated RBCs. The reticulocyte count is increased. The white blood cell count is usually normal but may be elevated; thrombocytopenia may develop in severe cases. Cord bilirubin is generally between 3 and 5 mg/dL; direct-reacting (conjugated) bilirubin may also be elevated, especially if there was an intrauterine transfusion. Indirect-reacting bilirubin rises rapidly to high levels in the 1st 6 hr of life.After intrauterine transfusions, cord blood may show a normal hemoglobin concentration, negative direct Coombs test, predominantly type O Rh-negative adult RBCs, and a relatively normal smear.

4. Diagnosis of hemolytic disease (HD) of the newborn

Definitive diagnosis of erythroblastosis fetalis requires demonstration of blood group incompatibility and corresponding antibody bound to the infant's RBCs.

Antenatal Diagnosis.

In Rh-negative women, a history of previous transfusions, abortion, or pregnancy should suggest the possibility of sensitization. Expectant parents' blood types should be tested for potential incompatibility, and the maternal titer of IgG antibodies to D antigen should be assayed at 12–16, 28–32, and 36 wk. Fetal Rh

status may be determined by isolating fetal cells or fetal DNA (plasma) from the maternal circulation. The presence of elevated antibody titers at the beginning of pregnancy, a rapid rise in titer, or a titer of 1 : 64 or greater suggests significant hemolytic disease, although the exact titer correlates poorly with the severity of disease. If a mother is found to have anti body against D antigen at a titer of 1 : 16 (15 IU/ml in Europe) or greater at any time during a subsequent pregnancy, the severity of fetal disease should be monitored by Doppler ultrasonography of the middle cerebral artery and then percutaneous umbilical blood sampling (PUBS) if indicated (see Chapter 96). If the mother has a history of a previously affected infant or a stillbirth, an Rh-positive infant is usually equally or more severely affected than the previous infant, and the severity of disease in the fetus should be monitored.

Assessment of the fetus may require information obtained from ultrasonography and PUBS. Real-time ultrasonography is used to detect the progression of disease, with hydrops defined as skin or scalp edema, pleural or pericardial effusions, and ascites. Early ultrasonographic signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. If pleural effusions precede ascites and hydrops by a significant length of time, causes other than fetal anemia should be suspected (see Table 103-3). Extramedullary hematopoiesis and, less so, hepatic congestion compress the intrahepatic vessels and produce venous stasis with portal hypertension, hepatocellular dysfunction, and decreased albumin synthesis.

Hydrops is present when fetal hemoglobin is <5 g/dL, frequent when <7 g/dL, and variable between 7 and 9 g/dL. Real-time ultrasonography predicts fetal well-being by the biophysical profile (see Table 96-2), whereas Doppler ultrasonography assesses fetal distress by demonstrating increased vascular resistance in fetal arteries (middle cerebral). In pregnancies with ultrasonographic evidence of hemolysis (hepatosplenomegaly), early or late hydrops, or fetal distress, further and more direct assessment of fetal hemolysis should be performed.

Amniocentesis was classically used to assess fetal hemolysis. Hemolysis of fetal RBCs produces hyperbilirubinemia before the onset of severe anemia. Bilirubin is cleared by the placenta, but a significant proportion enters the amniotic fluid and can be measured by spectrophotometry. Ultrasonographically guided transabdominal aspiration of amniotic fluid may be performed as early as 18–20 wk of gestation. Spectrophotometric scanning of amniotic fluid wavelengths demonstrates a positive optical density (OD) deviation of absorption for bilirubin from normal at 450 nm. Amniocentesis and cordocentesis are invasive procedures with risks to both the fetus and mother, including fetal death, fetal bleeding, fetal bradycardia, worsening of

alloimmunization, premature rupture of membranes, preterm labor, and chorioamnionitis. Noninvasive measurements to detect fetal anemia are desirable. In fetuses without hydrops, moderate to severe anemia can be detected noninvasively by demonstration of an increase in the peak velocity of systolic blood flow in the middle cerebral artery by Doppler ultrasound.

PUBS is the standard approach to assess the fetus if Doppler and real-time ultrasonography suggest an affected fetus. PUBS is performed to determine fetal hemoglobin levels and to transfuse packed RBCs in those with serious fetal anemia (Hct of 25–30%).

Postnatal Diagnosis.

Immediately after the birth of any infant to an Rh-negative woman, blood from the umbilical cord or from the infant should be examined for ABO blood group, Rh type, Hct and hemoglobin, and reaction of the direct Coombs test. If the Coombs test is positive, a baseline serum bilirubin level should be measured, and a commercially available RBC panel should be used to identify RBC antibodies present in the mother's serum, both tests being performed not only to establish the diagnosis but also to ensure selection of the most compatible blood for exchange transfusion should it be necessary. The direct Coombs test is usually strongly positive in clinically affected infants and may remain so for a few days up to several months.

5. Treatment of hemolytic disease (HD) of the newborn

The main goals of therapy are to (1) prevent intrauterine or extrauterine death from severe anemia and hypoxia, and (2) avoid neurotoxicity from hyperbilirubinemia.

Treatment of an Unborn Infant. Survival of severely affected fetuses has been improved by the use of fetal ultrasonography to identify the need for in utero transfusion. Intravascular (umbilical vein) transfusion of packed RBCs is the treatment of choice for fetal anemia, replacing intrauterine transfusion into the fetal peritoneal cavity. Hydrops or fetal anemia (Hct <30%) is an indication for umbilical vein transfusion in infants with pulmonary immaturity (see Fig. 103-1). **Intravascular fetal transfusion** is facilitated by maternal and hence fetal sedation with diazepam and by fetal paralysis with pancuronium. Packed RBCs are given by slow-push infusion after cross matching with the mother's serum. The cells should be obtained from a CMV-negative donor and irradiated to kill lymphocytes to avoid graft vs host disease. Of note, leukoreduction alone (without irradiation) does not prevent graft vs host disease. Transfusions should achieve a post-transfusion Hct of

45–55% and can be repeated every 3–5 wk. Indications for delivery include pulmonary maturity, fetal distress, complications of PUBS, or 35–37 wk of gestation. The survival rate for intrauterine transfusions is 89%; the complication rate is 3%. Complications include rupture of the membranes and preterm delivery, infection, fetal distress requiring emergency cesarean section, and perinatal death.

Treatment of a Liveborn Infant. The birth should be attended by a physician skilled in neonatal resuscitation. Fresh, low-titer, group O, leukoreduced, and irradiated Rh-negative blood cross matched against maternal serum should be immediately available. If clinical signs of severe hemolytic anemia (pallor, hepatosplenomegaly, edema, petechiae, ascites) are evident at birth, immediate resuscitation and supportive therapy, temperature stabilization, and monitoring before proceeding with exchange transfusion may save some severely affected infants. Such therapy should include correction of acidosis with 1–2 mEq/kg of sodium bicarbonate; a small transfusion of compatible packed RBCs to correct anemia; volume expansion for hypotension, especially in those with hydrops; and provision of assisted ventilation for respiratory failure.

Exchange Transfusion.

When an infant's clinical condition at birth does not require an immediate full or partial exchange transfusion, the decision to perform one should be based on a judgment that the infant has a high risk of rapid development of a dangerous degree of anemia or hyperbilirubinemia. Cord hemoglobin of 10 g/dL or less and bilirubin of 5 mg/dL or more suggest severe hemolysis but inconsistently predict the need for exchange transfusion. Some physicians consider previous kernicterus or severe erythroblastosis in a sibling, reticulocyte counts >15%, and prematurity to be additional factors supporting a decision for early exchange transfusion. Intrauterine, intravascular transfusions have decreased the need for exchange transfusion.The hemoglobin concentration, Hct, and serum bilirubin level should be measured at 4–6 hr intervals initially, with extension to longer intervals if and as the rate of change diminishes. The decision to perform an exchange transfusion is based on the likelihood that the trend of bilirubin levels plotted against hours of age indicates that serum bilirubin will reach the levels indicated in Figure 12 and Table 7 . Term infants with levels of 20 mg/dL or higher have an increased risk of kernicterus. Ordinary transfusions of compatible Rh-negative, leukoreduced, and irradiated RBCs may be necessary to correct anemia at any stage of the disease up to 6–8 wk of age, when the infant's own blood-forming mechanism may be expected to take over. Weekly determinations of hemoglobin or Hct should be done until a spontaneous rise has been demonstrated.

Careful monitoring of the serum bilirubin level is essential until a falling trend has been demonstrated in the absence of phototherapy. Even then, an occasional infant, particularly if premature, may experience an unpredicted significant rise in serum bilirubin as late as the 7th day of life. Attempts to predict the attainment of dangerously high levels of serum bilirubin based on observed levels exceeding 6 mg/dL in the 1st 6 hr or 10 mg/dL in the 2nd 6 hr of life or on rates of rise exceeding 0.5–1.0 mg/dL/hr can be unreliable. Measurement of unbound bilirubin may be a more sensitive predictor of the risk associated with hyperbilirubinemia.

Blood for exchange transfusion should be as fresh as possible. Heparin or citrate-phosphate-dextrose-adenine solution may be used as an anticoagulant. If the blood is obtained before delivery, it should be taken from a type O, Rh-negative donor with a low titer of anti-A and anti-B antibodies and should be compatible with the mother's serum by the indirect Coombs test. After delivery, blood should be obtained from an Rh-negative donor whose cells are compatible with both the infant's and the mother's serum; when possible, type O donor cells are generally used, but cells of the infant's ABO blood type may be used when the mother has the same type. A complete cross match, including an indirect Coombs test, should be performed before the 2nd and subsequent transfusions. Blood should be gradually warmed and maintained at a temperature between 35 and 37°C throughout the exchange transfusion. It should be kept well mixed by gentle squeezing or agitation of the bag to avoid sedimentation; otherwise, the use of supernatant serum with a low RBC count at the end of the exchange will leave the infant anemic. Whole blood or packed leukoreduced and irradiated RBCs reconstituted with fresh frozen plasma to an Hct of 40% should be used. The infant's stomach should be emptied before transfusion to prevent aspiration, and body temperature should be maintained and vital signs monitored. A competent assistant should be present to help monitor, tally the volume of blood exchanged, and perform emergency procedures.

With strict aseptic technique, the umbilical vein is cannulated with a polyvinyl catheter to a distance no greater than 7 cm in a full-term infant. When free flow of blood is obtained, the catheter is usually in a large hepatic vein or the inferior vena cava. Alternatively, the exchange may be performed through peripheral arterial (drawn out) and venous (infused in) lines. The exchange should be carried out over a 45–60 min period, with aspiration of 20 mL of infant blood alternating with infusion of 20 mL of donor blood. Smaller aliquots (5–10 mL) may be indicated for sick and premature infants. The goal should be an isovolumetric exchange of approximately two blood volumes of the infant (2 × 85 mL/kg).

Infants with acidosis and hypoxia from respiratory distress, sepsis, or shock may be further compromised by the significant acute acid load contained in citrated blood,

which usually has a pH between 7 and 7.2. The subsequent metabolism of citrate may result in metabolic alkalosis later if citrated blood is used. Fresh heparinized blood avoids this problem. During the exchange, blood pH and PaO_2 should be serially monitored because infants often become acidotic and hypoxic during exchange transfusions. Symptomatic hypoglycemia may occur before or during an exchange transfusion in moderately to severely affected infants; it may also occur 1–3 hr after exchange. Acute complications, noted in 5–10% of infants, include transient bradycardia with or without calcium infusion, cyanosis, transient vasospasm, thrombosis, apnea with bradycardia requiring resuscitation, and death. Infectious risks include CMV, HIV, and hepatitis. Necrotizing enterocolitis is a rare complication of exchange transfusion.

The risk of death from an exchange transfusion performed by an experienced physician is 0.3/100 procedures. With the decreasing use of this procedure because of the use of phototherapy and prevention of sensitization, the general level of physician competence is decreasing. Thus, it is best if this procedure is performed in experienced neonatal referral centers.

After exchange transfusion, the bilirubin level must be determined at frequent intervals (every 4–8 hr) because bilirubin may rebound 40–50% within hours. Repeated exchange transfusions should be carried out to keep the indirect fraction from exceeding the levels indicated in Table 7 for preterm infants and 20 mg/dL for term infants. Symptoms suggestive of kernicterus are mandatory indications for exchange transfusion at any time.

Late Complications.

Infants who have hemolytic disease or who have had an exchange or an intrauterine transfusion must be observed carefully for the development of anemia and cholestasis. **Late anemia** may be hemolytic or hyporegenerative. Treatment with supplemental iron, erythropoietin, or blood transfusion may be indicated. A mild graft vs host reaction may be manifested as diarrhea, rash, hepatitis, or eosinophilia.

Inspissated bile syndrome refers to the rare occurrence of persistent icterus in association with significant elevations in direct and indirect bilirubin in infants with hemolytic disease. The cause is unclear, but the jaundice clears spontaneously within a few weeks or months.

Portal vein thrombosis and portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. It is probably associated with prolonged, traumatic, or septic umbilical vein catheterization.

Prevention of Rh Sensitization.

The risk of initial sensitization of Rh-negative mothers has been reduced to less than 1% by the intramuscular injection of 300 μg of human anti-D globulin (1 mL of

RhoGAM) within 72 hr of delivery of an Rh-positive infant, ectopic pregnancy, abdominal trauma in pregnancy, amniocentesis, chorionic villus biopsy, or abortion. This quantity is sufficient to eliminate ≈ 10 mL of potentially antigenic fetal cells from the maternal circulation. Large fetal-to-maternal transfers of blood may require proportionately more RhoGAM. RhoGAM administered at 28–32 wk and again at birth (40 wk) is more effective than a single dose. The use of this technique, combined with improved methods of detecting maternal sensitization and measuring the extent of fetal-to-maternal transfusion, plus the use of fewer obstetric procedures that increase the risk of such fetal-to-maternal bleeding (version, manual separation of the placenta), should further reduce the incidence of erythroblastosis fetalis.

Hemolytic disease of the newborn caused by blood group A and B incompatibility

ABO incompatibility is the most common cause of hemolytic disease of the newborn. Approximately 15% of live births are at risk, but manifestations of disease develop in only 0.3–2.2%. Major blood group incompatibility between the mother and fetus generally results in milder disease than Rh incompatibility does. Maternal antibody may be formed against B cells if the mother is type A or against A cells if the mother is type B. Usually, the mother is type O and the infant is type A or B. Although ABO incompatibility occurs in 20–25% of pregnancies, hemolytic disease develops in only 10% of such offspring, and the infants are generally type A_1, which is more antigenic than A_2. Low antigenicity of the ABO factors in the fetus and newborn infant may account for the low incidence of severe ABO hemolytic disease relative to the incidence of incompatibility between the blood groups of the mother and child. Although antibodies against A and B factors occur without previous immunization (“natural” antibodies), they are usually IgM antibodies that do not cross the placenta. However, IgG antibodies to A antigen may be present and these do cross the placenta, so A-O isoimmune hemolytic disease may be found in first-born infants. Mothers who have become immunized against A or B factors from a previous incompatible pregnancy also exhibit IgG antibody. These “immune” antibodies are the primary mediators in ABO isoimmune disease.

Clinical manifestations. Most cases are mild, with jaundice being the only clinical manifestation. The infant is not generally affected at birth; pallor is not present, and hydrops fetalis is extremely rare. The liver and spleen are not greatly enlarged, if at all. Jaundice usually appears during the 1st 24 hr. Rarely, it may become severe, and symptoms and signs of kernicterus develop rapidly.

Diagnosis. A presumptive diagnosis is based on the presence of ABO incompatibility, a weakly to moderately positive direct Coombs test result, and spherocytes in the blood smear, which may at times suggest the presence of hereditary spherocytosis. Hyperbilirubinemia is often the only other laboratory abnormality. The hemoglobin level is usually normal but may be as low as 10–12 g/dL. Reticulocytes may be increased to 10–15%, with extensive polychromasia and increased numbers of nucleated RBCs. In 10–20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered.

Treatment.

Phototherapy may be effective in lowering serum bilirubin levels (see Chapter 102.4). In rare severe cases, treatment is directed at correcting dangerous degrees of anemia or hyperbilirubinemia by exchange transfusions with type O blood of the same Rh type as the infant. Indications for this procedure are similar to those previously described for hemolytic disease caused by Rh incompatibility. Some infants with ABO hemolytic disease may require transfusion of packed RBCs at several weeks of age because of slowly progressive anemia. Post-discharge monitoring of hemoglobin/Hct is essential in newborns with ABO hemolytic disease.

6. Other forms of hemolytic disease

Blood group incompatibilities other than Rh or ABO account for less than 5% of hemolytic disease of the newborn. The direct Coombs test is invariably positive, and exchange transfusion may be indicated for hyperbilirubinemia and anemia. Hemolytic disease, anemia, and hydrops fetalis as a result of anti-Kell antibodies are not predictable from the previous obstetric history, amniotic fluid bilirubin determinants, or the maternal antibody titer. Erythroid suppression may contribute to the anemia; PUBS is beneficial in actually measuring the fetal Hct.

Congenital infections such as cytomegalic inclusion disease, toxoplasmosis, rubella, and syphilis may be manifested as anemia, jaundice, hepatosplenomegaly, and thrombocytopenia, but the direct Coombs test result is negative and these conditions usually have other distinguishing clinical findings. Homozygous α-thalassemia may be associated with severe hemolytic anemia and a clinical picture resembling hydrops fetalis; it can be distinguished by a negative direct Coombs test result and characteristic clinical and laboratory findings. Anemia and jaundice may occur in infancy from hereditary spherocytosis and other red cell membrane defects, and, if untreated, can result in kernicterus. Hemolytic anemia pro ducing jaundice in

the 1st wk of life may also be secondary to congenital deficiencies in RBC enzymes, such as pyruvate kinase or G6PD.

7. Hemorrhagic disorder of the newborn

Hemorrhagic disorder of the newborn is a bleeding disorder that manifests in the first few weeks of life after delivery. The term hemorrhagic disorder of the newborn encompasses all hemorrhagic diseases, i.e., due to vitamin K deficiency, trauma, clotting factor deficiency, etc. When the cause is vitamin K deficiency, it is referred to as vitamin K deficiency bleeding or VKDB. Vitamin K is a fat-soluble vitamin mainly synthesized in adults by the gut bacteria. Newborns, however, have minimal vitamin K reserves in their liver during the time of delivery and are not able to synthesize vitamin K due to a sterile gut. Hence they are at risk of developing the hemorrhagic disease of the newborn. One of the main functions of vitamin K is gamma-carboxylation of coagulant factors- 2,7,9 and 10. This converts inactive clotting factors into an active state. Deficiency leads to the inadequate activity of these clotting factors, which results in bleeding.

Hemorrhagic disease of the newborn can be categorized into three groups. These groups are separated based on the age of onset.

1. Early: Occurs within the first 24 hours of birth, can also occur in-utero or during delivery.
2. Classical: 1 week of neonatal life (2nd through 7th day)
3. Late: From 8 days to up to 6-12 months.

7.1. Etiology and epidemiology vitamin K deficiency

Etiology for vitamin K deficiency can be grouped as idiopathic or secondary. The etiology of idiopathic causes is not known, but a few of the secondary causes have been explored. Vitamin K deficiency leads to decreased activity of clotting factors, resulting in hemorrhagic disease of the newborn. Adults can synthesize vitamin K in the large intestine through the gut bacteria, but neonates have reduced stores of vitamin K due to insufficient placental transfer, a sterile gut that fails to synthesize the necessary levels of Vitamin K, breast milk is deficient in vitamin K and poor hepatic storage.

Vitamin K deficiency can manifest in babies born to mothers on anti-tubercular drugs (isoniazid, rifampicin), antiepileptics (phenytoin, barbiturates, and carbamazepine), broad-spectrum antibiotics (cephalosporins) or vitamin K antagonists such as warfarin. Infants born with malabsorption diseases such as cystic fibrosis or hepatobiliary diseases such as biliary atresia have also been shown to develop

vitamin K deficiency. Mutations in genes encoding for the gamma-glutamyl carboxylase and epoxide reductase have also been reported.

Epidemiology. All infants irrespective of race, sex, color, religion, national origin, etc. are known to be affected by vitamin K deficiency bleeding. However, in a study conducted on 50 newborns, VKDB was found to have an increased incidence amongst male infants, breastfed infants, and those born via spontaneous vaginal delivery.

In early VKDB, the incidence in infants who have not received vitamin K prophylaxis ranges from about 6% to 12%. In classic VKDB, the incidence has gone down from 0.25% to 1.5% in earlier studies to 0.01 to 0.44% in recent studies. This has been achieved due to the inclusion of vitamin K prophylaxis in routine newborn care. In late VKDB, the incidence is 1 in 15,000 to 1 in 20,000 births and is seen predominantly in exclusively breastfed babies or babies with cholestasis or malabsorption (as vitamin K absorption is dependent on bile). The most common presenting symptom of late VKDB is intracranial bleeding, which has a mortality of 20–50% and associated morbidity.

7.2. Pathophysiology, history, physical and Evaluation

Pathophysiology.

Vitamin K is a fat-soluble vitamin that occurs in 2 forms- vitamin K1 or phylloquinone (present in green leafy vegetables) and vitamin K2 or menaquinone (synthesized by the gram-negative bacteria in the intestines). Although vitamin K has many other roles in the body, its major role involves the activation of clotting factors. It does so by gamma-carboxylation of glutamic acid residues of clotting factors 2,7,9 and 10 via post-translational modification.

A deficiency of vitamin K in the body leads to inadequate activation of these clotting factors and hence leads to bleeding in the body, which manifests as hemorrhagic disease of the newborn or, more specifically, known as VKDB.

History and, physical

If VKDB is suspected, it is important to take a proper history. The following points in the history that could lead to a proper diagnosis include

1. Drugs taken during pregnancy- anticonvulsants, anti-tubercular drugs, warfarin, salicylates, etc.
2. Gestation period- preterm babies are at a higher risk of having VKDB.

3. If breastfed or bottle-fed- as bottle/formula-fed infants are at lower risk due to fortified feed with essential vitamins and minerals.
4. Place of delivery- generally home-delivered infants do not have access to immediate vitamin K prophylaxis and hence are at a greater risk.

Physical findings in a patient with VKDB are:

1. Cephalhematoma
2. Intracranial bleeding
3. Intrathoracic bleeding, which can cause hemoptysis, and associated respiratory distress
4. Intra-abdominal bleeding- melaena or hematemesis
5. Bleeding from the skin- petechiae present over the skin
6. Bleeding from mucous membranes, including the gums, nose, etc.
7. Bleeding after circumcision
8. Bleeding from the umbilical stump after cutting the umbilical cord at birth
9. Bleeding from vaccination sites

Intracranial bleeding is mostly associated with late VKBD and presents with a floppy baby, lethargy, feeding difficulties, bulging fontanelles, decreased respiratory rate, altered consciousness, convulsions, or pallor.

Evaluation

History, physical examination, and laboratory investigations, along with any significant radiological findings, can help to arrive at the diagnosis early and start treatment.

Most commonly advised laboratory tests are:

1. Complete blood count- will have normal platelet levels (1.5-4 lacs/cubic mm)

2. Clotting profile:

- International normalized ratio (INR) greater than or equal to 4
- Prothrombin time (PT) more than 4 times the normal
- Prothrombin time will be increased due to decreased activity of factor 7

- Partial thromboplastin time (PTT) will also be increased due to decreased activity of factors 2,9 and 10
- Clotting time will be increased due to clotting factor deficiency
- Fibrinogen levels will remain normal

3. PIVKA estimation- PIVKA are proteins induced in vitamin K absence. These are evaluated by HPLC (high-pressure liquid chromatography), ELISA (enzyme-linked immunosorbent assay), or immuno-electrophoresis. Any amount of PIVKA is abnormal and indicates vitamin K deficiency. It disappears around day 5 of the administration of vitamin K.

4. Chest X-ray or ultrasound to determine if there is bleeding in body cavities- intrathoracic, intra-abdominal

5. Computed tomography (CT) and magnetic resonance imaging (MRI) studies to evaluate for intracranial hemorrhage

8. Treatment

Treatment of VKDB mainly focuses on prompt administration of vitamin K to the infant and then further investigation for the cause of the disease.

In cases of severe life-threatening bleeding, immediate blood transfusions can be given along with fresh frozen plasma to reduce the bleeding.

Late VKDB can present with intracranial hemorrhage. The most common form being sub-dural hemorrhage may require surgical evacuation or intracranial shunting to relieve increased intracranial pressure and associated symptoms.

Late VKDB can also present with neurological abnormalities despite treatment that will require regular follow-up and continuous monitoring. Physiotherapy can be advised to retain/strengthen neural function. If unable to suck or swallow, babies may require nutritional assistance.

Nonetheless, a single intramuscular (IM) dose of 1mg of vitamin K is known to improve the coagulation profile within 1 to 7 days.

Infants not protected from VKBD through prophylaxis have unrecognized liver disease.

Differential Diagnosis

The most common differential for VKDB is trauma- accidental or non-accidental injury. Other differentials include:

- Clotting factor deficiencies such as hemophilia A or hemophilia B. Non-reversal of condition despite administering clotting factors may help to determine the exact cause.
- Disseminated intravascular coagulation(DIC)- running laboratory studies will help to differentiate between DIC and VKDB.
- Thrombocytopenia, especially maternal immune thrombocytopenia as antibodies to platelets, can cross the placenta and decrease infant platelet count manifesting as purpura. However, in VKDB, the platelet count is generally normal.
- For infants presenting with isolated gastrointestinal bleed, intussusception can be a differential.

However, based on laboratory studies, it becomes easier to arrive at the diagnosis and treat the disease accordingly.

Treatment planning

For early and classic forms of hemorrhagic disease of the newborn, oral vitamin K (2mg dose) repeated at 2-4 weeks and at 6-8 weeks.

For the late form of the disease, oral vitamin K is not as efficacious as parenteral, and hence currently, 0.5-1mg single IM dose is administered to infants within 6 hours of birth.

For infants weighing less than 1500gm, 0.5mg IM single dose is given.

For infants weighing more than 1500gm, 1mg IM single dose is given.

All breastfed babies with diarrhea and malabsorption require an additional post-natal dose of vitamin K to prevent late vitamin K deficiency bleeding.

In the case of life-threatening hemorrhages, 10-20ml/kg of fresh frozen plasma should also be administered.

More than 20% of blood loss and features of shock require immediate blood transfusions.

Toxicity and Side Effect Management. There is no known toxicity or side effects associated with vitamin K1. Vitamin K1 is a naturally occurring, fat-soluble form of vitamin K. Before the introduction of Vitamin K1, vitamin K3 was used. Vitamin K3 is a synthetic, water-soluble derivative of menadione. In higher doses, it has been associated with kernicterus, hemolytic anemia, and hyperbilirubinemias.

Vitamin K was earlier thought to be associated with increased risk of childhood cancers. However, studies have shown no such association.

Due to having a safe profile, vitamin K1 is widely accepted as routine prophylaxis in most countries.

Prognosis. Vitamin K prophylaxis at birth has proven to significantly improve the prognosis by decreasing mortality. Patients presenting with intracranial hemorrhage might have associated morbidity in the form of neurological damage. However, vitamin K has reduced the incidence of hemorrhagic disease of the newborn, and its usage should be continued as effective prophylaxis.

Complications. The most important complication of hemorrhagic disease of the newborn is bleeding, which can often be fatal in infants. It is one of the most important causes of intracranial hemorrhage in the first year of life.

Morbidity is generally seen with the late Vitamin K deficiency bleeding, and it manifests as neurological defects such as hydrocephalus, encephalopathy, cerebral atrophy, seizures, and severe developmental delay.

Consultations. Consultations with neonatology, pediatrics, transfusion medicine, clinical pathology, and hematology are critical for the early detection and diagnosis of vitamin K deficiency bleeding. Routine follow-up should be scheduled to reduce morbidity and mortality.

Deterrence and Patient Education. Healthcare workers should work closely with the parents to make them understand the need for vitamin K prophylaxis and the severity of the disease. The benefit of using IM vitamin K injections should be explained to the parents. For those who refuse injection, counseling about the adverse effects of vitamin K deficiency should be explained. The alternate oral dose (2mg) should also be recommended, along with the repetition of the dose at 2 to 4 and 6 to 8 weeks of age.

Pearls and Other Issues. Breast milk is particularly deficient in vitamin K, and hence prophylaxis at birth will go a long way in preventing the diseases. However, as certain studies have found, formula-fed babies do not suffer from vitamin K deficiency as formula milk is already fortified with minerals and vitamins in sufficient quantities. According to a study conducted, formula-fed infants were found to have higher vitamin K1 fecal concentrations than breast-fed infants.

Enhancing Healthcare Team Outcomes. Hemorrhagic disease of the newborn is a life-threatening condition associated with high mortality and morbidity. But, it can easily be prevented by administering 1mg IM of vitamin K within 1 hour of birth.

Early and prompt diagnosis of hemorrhagic disease of the newborn can alleviate the devastating consequences. Strong interprofessional communication and care coordination by clinicians, nurses, and pharmacists can help improve outcomes and ensure patient safety. Parents should be counseled regarding the condition, and the severity and follow-up routine with the clinician should be scheduled on a regular basis to check the well-being of the patient.

General material and methodological support of the lecture: multimedia, posters, medical videos, list of students, lesson plan, drawing board, samples of medicines.

Questions for self-control:

1. Etiological factors for hemorrhagic and hemolytic disease of the newborn .
2. The typical clinical signs of hemolytic and hemorrhagic disease of the newborn .
3. The peculiarities of hemolytic and hemorrhagic disease of the newborn in preterm.
4. The principles of examination and data analysis of laboratory and instrumental investigations in hemolytic and hemorrhagic disease of the newborn.
5. The principles of emergency aid in basic emergency conditions arising during hemorrhagic and hemolytic disease of the newborn.
6. The features of differential diagnosis in infants with hemolytic and hemorrhagic disease of the newborn.
7. The principles of treatment and prevention of hemolytic and hemorrhagic disease of the newborn.
8. The peculiarities of life prognosis of newborns with hemolytic and hemorrhagic disease.
9. The main moral and deontological principles of the doctor and principles of professional subordination in neonatology.

Literature used by the lecturer to prepare the lecture

1. Nelson Textbook of Pediatrics, 2-Volume Set, 22nd Edition, 2024. Robert M. Kliegman, Joseph W. St. Geme III, Nathan J. Blum, et al.
2. Nelson Textbook of Pediatrics / R. M. Kliegman [et al.]; ed. R. E. Behrman. - 21th ed. - Edinburgh [etc.]: Elsevier, 2020. - Vol. 1. – LXXV**.**
3. Nelson Textbook of Pediatrics. Expert Consult Premium Edition. Enhanced Online Features and Print 19th Edition ISBN-13: 978-1437707557 https://cutt.ly/BkgT2bi
4. Hemolytic Disease of the Newborn (HHDN) — Causes and Symptoms Last update August 5, 2019 https://www.lecturio.com/magazine/HHDN-hemolytic-disease-newborn/
5. Hemorrhagic disease of the newborn. Alexey Portnov, medical expert Last reviewed: 11.04.2020

https://iliveok.com/health/hemorrhagic-disease-newborn_108785i15937.html

6. Ng E, Loewy AD. Guidelines for vitamin K prophylaxis in newborns. Paediatr Child Health. 2018 Sep;23(6):394-402. [PMC free article] [PubMed]

Electronic information resources:

1. http://moz.gov.ua– Міністерство охорони здоров'я України
2. www.ama-assn.org – Американська медична асоціація / American Medical Association
3. www.oapn.od.ua- ГО "Одеська Асоціація лікарів-педіатрів та неонатологів"
4. www.who.int – Всесвітня організація охорони здоров'я
5. www.dec.gov.ua/mtd/home/ - Державний експертний центр МОЗ України
6. http://bma.org.uk– Британська медична асоціація
7. www.gmc-uk.org- *General Medical Council* (*GMC*)
8. www.bundesaerztekammer.de – Німецька медична асоціація
9. https://www.who.int/workforcealliance/members_partners/member_list/ipa/en/ - Міжнародна асоціація педіатрів / International Pediatric Association (IPA).
10. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf GINA Global Initiative For Asthma. 2024
11. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2021-Glomerular-Diseases-Guideline_English_LN-2024-Update.pdf KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases
12. https://aamsmedacademy.com/ American Academy of Medical Sciences (AAMS)
13. https://nam.edu/ The National Academy of Medicine (NAM)
14. https://cutt.ly/utqqtt7I Підручник Нельсона з педіатрії - електронна книга Elsevier на VitalSource, 21-ше видання
15. https://www.amazon.com/Averys-Neonatology-Pathophysiology-Management-Pathophusiology/dp/1451192681