Hemolytic Disease of the Fetus and Newborn: Anti-K

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Hemolytic disease of the fetus and newborn (HDFN) is a significant challenge in perinatal medicine, especially when it is caused by antibodies against the Kell antigen system. Among the various causes of HDFN, anti-Kell antibodies are of particular concern because they can cause severe hemolytic reactions and adverse effects on the fetus. Understanding the pathophysiology, risk factors, clinical presentation, and specific management strategies due to anti-Kell antibodies is critical for effective prenatal care, timely diagnosis, and appropriate interventions to optimize both maternal and neonatal outcomes.

Case Study

During routine prenatal and pregnancy monitoring, a 27-year-old woman was found to develop anti-K antibodies for the first time in her first trimester, marking a significant development in her pregnancy. As the pregnancy progressed into the second trimester, the mother's anti- K antibody titration showed a marked increase, raising concerns about possible complications. Notably, the woman's blood group was identified as O Rh positive, and her phenotype showed the absence of the K antigen. Further research involving the father who tested positive for the K antigen revealing a genetic variation that put the fetus at risk of inheriting the antigen and triggered the mother's immune response against the fetus's red blood cells. With careful monitoring, the baby was born at 37 weeks. After birth, the continued presence of passively acquired antibodies affected the baby's red blood cells, causing ongoing problems such as persistent anemia, hypertension, lethargy, and difficulty latching on to the breast. The neonate required multiple transfusions while in the hospital and was discharged home four weeks later.

Disease History and Presentation

Karl Landsteiner and Alexander Weiner brought a revolution by first identifying the Rh antigen system in the 1940s. This discovery unraveled the impossible question of maternal-fetal alloimmunization. However, it wasn't until 1946 that Kell antigen was discovered as one of HDFN's critical participants. "The Kell blood

group system, a human blood type that is based on the presence of antigens on the surface of erythrocytes that are expressed by the KEL antigen and is characterized by polymorphism. As a result, studies of Kell's antigens have provided insight into the development of polymorphic traits in human development." (Rogers, 2022) The Kell system's cellular antigens are targets for antibodies that can result in fetal erythroblastosis and transfusion reactions.

Since its discovery nearly 80 years ago, the Kell blood group system has grown into a complex of 36 red blood cell antigens. Numerical and alphabetical terminologies similar to the Rh blood group system were developed for the Kell blood group system. All references to the blood group system are known as Kell. Appropriate references to systemic antigens are by numerical or alphabetical symbols. The original names of the Kell antigens are historical in context. K or KEL1 is the proper term for the original antigen. The Kell blood group system gene (KEL), which has 19 exons and is found on chromosome 7, was cloned in 1991. The gene encodes a protein called Kell glycoprotein, which is a membrane-spanning molecule. The inheritance of almost all antigens in the Kell blood group system is due to single nucleotide polymorphisms that result in single amino acid substitutions in the Kell glycoprotein.

In hemolytic disease of the fetus and newborn, maternal antibodies cross the placental interface and attach to fetal RBCs, resulting in hemolytic anemia. The maternal antibodies are made after exposure to foreign antigens from a blood transfusion or a previous pregnancy. After sensitization, the maternal immune system, mainly B cells, produces Kell antigen-specific IgG antibodies. During subsequent pregnancies, if the fetus inherits the Kell antigen from the father (which may be Kell positive), the mother's anti-Kell antibodies can cross the placenta and enter the fetal circulation after 20 weeks of gestation when the placenta becomes more permeable. Figures 1, 2 and 3 below illustrate possible inheritance patterns. In Figure 1, the child does not inherit the K antigen and is not at risk for HDFN. In Figure 2, 100% of the offspring of these parents would be K- positive because the father is homozygous for Kell. Figure 3 shows a heterozygous father who has a 50% chance of passing the gene to his offspring. (Bethesda, 2005)

The severity of HDFN depends on factors such as maternal Kell antibody titer, the degree of antigenic incompatibility between mother and fetus, and the gestational age at which antibodies cross the placenta. Subsequent pregnancies often result in a stronger immune response, which can worsen the severity of HDFN. In response to the destruction of red blood cells, fetal bone marrow can increase the production of red blood cells to compensate. However, in severe cases, this compensatory mechanism may prove insufficient, causing fetal distress. "Rare cases of HDFN caused by Kell immunization usually result in severe fetal anemia because maternal anti-Kell activity targets fetal erythrocyte precursors, preventing fetal RBC production." (Bethesda, 2005)

Laboratory Findings

Findings from different departments within the laboratory play a huge role towards the determination of HDFN caused by anti-Kell antibodies. In the immunohematology department, the direct antiglobulin test may reveal the presence of IgG antibodies attached to the surface of fetal red blood cells, indicating immune-mediated hemolysis. The antibody screen is used to detect maternal serum antibodies, including anti-Kell, that may react with fetal red blood cells. Antibody titration is used as a non-invasive way for providing insight into the risk of HDFN. In the hematology department, a complete blood count may show signs of hemolysis, including reduced hemoglobin and hematocrit levels, reticulocytosis, and nucleated red blood cells in the peripheral blood smear. These findings suggest ongoing destruction of fetal red blood cells by maternal antibodies. Clinical chemistry tests measure bilirubin levels, with elevated levels of unconjugated bilirubin indicating hemolysis and potentially leading to jaundice in the newborn.

At 28 weeks, the mother's antibody level increased, suggesting the presence of fetal RBCs with the K antigen in her system, leading to more antibody production. A repeat mean corpuscular volume (MCV) was performed determining average size of the red blood cells and indicated mild anemia. By 32 weeks, there was a sudden increase noted in the MCV. Cordocentesis revealed a fetal hemoglobin level of 6.2g/dl, levels less than 10.5 g/dl in the second trimester and less than 11.0 g/dl in the first and third trimesters are indictive of anemia along with a positive direct antiglobulin test and identification of anti-K in the eluate. "Cordocentesis

draws blood from the umbilical cord of the fetus in order to look for anomalies. Before a baby is born, it can identify certain issues like infections, blood disorders, and genetic mutations." (Cleveland Clinic Medical, 2022) Intrauterine transfusions were performed at 32, 34, and 36 weeks. Red blood cell transfusions after delivery were also required to maintain adequate oxygen and decrease symptoms of anemia.

Diagnosis and Treatment

Hemolytic disease of the fetus and newborn is an extreme complication to fetal and neonatal health, and in this scenario, is caused by antibodies targeting the Kell antigen system. Management of anti-Kell HDFN is an absolute multi- disciplinary approach. Treatment is aimed at reducing the results of hemolysis and ensuring neonate's survival. Antenatal management measures for HDFN mainly hinge on early location of the fetus and monitoring of the fetal well-being using diagnostic testing. Noninvasive assessment of fetal growth is done by ultrasound and doppler velocimetry which involves studies on the survey of growth of the fetus. Serial estimations of maternal counteracting antibody titers and other clinical indicators can provide an estimate for the probable degree of hemolysis and guide timing of key interventions. Although administration of Rhogam effectively prevents sensitization to Rh antigens, it does not protect against other blood group antigens such as Kell. Therefore, the goal is to avoid sensitizing events such as unnecessary blood transfusions or invasive procedures during pregnancy. Prenatal testing includes routine screening for maternal antibodies and additional tests such as amniocentesis or fetal blood sampling if needed for further evaluation.

In cases of severe HDFN such as this one, intrauterine transfusions (IUT) can be used to replace the red blood cells of the fetus lost to destruction, to stop further disintegration of the fetal hemoglobin levels and to decrease, but not entirely remove, the risk of hydrops fetalis. Figure 4 shows an illustration of fetal hydrops and anemia due to Kell alloimmunization. Generally, IUTs should be strictly regulated through fetal blood testing and conducted by high-level fetal medicine centers. Urgent measures include thorough clinical examination and search for anemia, jaundice, and hemodynamic instability in the newborn. Phototherapy should be initiated promptly to reduce the serum bilirubin to less than the levels at which kernicterus occurs. "Kernicterus, or bilirubin encephalopathy, is a neurological disease caused by bilirubin

that occurs when the blood level of unconjugated bilirubin exceeds 25 mg/dL due to any event that results in decreased elimination and increased production of bilirubin." (Reddy 2023) Figure 5 shows kernicterus description. (ABC Law Centers, 2024) Phototherapy treatment converts unconjugated bilirubin into water-soluble isomers, making it easier to excrete from the body. During treatment, the duration and effectiveness of phototherapy are determined by careful monitoring of serum bilirubin concentration and other vital parameters.

Conclusion

The family was educated on the inheritance pattern of the Kell antigen system and the possible risk of HDFN in future pregnancies. Long-term follow-up is crucial particularly for babies requiring intrauterine transfusions or exhibiting significant anemia. Additionally, assessing immune function and susceptibility to infections is imperative to identify and address potential immunodeficiencies that may arise because of intrauterine hemolysis and antibody exposure. Long-term cardiac evaluation in this case was warranted to detect and manage any cardiovascular complications stemming from severe fetal anemia. Beyond medical assessments, psychosocial support was integral for both the child and the family, acknowledging the emotional, financial, and social challenges posed by HDFN and its treatment. Moreover, genetic counseling served a crucial role in educating the family about the risk of recurrence in subsequent pregnancies and exploring alternative reproductive options to mitigate this risk

In summary, the treatment course needed for hemolytic disease of the fetus and newborn caused by anti-Kell antibodies entails antenatal diagnosis, intrauterine interventions, and postnatal care plans. In order to reduce morbidity and mortality, acceptable goals could include the ability to identify adequately those pregnancies at risk, closely monitor the status of the fetus, and institute appropriate therapies in time to improve the outcome of HDFN management.

	k	k
k	kk	kk
k	kk	kk

Figure 1.
Mother (on side) is negative for K (kk), father (at top) is also negative, homozygous kk.

	K	K
k	Kk	Kk
k	Kk	Kk

Figure 2.
Mother is negative for K (kk), father is homozygous KK

	K	k
k	Kk	kk
k	Kk	kk

Figure 3.
Mother is negative for K, father is heterozygous Kk.

Figure 4. Kell alloimmunization: Anti-K, Immunoglobulin G, cause fetal anemia and hydrops

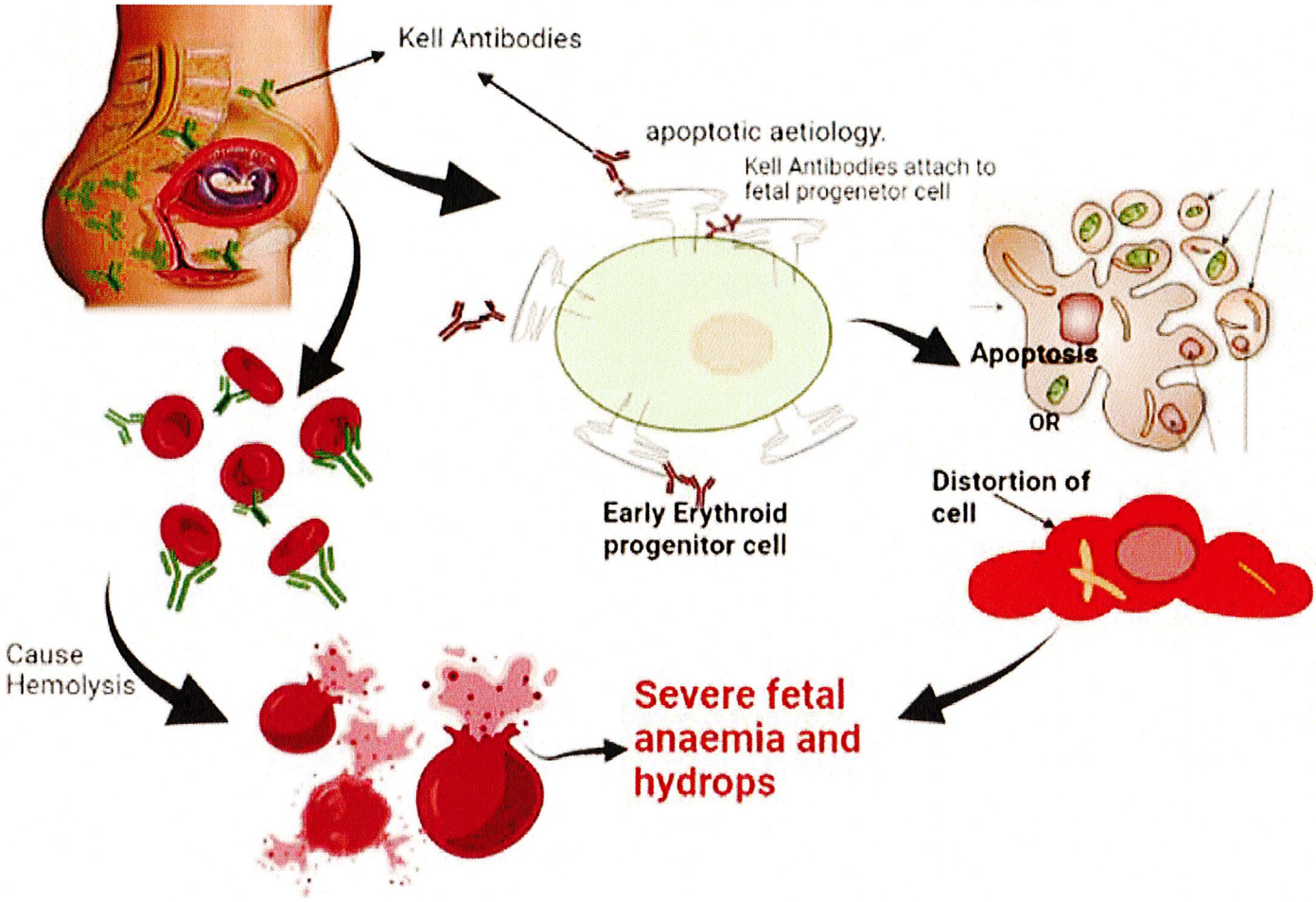
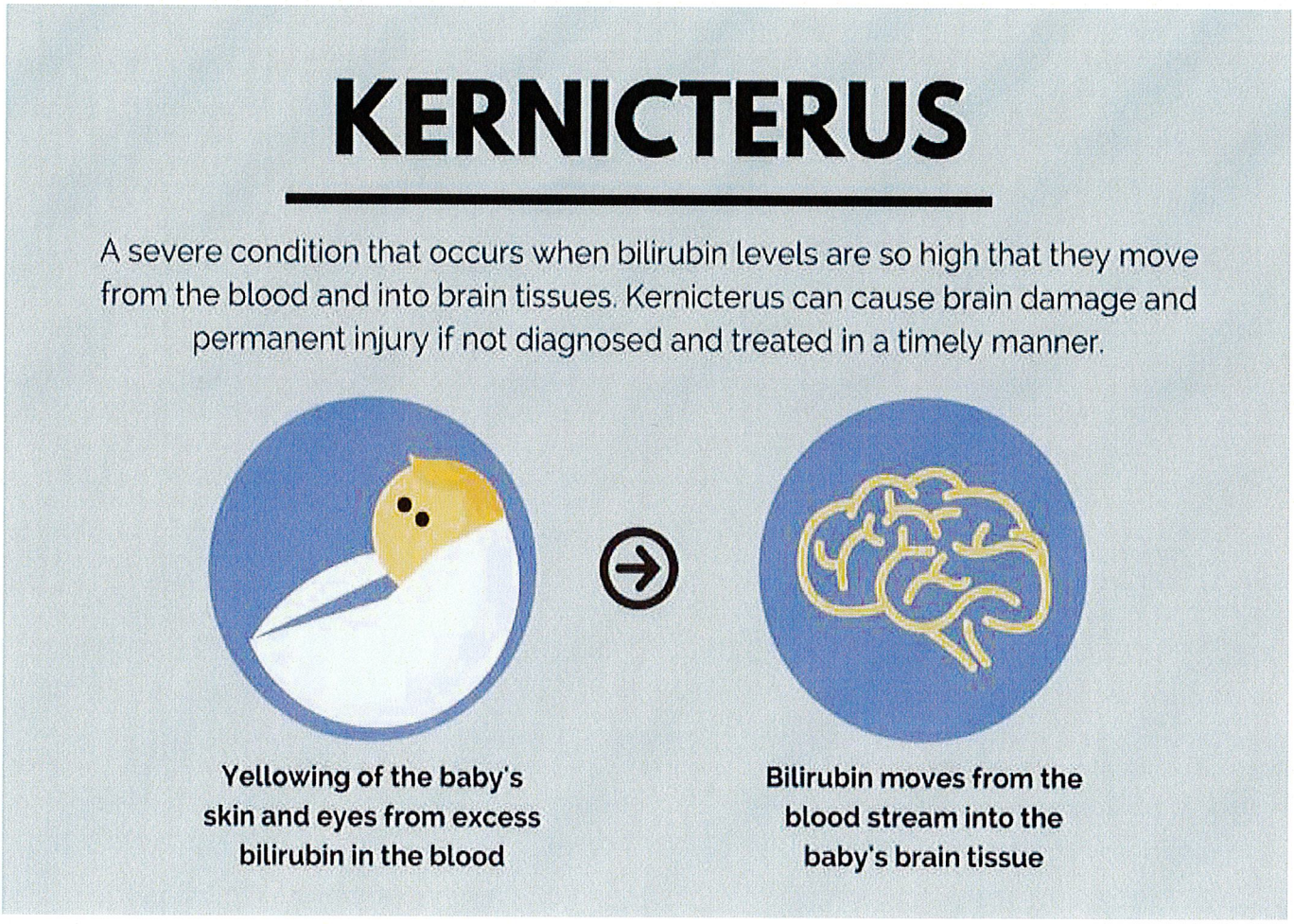


Figure 5. Kernicterus Description.



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