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THE ROLE OF MATERNAL FOETAL BLOOD GROUP INCOMPATIBILITY IN ERYTHROBLASTOSIS FETALIS: A COMPREHENSIVE REVIEW

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ABSTRACT

Red blood cells (RBCs) of the infant or foetus are destroyed as a result of maternal immunoglobulin G (IgG) antibodies in a disorder known as haemolytic disease of the foetus and new-born (HDFN), also known as alloimmune HDFN or erythroblastosis fetalis. When the mother's immune system reacts to foetal antigens, a process called isoimmunization takes place, leading to the formation of these antibodies. To be more precise, foetal erythrocytes that express RBC antigens that are absent from mother's blood cross the placenta and enter the maternal circulation. This immune reaction may result in haemolysis, the production of bilirubin, and anaemia as a result of the loss of foetal red blood cells. The severity of HDFN in the foetus is influenced by a number of variables. First and foremost, the mother's antibody production—both the quantity and quality—plays a critical role. Red cell breakdown and the problems that follow are more likely to occur when antibodies are present at higher amounts. The severity of the condition is also influenced by the foetus' gestational age. Because of the foetal immune system's immaturity and its diminished capacity to replace RBCs that have been killed, HDFN may be more severe at earlier gestational ages. The foetus' capacity to excrete bilirubin, a consequence of haemolysis, also plays a role in the sickness' overall severity. Hyperbilirubinemia and other possible problems, such as kernicterus, can result from impaired bilirubin clearance. Testing foetal blood and

determining the status of the mother's antibodies are required for the diagnosis of HDFN. Pregnant women who are sensitised and at risk for HDFN can be identified through maternal antibody screening. The state of the foetal RBC antigen and the level of haemolysis can be determined by foetal blood tests, such as cordocentesis or percutaneous umbilical blood sampling. In order to manage the illness and make educated decisions about the course of treatment and when to deliver the baby, it is essential to monitor maternal antibody levels and the health of the foetus through ultrasound exams. The prevention or reduction of the disease's consequences is the main goal of HDFN management and treatment. This entails vigilant foetal surveillance, thorough monitoring of maternal antibody levels, and potential bilirubin reduction measures. Intrauterine transfusions to refill the foetal RBC supply, immunoglobulin therapy to prevent the effects of antibodies, and phototherapy to control hyperbilirubinemia at the new-born stage are all possible treatments. In extreme circumstances, foetal interventions or an early birth may be required. Optimising outcomes for new-borns with HDFN require prompt and coordinated care from a multidisciplinary team of obstetricians, neonatologists, haematologists, and transfusion medicine experts.

KEYWORDS: Haemolytic disease of the foetus and new-born (HDFN), Alloimmune HDFN, Isoimmunization, Haemolysis, Replenishment of destroyed RBCs.

This review article examines the nuances of alloimmune HDFN, commonly known as haemolytic illness of the foetus and new-born (HDFN). The syndrome results from isoimmunization, in which maternal antibodies react with foetal antigens, causing red blood cells (RBCs) to be destroyed and haemolysis. The foetus's capacity to replace lost RBCs and fend off haemolysis is one of many variables that affect how severe HDFN is. For the creation of successful treatments and treatment plans, it is essential to comprehend the mechanisms driving this process and the potential for replenishment. This review attempts to clarify the pathophysiology of HDFN and pave the way for improved management strategies in affected neonates and their mothers by digging into the complex interplay between alloimmune responses, haemolysis, and the replenishment of RBCs.

INTRODUCTION

Red blood cells (RBCs) in the infant or foetus are destroyed by maternal immunoglobulin G (IgG) antibodies, which is a disorder known as hemolytic disease of the foetus and newborn (HDFN), also known as alloimmune HDFN or erythroblastosis fetalis. The goal of this

review article is to give readers a thorough grasp of the erythroblastosis fetalis pathophysiology, risk factors, clinical symptoms, and treatment options.[1]

When foetal RBCs are destroyed by maternal antibodies produced in response to a foetal antigen, HDFN develops. When foetal erythrocytes expressing particular RBC antigens that are absent in the mother cross the placenta and enter the mother's bloodstream, an immunological response known as isoimmunization takes place. As a result, the foetal RBCs are targeted and destroyed by antibodies of the IgG class that are produced by the maternal immune system in response to the recognition of these foreign antigens. Hemolysis, characterised by the release of bilirubin and subsequent anaemia, might result from this damaging process.[1]

The immunological response and the fetus's capacity to handle the ensuing hemolysis are two factors that affect how severe erythroblastosis fetalis is. The quantity and potency of antibodies the mother produces are a key factor. Higher antibody levels can increase the severity of foetal RBC destruction and the likelihood of problems. The severity of the illness is also influenced by the foetus' gestational age. The ability of the foetal immune system to properly remove bilirubin and replace RBCs that have been damaged may be less developed at earlier gestational ages.[2]

Erythroblastosis fetalis can have a variety of clinical effects, from moderate to severe. Jaundice, anaemia, and in severe cases, hydrops fetalis, a disorder characterised by severe generalised edoema and organ failure in the foetus, can all result from hemolysis and the consequent release of bilirubin. The rate and extent of RBC destruction, the foetus' capacity to make up for anaemia, and the bilirubin clearance all affect the severity and timing of clinical symptoms.

A multidisciplinary strategy comprising obstetricians, neonatologists, haematologists, and transfusion medicine experts is necessary for the treatment of erythroblastosis fetalis. For early detection and intervention, prenatal surveillance and ultrasound exams to measure maternal antibody titers and foetal health are essential. Intrauterine transfusions to replenish the foetal RBC supply, immunoglobulin therapy to prevent the effects of antibodies, and careful bilirubin level monitoring are all possible treatment options. Interventions that are timely and appropriate might greatly enhance results and lessen erythroblastosis fetalis-related problems.[1]

Recent developments in the study of the immunopathogenesis of HDFN have resulted in the creation of original therapy strategies. These include non-invasive methods for checking on the health of the foetus, including Doppler ultrasound, and cutting-edge therapies that target certain phases of the immune response. The use of hematopoietic stem cell transplantation and improvements in foetal transfusion methods also hold promise for enhancing outcomes in serious situations.[3]

In Conclusion, an intricate disorder known as erythroblastosis fetalis, also known as HDFN, is characterised by the maternal antibodies' destruction of foetal RBCs. Early detection and efficient management of this disorder depend on an understanding of the underlying mechanisms, risk factors, and clinical symptoms. This review article seeks to advance knowledge and enable better care for babies and mothers affected with erythroblastosis fetalis by examining the pathophysiology, clinical characteristics, and therapeutic approaches.[1]

METHODS AND DISCUSSION

Foetoscopically guided intrauterine intravascular transfusions have been used to treat erythroblastosis fetalis in severe cases. During fetoscopy, a foetal umbilical artery or vein is punctured in these infusions to acquire a sample of pure foetal blood for hematologic and biochemical analyses. Calculations based on menstrual dates are used to estimate the gestational age of the foetus, and ultrasound measures of the foetal biparietal diameter are used to corroborate this age. Red blood cells that have been packed and cross-matched against the mother are used in the transfusion to ensure compatibility. Depending on the gestational age and haematocrit values of the donor and the foetus, different amounts of donor blood are transfused.[2]

By comparing the foetus’s pretransfusion and posttransfusion haematocrit readings, the effectiveness of the transfusion is evaluated. A Coulter "S Plus" electronic cell counter is used to calculate these values as well as the donor blood's haematocrit value. In some circumstances, more blood may be infused to maintain acceptable levels if the posttransfusion haematocrit percentage drops below 40%. The assessment of fetoplacental blood volume does not, however, take the information from these additional transfusions into account. By avoiding the contamination of foetal blood samples with amniotic fluid and guaranteeing the effective collection of posttransfusion samples, it is crucial to assure the accuracy of the transfusion procedure.[2]

In this study, 57 foetuses between the ages of 18- and 31-weeks' gestation received a total of 121 transfusions, according to the data that were available for analysis. The outcomes and consequences of intrauterine intravascular transfusions in the treatment of severe erythroblastosis fetalis are crucial insights provided by these findings. Haematocrit readings, transfusion volumes, and their effects on foetal health are evaluated as part of the analysis. Researchers can evaluate the efficacy and safety of this intervention and make defensible choices about whether to apply it in clinical practise by looking at this data.[1]

This study's description of the foetoscopically guided intrauterine intravascular transfusion technique illustrates a viable treatment option for severe erythroblastosis fetalis cases. This method enables precise monitoring of transfusion volumes and hematologic parameters by directly accessing the foetal circulation. To assess the long-term effects and potential side effects of this intervention, more study and analysis of a larger cohort are required. As this field develops further, it may be possible to improve the transfusion process and develop better management plans for foetuses with severe erythroblastosis fetalis.[2]

Calculation of blood volume

The following presumptions used as the foundation for blood volume estimation.

(1) The last sample of foetal haemoglobin was obtained after the infused blood had been fully mixed with the circulating blood volume.

(2) The volume of foetal blood at the conclusion of the transfusion (V,) was equal to the sum of the volume of foetal blood at the beginning of the transfusion (V,) and the volume of the transfusion (Vd), less the volume of the initial foetal blood sample (V,) V, = V, + Vd – V

(3) The initial haematocrit value (H,) multiplied by the initial blood volume (V;) and the volume of the transfusion (Vd) multiplied by the initial haematocrit value of the donor blood (Hd) less the volume of the sample (V,) multiplied by the initial haematocrit value (H,) are added to determine the red blood cell (RBC) volume in the foetal circulation at the end of the transfusion: RBC volume equals V,H, + VdHd-V,H

(4) The haematocrit value at the end of the transfusion (Hr) equals the final red cell volume divided by the final blood volume.

$$H_f = \frac{V_i H_i + V_d H_d - V_s H_i}{V_i + V_d - V_s} \qquad \text{Equation 3}$$

Equation 3 can be rearranged to give:

$$V_i = \frac{V_d(H_d - H_f) + V_s(H_f - H_i)}{H_f - H_i} \qquad \text{Equation 4}$$

Equation 4's right-hand side variables are all measured at the time of foetal transfusion, allowing for the calculation of V, or the initial fetoplacental blood volume.[2]

Statistical investigation

To the nearest full week of amenorrhea, gestational age was rounded. On an IBM PC personal computer, polynomial regression using the least-squares method was performed using a programme created by Italian programmers Giuricin Matteo and Riccardo Brach-dente of Florence.[2]

RESULTS

The relationship between foetal blood volume and gestational age in foetuses with erythroblastosis fetalis is depicted in the fetoplacental blood volume figure. At the time of their transfusion, 27 foetuses had ultrasonographic evidence of hydrops fetalis.

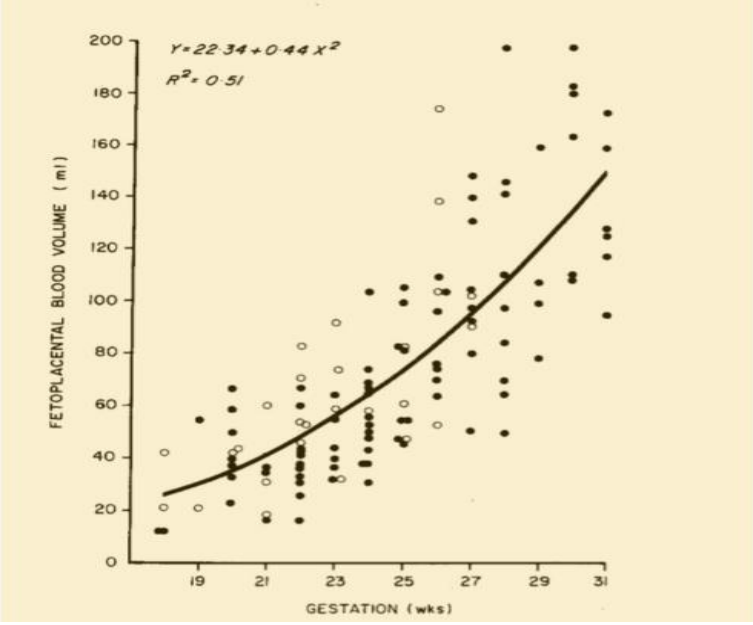


Fig-1: Estimated fetoplacental blood volume.

Open symbols denote hydropic foetuses. As is evident, there is no distinction between the estimated blood volumes for these two groups. A quadratic function performed better than a linear one in describing the link between fetoplacental blood volume and gestational age. The regression line provided the best estimation of fetoplacental blood volume at 18 weeks, which was 25.87 ml, and at 31 weeks, which was 151.7 mi.

The amount of foetal placental blood is shown in Fig. 2 as millilitres per kilogramme of foetal weight. The volume was 117 ml/kg at 18 weeks of gestation and 93.1 ml/kg at 31 weeks. 101 13.6 (2 X SD) ml/kg was the total mean value. This method of computing the volume per kilogramme of foetal weight showed a correlation with gestational age. We utilised the fifty-fifth percentile for normal foetal weight established by Brenner et al. and the blood volume estimate from the regression line in Fig. 1 because foetal weight for patients in this investigation at the time the blood volume was assessed was unknown. The British population has a comparable infant weight distribution, thus although though these weights were calculated for the patient population of Chapel Hill, North Carolina rather than the United Kingdom, it is unlikely that this would result in a substantial inaccuracy. Despite having erythroblastosis fetalis, the foetuses in this study had ultrasonographic measurements of foetal growth that were within the usual range for gestation, including head circumference, belly circumference (apart from in cases with hydroplasia fetalis), biparietal diameter, and femur length.8 Brenner et al. did discover that foetal growth patterns varied significantly.[3]

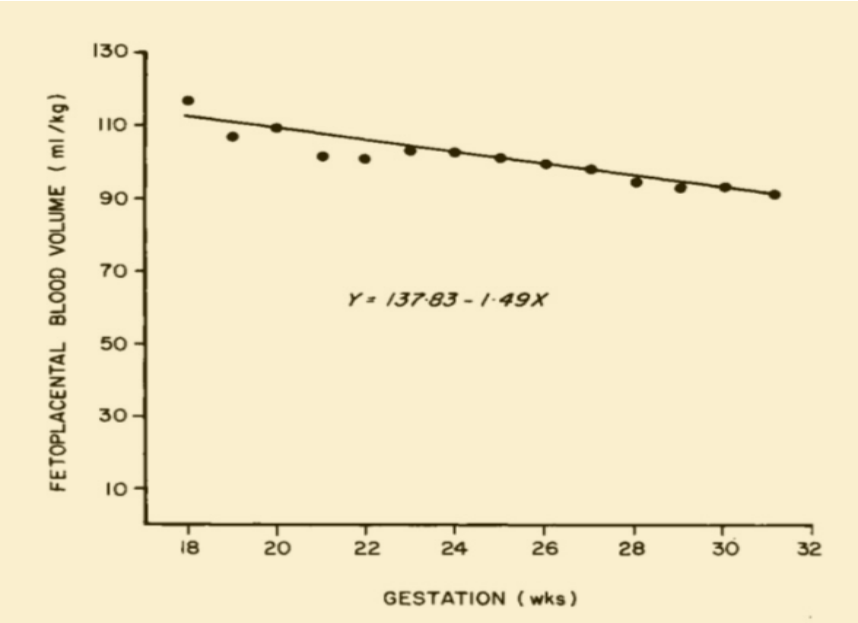


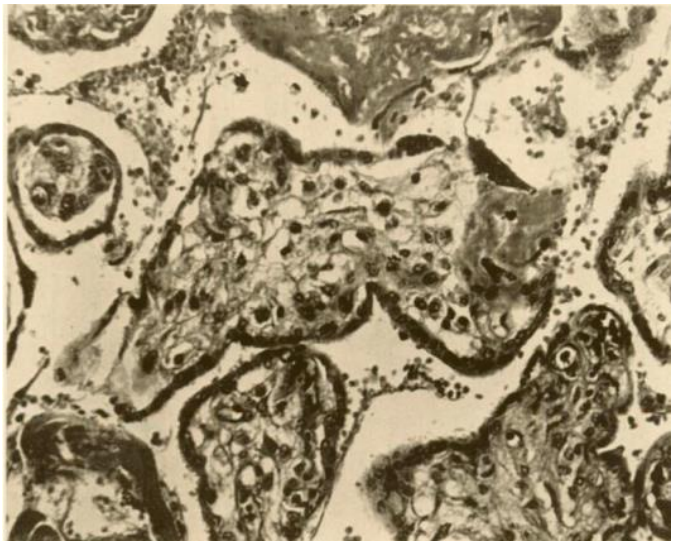
Fig. 2: Estimated fetoplacental blood volume expressed as mil- liliters per kilogram estimated fetal weight.

Weight was correlated with maternal social status and foetal sex, although these effects weren't seen until 36 weeks of gestation. It appears unlikely that there would be a significant variation between the weights of our foetuses and those reported by Brenne because our study contained foetuses under 32 weeks' gestation.

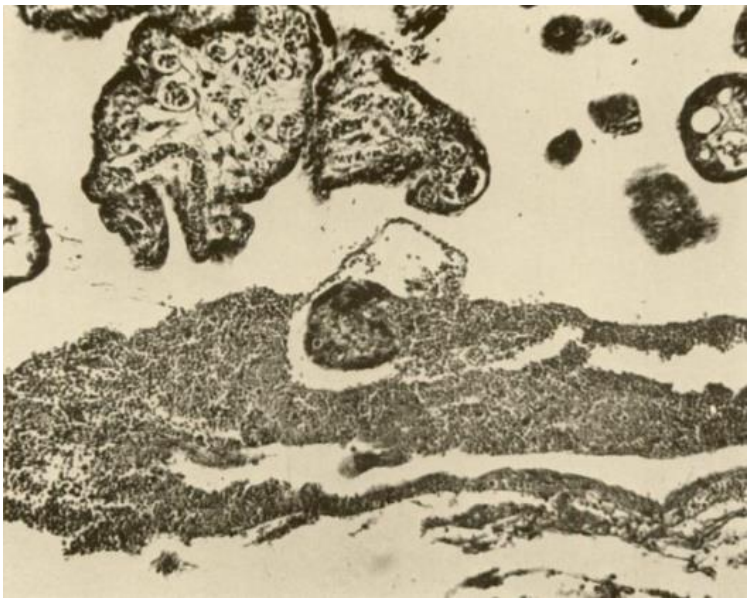
In a case of erythroblastosis fetalis where the infant survived for 33 minutes, the placenta from an 8-month pregnancy was examined under a microscope and substantial discoveries were found. Due to the presence of fibrin and agglutinated red blood cells, many villi and trunks of the placenta sections showed blockage of peripheral blood arteries. Additionally, there were instances of foetal blood ruptures and haemorrhages into the nearby intervillous spaces, as well as signs of necrosis in the walls and local tissues in some places. Notably, entire nucleated red blood cells were present in the foetal blood. These findings point to the development of vascular thromboses, which compromise placental blood flow and have negative effects on foetal circulation. Additionally, through the damaged surfaces, maternal blood was seen in direct contact with the foetal circulation, suggesting that there may have been a transfer of maternal components into the foetal system.[3]

Similar findings were found when the placental sections were examined in another case of erythroblastosis fetalis, this time in a 7-month pregnancy where the infant survived for 25 minutes. Similar to the prior occurrence, agglutinated red blood cells and fibrin clearly occluded peripheral blood arteries in multiple villi and trunks. Vascular thromboses caused the walls and local tissues to necrose, which caused foetal blood to burst and bleed into the intervillous spaces. Notably, entire nucleated red blood cells were present in the foetal blood. These results lend more evidence to the interruption of placental blood flow and its associated effects on foetal health. Additionally, the fractured surfaces permitted direct blood-to-blood contact between the mother and the foetus, possibly promoting the transfer of maternal components into the foetal system.[3]

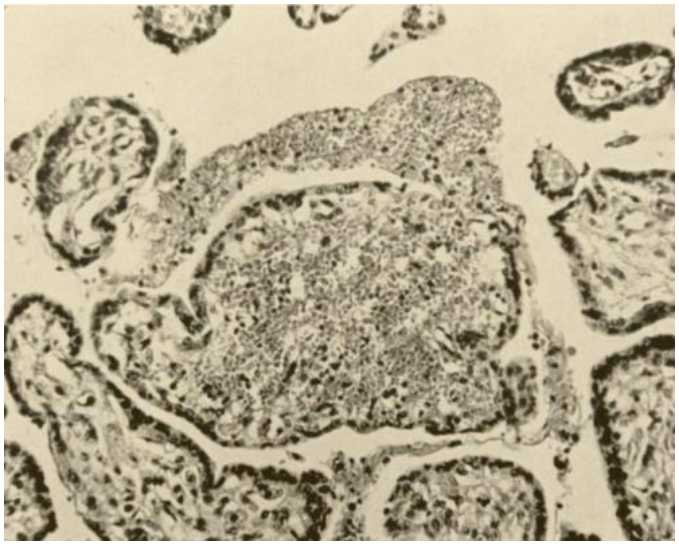
The microscopic analysis of the placentas from erythroblastosis fetalis-affected pregnancies in both cases revealed major pathological characteristics, such as arterial occlusions, necrosis, haemorrhages, and contact between maternal and foetal blood. These findings draw attention to the complex character of the erythroblastosis fetalis-related placental anomalies and shed light on the underlying causes of the unfavourable outcomes seen in these individuals.



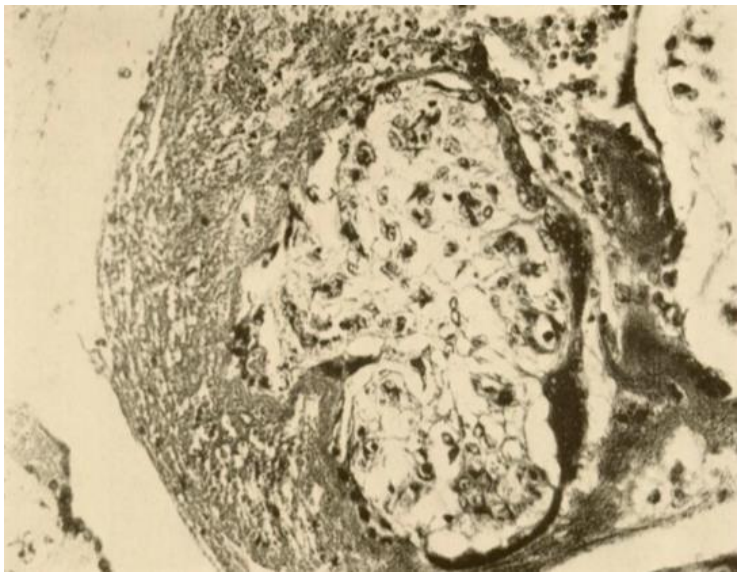
Placenta #1979 of 8 month pregnant. Case of erythroblastosis foetalis. (Magnification about 300 ×.) (Right middle area.) Occlusion of blood vessel of villus by agglutinated red blood cells and fibrin. Necrosis of walls and of regional tissues with rupture.[3]



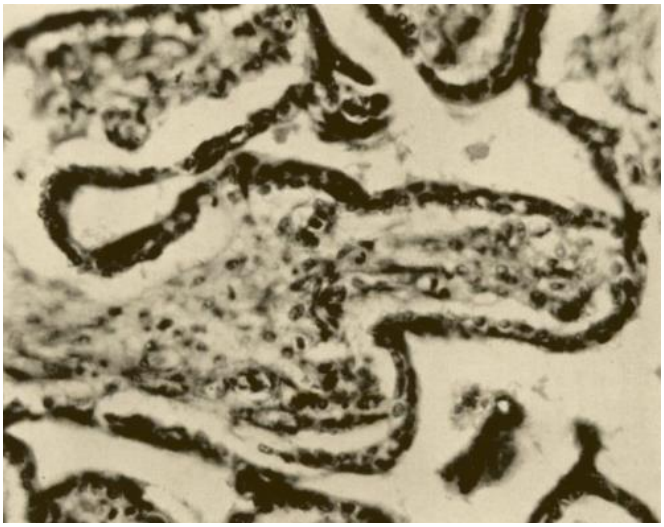
Placenta #2243 of 7 month pregnant. Case of erythroblastosis fetalis. (Magnification about 150 ×.) (Middle, lower area.) Very recent hemorrhage from villus into regional intervillous spaces. (Many of the fetal red blood cells are nucleated.)[3]



Placenta #2243. (Magnification about 200 ×.) (Center) Recent hemorrhage from villus into regional intervillous spaces showing early formation and molding of clot. (Soms of the fetal red blood cells are nucleated.)[3]



Placenta #1979. (Magnification about 300 ×.) (Left and upper.) Recent clot containing numerous intact and degenerating nucleated fetal red blood cells (especially upper right) following hemorrhage from villus. (Reprinted by permission of the American Journal of Obstetrics and Gynecology.)[3]



Placenta #2330 of a 9 month pregnant. Case of erythroblastosis fetalis. (Magnification about 400 ×.) Villi with double epithelial lining, and thick stroma.[3]

Infant exchange transfusions have been a common practise for more than 20 years. Surprisingly, a literature search turned up a case report from 1925 that described how this therapy had successfully treated a newborn with icterus gravis. According to Hart's account of the incident, the baby in question was the ninth pregnancy's offspring, weighed eight pounds at birth, and initially showed no signs of jaundice. But the previous seven offspring of the same mother had all passed away after developing jaundice. The baby was diagnosed with jaundice on the fourth day of life, and an exchange transfusion was decided upon to remove toxins from the blood and slow the disease's growth. The late Bruce Robertson had created the method, and J.L. McDonald had carried out the actual process.[4]

300 cc of blood were taken out of the longitudinal sinus during the exchange transfusion, and 335 cc of donor blood were injected into the saphenous vein along with 60 cc of a 5 percent glucose solution. The infant's overall condition significantly improved the next day as the jaundice's severity decreased. By the fourth day, it had completely disappeared. When the child was three weeks old, the jaundice did return, but it went away on its own four days later. In addition to highlighting the success in this particular case, this historical case reveals the early use of exchange transfusion as a therapeutic strategy for treating acute jaundice in neonates.[4]

The example described by Hart highlights the importance of this intervention in treating severe cases of icterus gravis in addition to offering insightful information on the early application of exchange transfusions. The successful outcome shown in this infant illustrates

the potential advantages of eliminating toxins from the blood to stop the advancement of the disease, despite the difficulties and restrictions of the operation at the time. This historical account establishes the groundwork for future developments and improvements in the exchange transfusion procedure, ultimately enhancing the care and results for children with diseases like acute jaundice.[4]

TABLE I

RESULTS OF GROUPING AND Rh-Hr TESTS IN CASE 1

Blood of:	*Group and Subgroup*	*M-N Type**	*Rh-Hr Type*
Father	A_1	M	Rh_1Rh_2
Mother	A_1	MN	rh
Daughter	A_1	MN	Rh_1rh

* The M-N types are not important clinically, but are given for the sake of completeness.

Tests for Rh antibodies on the mother's serum gave the following results.

Agglutination Test-Negative

Conglutination Test-Positive (12 units)

Erythroblastosis fetalis with exchange transfusion

1. A summary of the Case I's most significant hematologic findings has been provided.
2. The illustration of Case I bears a striking resemblance to one that was previously published and depicted an instance of erythroblastosis fetalis that was successfully treated with straightforward infusions of Rh-negative blood.
3. This parallelism exists because a complete exchange transfusion was virtually accomplished in the earlier event.
4. The previous case's circumstances were very similar to Case I's because the husband was homozygous Rh positive (type RhRh2) and the mother had previously given birth to an erythroblastotic child by caesarean section.
5. A group 0 professional donor gave 500 c. of blood in preparation for an exchange transfusion.
6. However, after the baby was delivered through caesarean section, it was found that hemolytic anaemia had caused the infant to become extremely anaemic and nearly exsanguinated.
7. A transfusion of 160 c. of blood was given to the infant right away, and another 75 c. was given afterwards.

8. Despite sparing the infant from bleeding, this method enabled the completion of an exchange transfusion.

9. By using this method in the prior example, it was shown to be beneficial in treating the severe hemolytic anaemia brought on by erythroblastosis fetalis.

10. The success seen in Case I and the prior case highlights the importance of adequate transfusion therapies in the management of erythroblastosis fetalis.

11. The similarity between the hematologic results in Case I and the previously published figure lends more credence to the idea that exchange transfusion is essential for treating the hemolytic anaemia type of erythroblastosis fetalis.

12. These cases emphasise the significance of taking into account the particular circumstances, such as the prior delivery of an erythroblastotic infant and the parents' Rh status, while deciding on the best course of action.

13. This technique in severe hemolytic anaemia has the potential to save lives because it can complete exchange transfusions even in challenging situations.

14. These results add to the expanding body of research that shows exchange transfusions are effective and relevant for treating erythroblastosis fetalis.

15. To perfect and optimise the use of exchange transfusions in treating erythroblastosis fetalis and similar disorders, further clinical experience and study are required.

RESULTS OF HEMATOLOGIC STUDIES IN CASE 2

	Time when tests were made									
	3rd day; before exchange transfusion	*4th day*	*6th day*	*10th day*	*15th day*	*22nd day*	*43rd day*	*57th day*	*71th day*	*90th day*
Hemoglobin per cent	117	113	95	90	90	90	70	75	75	72
RBC (mill./mm.)	5.5	—	4.3	4.3	4.7	4.3	3.51	3.69	—	—
WBC (mill/c.mm.)	16,000	—	11,400	9,800	15,600	12,800	—	—	—	—
Neutrophiles: segmented	40	44	49	45	45	31	18	28	18	—
band	4	5	5	2	3	2	1	1	1	—
Lymphocytes	45	39	30	46	42	56	70	58	74	—
Monocytes	7	8	13	3	8	7	7	6	3	—
Eosinophiles	2	3	3	3	3	3	4	7	4	—
Basophiles	1	0	0	1	0	1	0	0	0	—
Myelocytes	1	1	0	0	0	0	0	0	0	—
Nucl. RBC/100 WBC	2	none	none	none	none	none	0	0	0	—
Reticulocytes	3%	none	none	none	1/2 %	1/2 %	1/2 %	1/2 %	1%	1/2 %
Differential agglutination	100% Rh	1/10Rh + 9/10rh	100%rh	100%rh	100%rh	1/20Rh + 19/20rh	1/2Rh + 1/2rh	11/12Rh + 1/12rh	—	99% Rh

ABO—Hemolytic Disease of the Newborn (ABO-HDN)

Although the majority of cases are not clinically significant and do not require treatment, ABO incompatibility is the most common cause of hemolytic illness in foetuses and newborns. ABO-HDN frequently affects the firstborn child, unlike Rh incompatibility. Mothers with blood group O and newborns with blood types A, B, or AB make up the

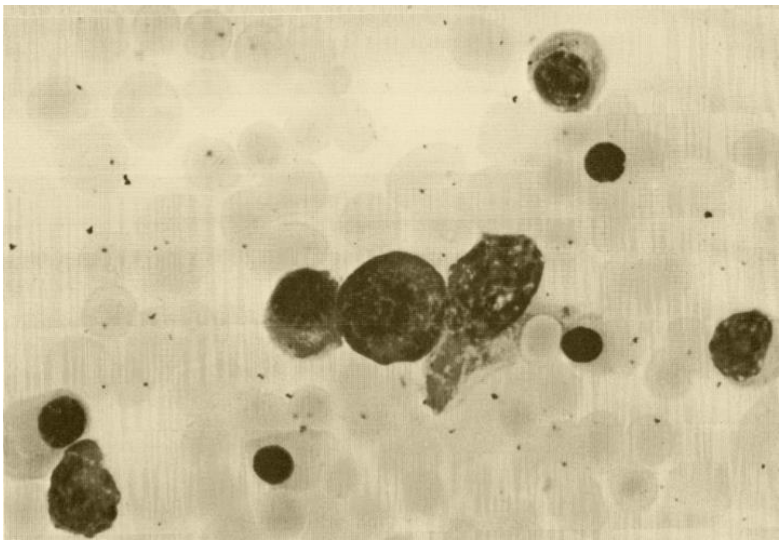
majority of those affected. ABO-HDN has a pathogenesis with HDN brought on by antibodies to erythrocytic antigens of the Rh system.[5]

Typically, after excluding out other possible causes of early postpartum hyperbilirubinemia, the diagnosis of ABO-HDN is determined. Because the existence or severity of the hemolytic process is not accurately detected by the detection of immunological anti-A or anti-B antibodies in maternal serum, prenatal testing cannot consistently predict ABO-HDN. It is critical to identify the ABO group and Rh type of neonates who experience hyperbilirubinemia soon after birth in order to diagnosis ABO-HDN. Additionally, erythrocytes from the newborn should be tested for direct antiglobulin. If the test is positive, additional research should be done to determine the specificity of the mother's antibodies by comparing her serum to a red cell panel. When the direct antiglobulin test yields a marginally positive result, there is typically ABO incompatibility between the mother and the child. The presence of antibodies other than anti-A and anti-B must be taken into account, and their clinical significance must be determined.[5]

The most accurate method for identifying fetal-maternal ABO incompatibility is the elution of ABO antibodies from the red blood cells of the child who is incompatible. Then, adult A and B red cells are used to test the eluate. The diagnosis of ABO incompatibility can be supported by the finding of free antibodies in the serum of infants. Hematologic indicators of fetal-maternal ABO incompatibility frequently include spherocytosis, reticulocytosis, and moderate anaemia. Jaundice, which often emerges during the first 24 hours of life, is the main symptom of ABO illness. However, it seldom gets bad enough to for kernicterus to form.[5] When necessary, phototherapy is frequently used to treat ABO-HDN. Rarely, a transfusion exchange may be necessary. To determine the need for the type of therapy, serial indirect serum bilirubin concentrations and reserve albumin binding capacity are employed. Fresh, saline-washed, packed erythrocytes of blood group O are used if an exchange transfusion is necessary.[5]

In conclusion, the most frequent factor causing hemolytic illness in foetuses and newborns is ABO incompatibility. ABO-HDN can affect firstborn children, and it typically affects moms with blood group O and newborns with blood types A, B, or AB. The majority of cases do not require treatment. The diagnosis of ABO-HDN is often made upon birth by ruling out other possible causes of hyperbilirubinemia because prenatal testing for the condition has a limited ability to predict outcomes. Infants with ABO-incompatible blood can have free

antibodies found in their serum to help confirm the diagnosis. Mild anaemia, minor reticulocytosis, spherocytosis, and jaundice are traits of ABO-HDN. The bulk of treatment is phototherapy, and exchange transfusions utilising packed erythrocytes from blood group O are only seldom necessary.[5]



Immature red blood cells in peripheral blood in severe erythroblastosis.[5]
Note: rubriblast, prorubricyte, rubricyte, and metarubricytes.

The criteria which we have used to determine whether the infant required transfusion therapy are the following.

1. **Jaundice**: One of the most crucial signs that therapy was required was the development of jaundice within the first 36 hours of life or the presence of jaundice at birth.
2. **Anaemia**: According to Wintrobe's reference, normal newborn infants' haemoglobin levels on their first day of life are around 19.5 g/dL 5.0 g/dL. The average haemoglobin level on the first day of life in the hospital's assessment of 20 healthy newborn newborns was 19.8 g/dL. For newborn newborns, the hospital uses 10 g/dL of haemoglobin as the benchmark. A newborn with erythroblastosis is deemed anaemic and in need of a blood transfusion if their haemoglobin level falls to 15 g/dL or lower within 36 hours of birth. The hospital also views 4.0 million red blood cells per cubic millimetre (mm3), or roughly 70% of their criterion for normal neonates, as a key number in conjunction with the haemoglobin decline in erythroblastotic infants.
3. **Erythroblastosis**: An key indicator of this condition is the presence of an abnormally high number of nucleated red cells in peripheral blood. According to Wintrobe19, 200 nucleated red cells per cubic millimetre is the top limit of normal for newborn infants.

Although the levels in the majority of our cases were significantly higher, we believe that the presence of nucleated red cells, while a helpful diagnostic indicator, must be taken into account in conjunction with other information, such as anaemia and jaundice, and should not be used as a stand-alone signal for therapy.

4. **Agglutinins**: The presence of anti-Rh agglutinins in the mother's serum along with evidence that the newborn is Rh positive or has blocking antibodies linked to its red cells (Coombs antiglobulin test) constitute another significant symptom. If the mother's and child's ABO blood types differ, the mother's serum should show an unusually high titer of anti-A or anti-B agglutinins if the erythroblastosis appears to be caused by this.
5. **History**: When determining whether a newborn with erythroblastosis needs to be treated, it's vital to take into account whether the mother has a history of having additional children with the condition as well as any instances in which a Rh negative mother has been sensitised by a Rh positive transfusion.[6]

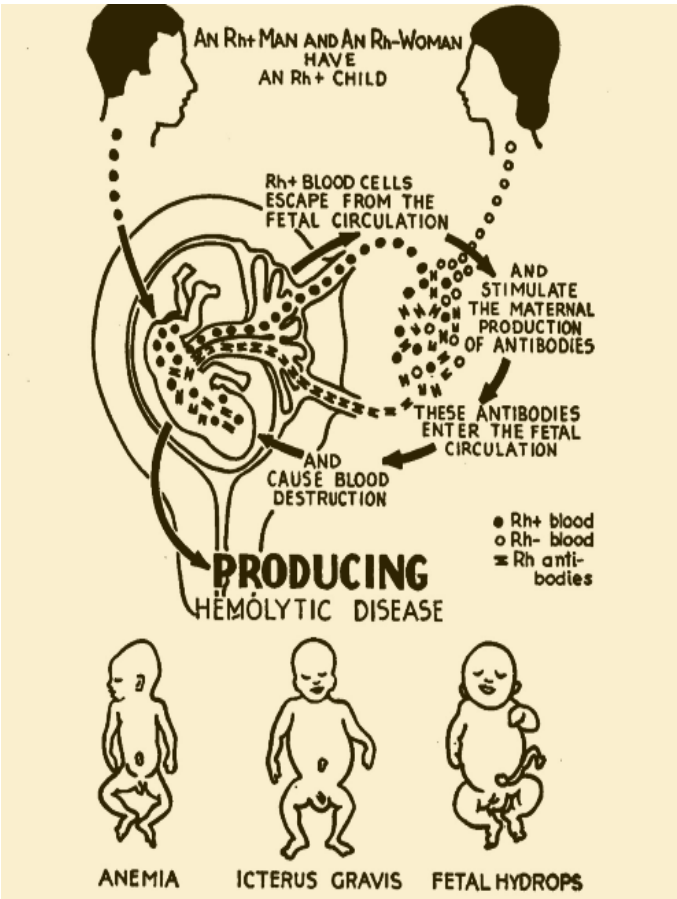
Clinical Manifestations

Foetal red blood cells are hemolyzed as a result of a response between maternal-fetal antibodies and antigens, which results in erythroblastosis fetalis. Rh(D) incompatibility is the most frequent cause, and it may now be effectively avoided thanks to the introduction of anti-Rh(D) immunoglobulin in the middle of the 1960s. Rh(D) antibodies are one class of blood antibodies, but there are many other classes of "irregular" antibodies that can similarly destroy red blood cells. The Kell system is the most effective irregular antibody, albeit it is not very common. Anti-Rh(D) and anti-Kell erythroblastosis fetalis share the same aetiology. Hemolysis is brought on by maternal antibodies that coat the foetal red blood cells. As the foetus becomes anaemic, the amount of bilirubin in the amniotic fluid rises. Extramedullary erythropoiesis is a form of compensation carried out by the kidneys, spleen, and liver.[7]

This illness is known as erythroblastosis fetalis, and infants that have it severely display paleness, anaemia, hepatosplenomegaly, edoema, and ascites. Shortly after delivery, jaundice develops as a result of high bilirubin levels. In the past, untreated jaundice was frequently linked to brain impairment in children with erythroblastosis fetalis, which resulted in a syndrome known as kernicterus. This led to cerebral palsy, whether or not it was accompanied by mental impairment. However, significant medical intervention to lower neonates' bilirubin levels and prevent bilirubin encephalopathy has lessened its severity.[7]

Some children with erythroblastosis fetalis also exhibit enamel abnormalities. The cusps of the permanent first molars may be affected or only the primary dentition may be affected by these anomalies. The time of the metabolic disruption and the severity of the dental problem are related. Due to the inclusion of biliverdin, a bilirubin by-product that causes jaundice, 15% of affected children exhibit tooth discoloration. The severity of enamel flaws and discoloration can vary independently of one another, and the discoloration can range from yellow to dark colours of green.[7]

When a mother develops iso-immunity to the type of blood present in her foetus, erythroblastosis fetalis, a haemolytic disease, happens. Around 95% or more of instances are brought on by Rh-negative moms who produce antibodies against their Rh-positive foetuses. Iso-immunization to less prevalent antigens causes the remaining instances. The percentage of rh-negative people in the white, coloured, and oriental races is about 15%, 4%, and 0.4%, respectively. Rh auto-immunization is extremely uncommon in people of pure coloured races and almost nonexistent in those of Oriental descent. However, based on findings from a large series of patients observed at the hospital, the incidence of erythroblastosis fetalis is substantially lower than this, even though a family structure consisting of a Rh-positive husband and a Rh-negative wife occurs in around 1 in 13 marriages. Over time, different approaches of erythroblastosis fetalis treatment have been used. Replacement transfusion, also known as exsanguination transfusion, was first established by Dr. Ross Robertson at the hospital and is a widely utilised strategy today. Dr. A. P. Hart applied this technique to successfully treat the first instance of erythroblastosis fetalis at the same hospital in 1925. Other family members who did not receive this treatment either died from kernicterus or suffered severe neurological abnormalities, whereas this method proved to be curative in the treated patient.[8]



A 1946 article by Wallerstein described the procedure for giving newborns type 0 Rh-negative blood in place of their own blood. Diamond improved and honed this technique further. Before 1941, Diamond noticed that infants who were referred to him had a high mortality rate of 35 to 40%. However, the mortality rate decreased to 20% or even 10% with the introduction of replacement transfusion. The earlier referral of newborns for therapy was one cause in the decline in mortality. Only around one out of every eight children referred to Diamond in 1947 needed a replacement transfusion, according to Diamond.[10]

Serological Findings

Both the direct and indirect Coombs tests were negative, and the mother's blood type was 0Rh positive. The father had a direct Coombs' test result of A Rh positive and no. The cord cells tested positive for group A Rh. The direct Coombs' test was negative with anti-C3d reagent but substantially positive with both polyspecific and mono-specific IgG anti-human globulin reagents. The IgGI and IgG2 subclasses of IgG antibodies were found to coat the cord cells. A cord cell-derived ether eluate demonstrated anti-A specificity. After the anti-A component was absorbed, the eluate failed to react with the father's red blood cells, ruling out the notion that HDN could be caused by an antibody against a low incidence antigen.[11]

Additional research on the maternal serum revealed that it included an extremely robust antibody (IgG) anti-A responding to a titer of 4,000. Additionally proven was complement binding hemolytic (IgM) anti-A. There is no chance that HDN is caused by an antibody against a low incidence antigen because both parents' tests for syphilisserology and abnormal haemoglobins came back negative.

The notion put forth by Klein and Weidenreich that eosinophil granules are made of haemoglobin itself cannot currently be empirically or histochemically verified. Eosinophilia has, however, occasionally been seen in erythrocytic system illnesses, including polycythemia vera, pernicious anaemia, and hypoplastic anaemia brought on by exposure to benzene. Although Ringoen, Pescatori, and others have connected eosinophilia in these patients to anaphylaxis, allergies, or hypoxia, the precise mechanism behind it is still unknown.[12]

Dohnert and Tischendorf found that the greatly increased red bone marrow, which is frequently seen in cases of liver cirrhosis, included a significant amount of eosinophils around erythroblastic foci. They imply a close connection between haemoglobin or its precursors and eosinophil granules. Amano has also identified some ontogenetic and phylogenetic relationships between eosinophil granules and haemoglobin. They make the following arguments: 1) Eosinophil myelocytes are the earliest granulocytes in the liver, arriving following the formation of second-generation erythroblasts in 1.3 cm embryos, which represent the start of the hepatic phase of hematopoiesis. 2) Some invertebrates with erythrocytes or haemoglobin have granulocytes that are either eosinophilic or have a positive peroxidase reaction.[12]

Despite the fact that it is still unknown where eosinophil granules come from and how they are related to haemoglobin or its precursors, observations of erythrocytic system disorders and the presence of eosinophils in particular anatomical contexts offer information about possible connections between eosinophils and hemoglobin-related processes. To completely comprehend the mechanisms underlying these linkages, more investigation is necessary.[12]

According to Amano, cytochrome, which is highly present in eosinophil granules, and peroxidase in eosinophils are all related to -haemoglobin in erythrocytes. Haemoglobin, cytochrome, and peroxidase all include a prosthetic group known as an etioporphyrin type III, according to Fischer and Zeile. This suggests that haemoglobin and cytochrome or

peroxidase have a similar component. The accumulation of porphyrin in the bone marrow is therefore thought to be caused by problems in haemoglobin synthesis, such as those found in hypoplastic anaemia (a suppression of regeneration) and erythroblastosis fetalis (a suppression of maturation despite hyperplasia). As a result, excessive amounts of porphyrin are used in the growth and maturation of eosinophil granules, which aids in the emergence of eosinophilia. Disturbances in haemoglobin synthesis result in the accumulation of porphyrin in the bone marrow in situations such hypoplastic anaemia, where regeneration is suppressed, and erythroblastosis fetalis, where maturation is suppressed despite increasing cell production. It is thought that the accumulating porphyrin contributes to the excessive maturation and production of eosinophil granules. Eosinophilia therefore develops. Porphyrin is a prosthetic group that is present in haemoglobin, cytochrome, and peroxidase, which suggests a common factor that affects the formation and maturation of eosinophil granules.[13]

It's crucial to remember that these hypotheses are founded on the findings and theories advanced by Amano and others. To completely comprehend the intricate interaction between -haemoglobin, cytochrome, peroxidase, porphyrin accumulation, and eosinophilia in the setting of hypoplastic anaemia and erythroblastosis fetalis, more research is required.[13]

CONCLUSIONS

Icterus gravis neonatorum, global edoema of the foetus, and neonatal anaemia are the three subtypes of the complicated condition known as erythroblastosis fetalis. Common pathogenic traits across these entities include the persistence of an embryonal blood pattern and a severe anaemia. The antigen-antibody response, specifically one involving the anti-Rh antibody, has been widely blamed for the disease's aetiology. When a Rh-negative mother is exposed to Rh-positive foetal blood during pregnancy, she develops this antibody.

This idea offers a satisfactory explanation for the aetiology of erythroblastosis fetalis, even though several parts need more research. Notably, new studies by Witebsky have illuminated the anti-Rh factor's existence in breast milk from moms of erythroblastic infants. The study showed that Rh antibodies may be found in mother's milk that was collected around a week after the baby was born. This discovery advances our knowledge of the anti-Rh factor's transmission, secretion, and possible effects on erythroblastosis fetalis.

Overall, addressing the erythroblastosis fetalis-related consequences, including as anaemia and red blood cell loss, presents major difficulties. To better understand the biology of the

disease and create efficient prevention and treatment plans, more study is required. Future studies and potential therapies to enhance outcomes for affected newborns can be built on a firm basis provided by knowledge of the antigen-antibody response and the function of the anti-Rh antibody.

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