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Effect of Rhesus factor incompatibility on maternal outcome (fertility): A comprehensive review

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Abstract

Rh incompatibility, also known as Rh disease, is defined as a condition that occurs when a woman with Rh-negative blood type is exposed to Rh-positive blood cells, leading to the development of Rh antibodies. The incidence of occurrence is more frequently among those of Caucasian (North American and European) descent (15% to 17%) compared to those of African (4% to 8%) or Asian descent (0.1% to 0.3%). Worldwide, the prevalence of Rh disease is estimated to be 276 per 100,000 live births, which is significant considering that an estimated 50% of untreated cases of haemolytic disease of the neonate (HDN). HDN will either die or develop brain damage due to the disease. The condition is due to: If a Rhesus negative (Rh^-) woman is impregnated by a man with Rhesus negative (Rh^-) there wouldn't be any problem. If a Rhesus negative woman (Rh^-) is impregnated by a man with Rhesus positive (Rh^+) and the baby inherited the rhesus positive (Rh^+) from the father there will be a problem or when an Rh-negative mother is exposed to the Rh D antigen, the D antigen is perceived as a foreign threat leading to the haemolysis of the fetal erythrocytes, common signs and symptom include; Jaundice, a yellowing of the skin and whites of the eyes, lethargy, heart failure, enlarged organs. It can be prevented and treated by administering an injection of RhoGAM during the second trimester, and 28th week of pregnancy respectively, exchange transfusions either before birth or after delivery. Phototherapy is also another treatment modality which break down excess bilirubin into less toxic substance that the new borns liver can remove.

Keywords: Rhesus factor; Incompatibility; Infertility; Birth; Pregnancy

1. Introduction

According to Oxford Dictionary of Nursing (fifth edition), Rhesus factor is a group of antigens that may or may not be present on the red blood cells. It is a type of protein found on the outside of red blood cells. The protein is genetically inherited. If you have the protein, you are Rh positive, if you did not inherit the protein, you are Rh-negative. Rh incompatibility is dependent on the prevalence of Rh-negative blood types, which varies among different populations. Researchers estimate that the frequency of the Rh-negativity occurs more frequently among those of Caucasian (North American and European) descent (15% to 17%) compared to those of African (4% to 8%) or Asian descent (0.1% to 0.3%). Worldwide, the prevalence of Rh disease is estimated to be 276 per 100,000 live births, which is significant considering that an estimated 50% of untreated cases of HDN will either die or develop brain damage due to the disease. In comparison, the prevalence of Rh disease in developed countries has been reduced to 2.5 per 100,000 live births,

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which can be attributed to higher-quality perinatal-neonatal care [1,2]. Majority of people about 85% are Rh-positive. The (+) and (-) in front of the blood group is the Rhesus factor.

The term "Rh" was originally an abbreviation of "Rhesus factor." It was discovered in 1937 by [3] who, at the time, believed it to be a similar antigen found in rhesus macaque red blood cells. It was subsequently discovered that the human factor is not identical to the rhesus monkey factor, but by then, "Rhesus Group" and like terms were already in widespread, worldwide use. Thus, notwithstanding it is a misnomer, the term survives (e.g., rhesus blood group system and the obsolete terms rhesus factor, rhesus positive, and rhesus negative – all three of which actually refer specifically and only to the Rh D factor and are thus misleading when unmodified). Contemporary practice is to use "Rh" as a term of art instead of "Rhesus" (e.g., "Rh Group,""Rh factors,""Rh D," etc.). Most people are Rh positive. Negative Rh factor occurs in about 15 percent of white people, between 4 and 8 percent of Black people and 0.3 percent of Asian people. Rhesus (Rh) incompatibility occurs when a woman who is Rh-negative becomes pregnant with a baby with Rh-positive blood. With Rh incompatibility, the woman's immune system reacts and creates Rh antibodies. These antibodies help drive an immune system attack against the baby, which the mother's body views as a foreign object. Antibody formation can happen after blood transfusions or when fetal blood enters the mother's circulation in condition such as; Early pregnancy complications such as miscarriages, ectopic pregnancies, or terminations, injury to the stomach area during pregnancy, bleeding during pregnancy, tests that require cells or fluids to be withdrawn from a pregnant woman (like amniocentesis and chorus villus sampling), delivery of a baby (either spontaneous vaginal delivery or cesarean section).

Rh incompatibility usually arises when mother is Rh negative (dd) and carries Rh positive (DD or Dd) fetus, who has derived D antigen from father. The chances of Rh negative mother becoming sensitized to the Rh antigen increases, if significant hemorrhage leading to immunization occur at delivery or in association with other intra- partum episodes such as amniocentesis, external version or abortion and thus having children affected with hemolytic disease in the succeeding pregnancies. If the husband is homozygous for D antigen (DD), all infants will be Rh positive but if he is heterozygous (Dd), any pregnancy has 50% probability of producing Rh negative child. Phenotype (blood group) and zygosity of the male partner (husband) and antibody titer of female partner (wife) are important determinant of the maternal sensitization [4]. Among other consequence is that the fetus develops anaemia and reticulocytosis. The disease may range from mild to very severe, and could even result in death of fetus from severe heart failure, a condition known as hydrops fetalis. In severe and moderate condition of the disease, many immature red blood cells (erythroblasts) are present in the fetal blood; hence it is referred to as erythroblastosis fetalis [5,6]. HDFN denies the fetus its immune privilege or some other form of impairment of the immune tolerance of pregnancy. The purpose of this review is to shed light on Rhesus incompatibility in intending couples and subsequently parent in the society on the need for Rhesus compatibility test being one of the criteria for tying the knot, and health professionals on the need to educate prospective marriage mate with a view to preventing potential damage (abortion, still birth). [7] reported In this paper we have looked into the role of a specific type of mortality, perinatal mortality. A substantial part of all infant deaths takes place during the first week, especially in the contemporary world but also in historical settings. Before or during the mortality transition both neonatal deaths and stillbirths were quite frequent. conclusions were made that Rh disease represented a large part of the all stillbirths and perinatal deaths. This is especially the case in higher parities. Without Rh disease, the stillbirth rate would have been about a third smaller and in higher parities even more. The Rh negative mothers having that many children most probably became sensitized at the higher parities. Without the disease infant mortality would have been lower and the effect would have been even stronger in perinatal mortality. Still, much of especially the infant mortality cannot be explained by Rh disease. It is only one component in the risk panorama of newborn infants at this time. Nevertheless, it is a factor that has significant impact that needs to be considered in the analysis of infant mortality. Our estimates indicate a considerable number of cases related to the disease. We can thus safely conclude that it had a substantial impact on the survival at the time. Even if it was a rather small part of the risks for the foetus, it was a factor that had impact at the time and killed many children.

2. Pathophysiology of Rh incompatibility

When an Rh-negative mother is exposed to the Rh D antigen, the D antigen is perceived as a foreign threat similar to how bacteria and viruses are perceived. This leads to a series of activations of immunogenic pathways that culminates in the production of anti-D antibodies. Those antibodies can bind to the D antigen present on the erythrocytes of Rh-positive fetuses to further activate immunologic pathways that lead to the haemolysis of the fetal erythrocytes.

2.1. Factor that trigger Rh incompatibility

- Exposure to fetal Rh-positive blood
- Delivery (i.e., vaginal, Cesarean section)

- Threatened miscarriage, miscarriage
- Antepartum hemorrhage (e.g., placenta previa, abruption, vasa previa, uterine rupture)
- Trauma
- External cephalic version
- Invasive procedures (e.g., chorionic villus sampling, amniocentesis)
- Ectopic Pregnancy
- Molar pregnancy
- Non-fetal exposure to Rh-positive blood
- Transfusion
- Bone marrow transplantation

3. Signs & Symptoms of Rh incompatibility

Jaundice, a yellowing of the skin and whites of the eyes, lethargy, heart failure, enlarged organs, otherwise known as hydropsfetalis (The baby's stomach, scalp, liver, heart, spleen and lungs may swell), pale skin because of anaemia, fast breathing, fast heart rate, swelling under the baby's skin

3.1. Prevention

Rh incompatibility is almost completely preventable. Rh-negative mothers should be followed closely by their health care providers during pregnancy. Special immune globulins, called rhod immune globulin human (Rho GAM), are now used to prevent Rh incompatibility in mothers who are Rh-negative [8]. If the father of the infant is Rh-positive or if his blood type is not known, the mother is given an injection of Rho GAM during the second trimester. If the baby is Rh-positive, the mother will get a second injection within a few days after delivery. These injections prevent the development of antibodies against Rh-positive blood. However, women with Rh-negative blood type must get injections: During every pregnancy, after a miscarriage or abortion, after prenatal tests such as amniocentesis and chorionic villus biopsy, after injury to the abdomen during pregnancy [9].

4. Rhesus factor incompatibility and miscarriage (infertility)

If a Rhesus positive (Rh^+) woman is impregnated by a man with Rhesus positive (Rh^+) there wouldn't be any problem. If a Rhesus negative (Rh^-) woman is impregnated by a man with Rhesus negative (Rh^-) there wouldn't be any problem. However if a Rhesus negative woman (Rh^-) is impregnated by a man with Rhesus positive (Rh^+) and the baby inherited the rhesus positive (Rh^+) from the father there will be a problem, we have what is medically called Rhesus factor incompatibility.

During child birth, once the baby's (Rh^+) come in contact with the woman (Rh^-) during delivery, the antibodies are immediately activated by the woman body immune system. The activated antibodies would see the Rh^+ baby as a foreign body or a threat and consequently they would be at alert to attack and get rid of the foreign body. In the mothers first pregnancy there is often no problem because there is no sufficient time for the mother to produce enough anti-Rh antibodies to harm the fetus. However in the subsequent pregnancy the anti Rh antibodies already in her system can cross the placenta and enter the fetal blood and react against the D antigens on the red blood cells of the fetus and results to the agglutation and haemolysis of the fetus red blood cells called Haemolytic Disease of New born. Unfortunately, as such after this particular child birth, the woman would keep having miscarriage because of the activated antibodies which would be subsequent in Rh^+ pregnancies as foreign bodies and would keep fighting and taking them (fetus) off. Woman with Rh^- activated antibodies are said to Rh^- sensitized and once these antibodies are activated, they can never be deactivated until the woman dies. Rh^- antibodies are activated by Rh^- woman by child birth, abortion, miscarriage, ectopic pregnancy. If Rh^- woman commits an abortion for Rh^+ man and the antibodies in her system are activated, the woman might end up childless throughout her life, except if she later marries another man with Rh^-. The possibility of Rh^- woman finding Rh^- man is slim as about 85% of human beings are Rh^+. If you are a woman with Rh^- and your finance is Rh^+ and you haven't committed any abortion for him and you don't want to leave him, then you need to take note, in order to prevent the activation of the antibodies [10].

According to [11], during pregnancy, maternal and fetus blood do not usually mix. But sometimes a small amount of blood from the fetus can mix with maternal blood. This may occur during labor and birth. It may also occur with amniocentesis or chorionic villus sampling (CVS), bleeding during pregnancy, attempts to manually reposition a fetus to be head-down for birth (move the fetus out of a breech presentation), trauma to the abdomen during pregnancy. More so, when the blood of an Rh-positive fetus gets into the bloodstream of an Rh-negative woman, the body recognizes

that the Rh-positive blood is not hers, and will try to destroy it through the production of anti-Rh antibodies. These antibodies are able to cross the placenta and attack the fetus's blood cells. This can lead to serious health problems, even death, for a fetus or the newborn [12].

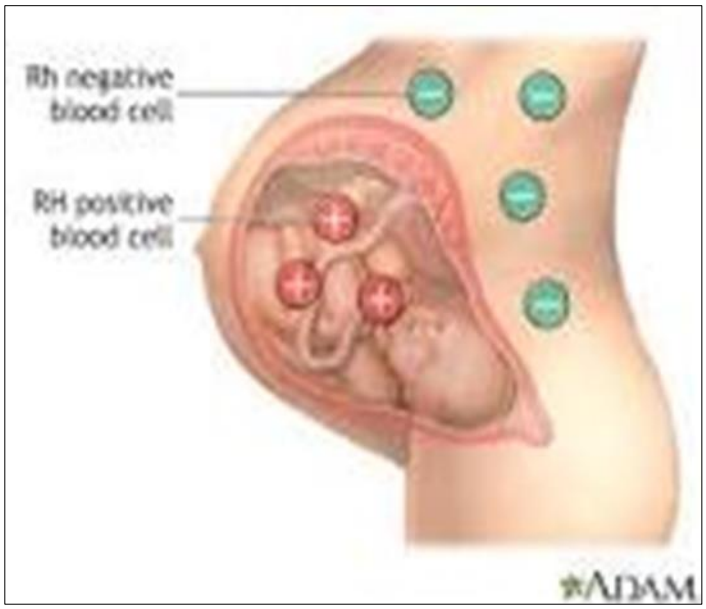

Figure 1 Maternal and fetal outcome in Rh negative pregnancy

During a pregnancy, Rh antibodies made in a woman's body cross the placenta and attack fetal blood cells. This causes serious anaemic responses in the fetus in which red blood cells are destroyed faster than the body can replace them. Red blood cells carry oxygen to all parts of the body. Without enough red blood cells, the fetus fails to get enough oxygen. In some cases, a fetus or a newborn can die from anaemia [11]. Rh incompatibility would further cause jaundice in a newborn [13]. As previously mentioned, maternal sensitization occurs in Rh-negative mothers due to exposure to the Rh D antigen. This typically occurs when the Rh-negative mother is carrying an Rh-positive fetus or has been exposed to Rh-positive blood differently. However, if the exposure to the Rh D antigen occurs during the mother's first pregnancy, the adverse consequences of Rh incompatibility do not typically affect that initial pregnancy because the fetus often is delivered before the development of the anti-D antibodies. Once the mother has been sensitized, future pregnancies are at risk for the development of hemolytic disease of the new bornsecondary to Rh incompatibility if the fetus is Rh-positive [14].

[4] reported that Rh among the compatible and incompatible group was not significantly different. Fertility, reproductive outcome, were found independent with compatibility. [15] and his team of researchers concluded that the Rh incompatibility is the most common cause of hemolytic disease of newborn. [16] also revealed that Rh-D allo-immunization and its sequelae have greatly been diminished. As a result, ABO incompatibility is now the single largest cause of HDN in the western world. [17] also described that only three cases of hydropsfetalis with neonatal survival have been described in association with ABO incompatibility. Moreover [18] concluded that ABO incompatibility was the leading cause of hemolysis followed by Rh incompatibility. In a similar vein [7] Erling et al., 2010 opined that a substantial part of all infant deaths takes place during the first week, especially in the contemporary world but also in historical settings. Before or during the mortality transition both neonatal deaths and stillbirths were quite frequent. it was conclude that that Rh disease represented a large part of the all stillbirths and perinatal deaths. This is especially the case in higher parities. Without Rh disease, the stillbirth rate would have been about a third smaller and in higher parities even more. The increased risks at higher parities thus have the consequence that a decline in fertility would lower the frequency of Rh disease in particular but also of perinatal mortality in general. It is a well known fact that mothers loosing their children shortly after delivery have a shortened birth interval to the next. This could be due to compensation but usually it is an effect of no lactation after the death of a child and consequently an earlier onset of ovulation. Those having high infant mortality, especially perinatal and neonatal mortality, thus had more children and more children of higher parities. Mothers that became sensitized could be expected to have more children, which would lead to more children with Rh disease. Rh disease was furthermore an important factor explaining some of the clustering of mortality we find. If a sensitized mother continued to give birth to children, they would by necessity constitute a cluster. [19] Jain et al., 2021 reported that out of 88 women, 85 (96.5%) women gave birth to a live baby. 2 women (2.27%) had fresh stillbirth and 1 woman (1.13%) had macerated stillbirth, due to incompatible rhesus factor

5. Blood Group Test for Newly Married Couples

As it is important for newly married couples to test blood group, the type of Rh is of high importance to the fetus in certain cases. The following cases should be under consideration for newly married couples:

- The pregnant mother has (Rh+) and the husband has either Rh+ or Rh- factor: No negative effect on the fetus because the blood of Rh+ accepts the blood of the Rh- due to the absence of antibodies.
- The mother's blood is of Rh- and her husband is of Rh+ factor:
    - If the fetus's blood has Rh-: No negative effects.
    - If the fetus's blood has Rh+: Possible negative effects occur on the fetus once he delivered. At birth, fetus's blood transfer to his mother at a small extent (through cut the umbilical cord), which force her immune system to form antibodies as a normal response to the foreign protein (Rh+). Thus, a certain risk is expected for the next pregnancy, where the fetus will expose to severe jaundice or even develop into death due to blood decomposition. To overcome such fetal danger, anti-D injection is required for the mother within 72 hours after the first delivery. The anti-D injection will help the mother to get rid of any blood that has leaked from the first fetus during childbirth so that her blood will not produce antibodies, which could affect the next pregnancy [20-24].

Summarily, when an Rh-negative mother is exposed to the Rh D antigen, the D antigen is perceived as a foreign threat similar to how bacteria and viruses are perceived. This leads to a series of activations of immunogenic pathways that culminates in the production of anti-D antibodies. Those antibodies can bind to the D antigen present on the erythrocytes of Rh-positive fetuses to further activate immunologic pathways that lead to the hemolytic of the fetal erythrocytes and fetal death. Health problems usually do not occur during an Rh-negative woman's first pregnancy with an Rh-positive fetus. This is because the pregnant mother's body does not have a chance to develop a lot of antibodies. But if treatment is not given during the first pregnancy and the woman conceives again with an Rh-positive fetus, the production of more antibodies put a fetus at risk and miscarriage will occur. It is important to note that being Rh-negative in and of itself does not cause miscarriage or pregnancy loss. A women is only at risk if she have been sensitized. The risk is very small if the recommended RhoGAM shots is given during pregnancy, or after an ectopic pregnancy, pregnancy loss, or induced abortion.

5.1. Treatment of Rh incompatibility

If a pregnant woman has the potential to develop Rh incompatibility, doctors give her a series of two Rh immune-globulin (RhoGAM) shots during her first pregnancy. She will get: The first shot is on the 28th week of pregnancy, the second shot is within 72 hours of giving birth. Rh immune-globulin acts like a vaccine. It prevents the mother's body from making any Rh antibodies that could cause serious health problems in the new born or affect a future pregnancy. A woman also might get a dose of Rh immune-globulin if she has a miscarriage, an amniocentesis, or any bleeding during pregnancy. If a woman has already developed Rh antibodies, her pregnancy will be closely watched to make sure that those levels are not too high. Treatment of babies with HDN may include; In rare cases, if the incompatibility is severe and a baby is in danger, the baby can get special blood transfusions called "exchange transfusions" either before birth (intrauterine fetal transfusions) or after delivery. Exchange transfusions replace the baby's blood with blood with Rh-negative blood cells. Phototherapy which break down excess bilirubin into less toxic substance that the new borns liver can remove [25].

6. Conclusion

Rh incompatibility leads to infertility: once the baby's (Rh^+) come in contact with the woman (Rh^-) during delivery, the antibodies are immediately activated by the woman body immune system. The activated antibodies would see the Rh^+ baby as a foreign body and attack and get rid of the foreign body. In the mothers first pregnancy there is often no problem. However in the subsequent pregnancy the anti Rh antibodies already in her system can cross the placenta and enter the fetal blood and react against the D antigens on the red blood cells of the fetus and results to the agglutation and haemolysis of the fetus red blood cells (Haemolytic Disease of New born).

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest was declared by the authors.

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