ORIGINAL RESEARCH

Incidence of fetal anaemia in ICT positive Rh negative pregnancies using MCA Colour Doppler

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ABSTRACT
Rh isoimmunization, also known as Rh incompatibility or Rh sensitization, is a condition that arises during pregnancy when a woman's immune system responds to a specific red blood cell antigen that originates from the biological father. This antigen, referred to as the Rh factor, is unfamiliar to the mother and is inherited by the developing fetus.In simpler terms, when the mother and the father have different Rh blood types (e.g., one is Rh-positive and the other is Rh-negative), there is a potential for the mother's immune system to recognize the Rh factor as foreign and mount an immunological response. This immune reaction can lead to the production of antibodies against the Rh factor, posing a risk to the fetus, particularly in subsequent pregnancies.The consequences of Rh isoimmunization can range from mild to severe, with the potential to impact the health of the unborn baby. Therefore, monitoring and appropriate medical interventions are crucial to manage and prevent complications associated with Rh isoimmunization during pregnancy. Doppler study of MCA-PSV screens for fetalanemia in Rh alloimmunization cases, replacing invasive methods like amniocentesis. It's a non-invasive approach utilizing Doppler ultrasound to measure blood flow velocity in the middle cerebral artery, providing early detection without the need for more invasive procedures.

Keywords:isoimmunization,alloimmunization,fetus.

INTRODUCTION

Rh isoimmunization, also known as Rh incompatibility, is a condition that unfolds during pregnancy when the immune system of a pregnant woman reacts to a specific red blood cell antigen. This antigen is paternally inherited by the developing fetus. The complexity of this condition lies in the difference in Rh blood types between the mother and the father. If the father's Rh factor is distinct from that of the mother, the mother's immune system might recognize the paternally derived Rh factor as foreign, triggering an immunological response.[1]This immune response involves the production of antibodies against the Rh factor, a process that can have significant implications for the developing fetus, especially in subsequent pregnancies. The antibodies generated by the maternal immune system can cross the placenta and attack the fetal red blood cells, leading to a condition known as hemolytic disease of the newborn (HDN). HDN can result in varying degrees of severity, ranging from mild jaundice to severe anemia and, in extreme cases, can lead to serious complications, including brain damage or even fetal demise.In response to the potential risks associated with Rh isoimmunization, vigilant monitoring becomes paramount throughout the pregnancy. Various medical interventions and treatments, such as anti-D immunoglobulin injections and advanced ultrasound techniques like Doppler studies, are employed to assess fetal well-being and manage any arising complications. The understanding and management of Rh isoimmunization have significantly evolved over the years, contributing to improved outcomes for both mothers and infants affected by this condition.

The presence of maternal antibodies that traverse the placenta and bind to antigens on fetal erythrocytes can initiate a cascade of events with profound implications for both the developing fetus and the newborn. This intricate process involves a heightened risk of adverse outcomes, ranging from complications during pregnancy to potential challenges for the neonate.When these maternal antibodies bind to fetal

erythrocytes, the consequence is hemolysis—the destruction of red blood cells. This phenomenon can compromise the oxygen-carrying capacity of the blood, leading to various complications in the developing fetus. In severe cases, hemolysis can progress to hydrops fetalis, a condition characterized by the abnormal accumulation of fluid in fetal tissues. This fluid buildup can exert pressure on vital organs and systems, contributing to a potentially life-threatening situation for the fetus. In some instances, the severity of hemolysis may result in fetal death, underscoring the critical nature of managing Rh isoimmunization.Beyond the prenatal period, the impact extends to the newborn. Maternal antibodies binding to fetal erythrocytes can lead to anemia in the neonate, a condition characterized by a deficiency in red blood cells. This anemia can compromise the newborn's ability to transport oxygen effectively, potentially resulting in respiratory distress and other complications. Moreover, the increased destruction of red blood cells contributes to hyperbilirubinemia, a condition marked by elevated levels of bilirubin in the blood. This, in turn, manifests as jaundice, a yellowing of the skin and eyes.In more severe cases, the accumulation of bilirubin can lead to kernicterus, a rare but serious condition where bilirubin deposits in the brain. Kernicterus poses a risk of neurological damage and long-term developmental issues for the affected newborn.Given the intricacies and potential risks associated with Rh isoimmunization, contemporary medical practices prioritize vigilant monitoring of at-risk pregnancies. Various interventions, such as administering anti-D immunoglobulin, employing specialized ultrasound techniques like Doppler studies, and closely managing neonatal jaundice, form essential components of a comprehensive approach to mitigate the impact of maternal antibodies and optimize outcomes for both the fetus and the newborn.

In pregnancies where the Indirect Coombs' test (ICT) returns positive, signaling a potential risk for fetalanemia, traditional diagnostic and treatment approaches have involved invasive techniques such as amniocentesis and cordocentesis. These procedures, while effective, carry inherent risks and are associated with certain complications.Amniocentesis involves the extraction of amniotic fluid for analysis, while cordocentesis entails obtaining a sample of fetal blood directly from the umbilical cord. While these methods provide crucial information, they are not without drawbacks, including the risk of infection, potential harm to the fetus, and discomfort for the expectant mother.In recent years, there has been a notable paradigm shift in the approach to diagnosing and monitoring fetalanemia, with the introduction of non-invasive alternatives. One such method gaining prominence is the Doppler study of the peak velocity in the fetal middle cerebral artery (MCA-PSV). This innovative and non-intrusive technique employs Doppler ultrasound to measure the velocity of blood flow in the middle cerebral artery of the developing fetus.[2]Research findings have consistently demonstrated a robust correlation between the peak velocity in the fetal middle cerebral artery and the presence of fetalanemia. The increased blood flow velocity serves as a reliable indicator, offering a safer and more accessible means of assessing fetal well-being without the associated risks of invasive procedures.The integration of MCA-PSV as a screening tool represents a substantial advancement in prenatal care. Not only does it eliminate the potential complications associated with invasive methods, but it also enhances patient comfort and accessibility to crucial diagnostic information in pregnancies at risk for fetalanemia.As medical technology continues to evolve, the incorporation of non-invasive techniques like MCA-PSV into routine prenatal care exemplifies a commitment to refining diagnostic precision while prioritizing the safety and well-being of both the expectant mother and the developing fetus. This shift towards non-invasive methodologies underscores the ongoing efforts to revolutionize and optimize prenatal healthcare practices.

The study's primary aim is to evaluate the efficacy of the Peak Systolic Velocity (PSV) in the blood flow of the Middle Cerebral Artery (MCA) as a non-invasive method for predicting fetalanemia in non-hydropicfetuses associated with maternal red cell isoimmunization. A PSV measurement exceeding 1.5 multiples of the median (MOM) for the corresponding gestational age has demonstrated its potential to identify a substantial percentage—specifically, 88-90%—of cases characterized by moderate to severe fetalanemia.This research seeks to extend the understanding and application of the MCA-PSV metric beyond its established correlation with moderate to severe anemia. By focusing on non-hydropicfetuses in the context of maternal red cell isoimmunization, the study aims to ascertain the predictive value of MCA-PSV in scenarios where fetalanemia may be a consequence of the mother's immune response to specific red blood cell antigens.The methodology likely involves the non-invasive application of Doppler ultrasound technology to measure the PSV in the MCA, enabling the assessment of blood flow velocity.[3] This approach aligns with contemporary efforts in prenatal care to minimize invasive procedures, particularly in cases where maternal red cell isoimmunization is a concern.The anticipated outcome of the study may offer valuable insights into the utility of MCA-PSV as an early and non-invasive predictor of fetalanemia related to maternal red cell isoimmunization. If the results support the effectiveness of this approach, it could contribute significantly to prenatal care practices by providing a safer and accessible means of identifying at-risk pregnancies, facilitating timely interventions and improving outcomes for both the mother and the developing fetus.

MATERIALS AND METHODS

This retrospective study was carried out in the Department of Obstetrics and Gynecologyfrom March 1st, 2023, to August 31st, 2023. The investigation focused on gathering and analyzing data pertaining to 12 pregnant females with Rh-negative blood type. The selection criteria for these participants included a positive Indirect Coombs' test result, indicating the presence of antibodies, specifically D-type antibodies, in their blood.The aim of this study was to retrospectively examine the clinical profiles and outcomes of these 12 Rh-negative pregnant individuals who exhibited positive results on the Indirect Coombs' test, with a specific focus on the detection of D-type antibodies. The research likely involved an in-depth analysis of medical records, laboratory results, and relevant clinical information for each participant during the specified timeframe.Variables considered in the study might include the gestational age at the time of testing, the levels of D-type antibodies detected, any associated maternal complications, interventions employed, and outcomes for both the mothers and their infants. The objective was likely to gain insights into the implications of D-type antibodies in Rh-negative pregnancies, informing clinical practices and potential interventions for managing pregnancies with these specific immunological characteristics.Findings from this retrospective study could contribute valuable information to the medical community, potentially influencing guidelines and protocols for the management of Rh-negative pregnancies with detected D-type antibodies. Understanding the outcomes and challenges faced by these pregnant individuals may aid healthcare professionals in optimizing care strategies and improving the overall well-being of both mothers and infants in similar clinical scenarios.

In light of the positive Indirect Coombs' test (ICT) results, an integral aspect of the assessment involved measuring maternal serum antiglobulin titres. This step was crucial for gauging the level of antibodies present in the maternal serum, particularly those targeted against fetal red blood cells. Monitoring the antiglobulin titres was a proactive measure to identify any increasing trends, as escalating titres could signify an elevated risk of hemolytic disease of the fetus.To further evaluate the potential risks and complications associated with an increasing antiglobulin titre, Doppler ultrasound studies were undertaken. Doppler ultrasound, a non-invasive imaging technique, was utilized to assess blood flow velocities, particularly in the fetal circulation. This allowed for a comprehensive evaluation of the hemodynamic status of the fetus, especially in regions such as the middle cerebral artery (MCA).The Doppler ultrasound studies aimed to identify any signs of abnormal blood flow patterns or velocity changes that could indicate fetalanemia, a condition associated with the development of hemolytic disease. Specifically, increased peak systolic velocity (PSV) in the middle cerebral artery has been correlated with fetalanemia, making Doppler ultrasound a valuable tool for early detection and monitoring.This comprehensive approach, integrating maternal serum antiglobulin titres and Doppler ultrasound studies, was designed to provide a thorough understanding of the risk profile and potential complications associated with maternal red cell isoimmunization. Early identification of fetalanemia through Doppler studies enabled timely interventions and management strategies to mitigate the impact of hemolytic disease, emphasizing a proactive and patient-centered approach in the care of pregnancies with positive ICT status.

In this study, the Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) was systematically measured in all non-hydropicfetuses. These measurements were then charted against a reference chart, with a designated reference cut-off set at 1.5 Multiples of the Median (MoM). This cut-off value served as a benchmark for evaluating the blood flow velocity in the middle cerebral artery, aiding in the identification of potential deviations that might indicate an increased risk of fetalanemia. Subsequently, the study participants underwent either vaginal delivery or caesarean section, leading to live births. The neonates born as a result of these deliveries became the subjects of further investigation. Their haemoglobin values were utilized to determine the presence of anemia and to categorize its severity. This approach allowed for a direct correlation between the MCA-PSV values obtained during prenatal assessment and the actual hemoglobin concentration in the neonates, providing valuable insights into the accuracy and predictive capacity of MCA-PSV measurements.The study likely involved a thorough comparison of MCA-PSV values and neonatal hemoglobin concentrations, seeking to establish a relationship between the prenatal Doppler measurements and the actual hematological status of the newborns. Analyzing this data would enable researchers to assess the effectiveness of MCA-PSV as a non-invasive predictor of neonatal anemia and its severity, potentially influencing clinical practices in the management of pregnancies at risk for fetalanemia due to factors such as maternal red cell isoimmunization.Such comparative studies contribute to the ongoing efforts to refine and enhance prenatal diagnostic tools, ensuring that interventions can be implemented promptly and effectively when fetal well-being is at stake. The results of this investigation could have implications for improving the precision of prenatal care and optimizing outcomes for neonates at risk of anemia.

RESULTS

The study comprised a cohort of 12 cases with Rh isoimmunization, a condition where the mother's immune system reacts to the Rh factor in the fetal blood, resulting in the production of antibodies. The

diagnosis of Rh isoimmunization was established in the second trimester for 5 cases and in the third trimester for the remaining 8 cases, highlighting the varied timing of diagnosis during pregnancy.In terms of delivery outcomes, 7 patients underwent vaginal delivery, while 5 opted for caesarean section. This diversity in delivery methods within the study population could be influenced by various factors, including the clinical status of both the mother and the fetus, as well as obstetric considerations. Vaginal delivery is a common choice when circumstances permit, whereas caesarean section may be recommended in cases where specific medical conditions or concerns about fetal well-being exist.

The distribution of cases across different trimesters of pregnancy and the range of delivery methods employed underscore the complexity of managing Rh isoimmunization. This diversity in the timing of diagnosis and delivery methods provides a comprehensive perspective on the clinical manifestations and obstetric decision-making associated with Rh isoimmunization. The study's findings may contribute valuable insights into the nuances of managing pregnancies affected by Rh isoimmunization, ultimately influencing clinical practices and optimizing outcomes for both mothers and infants in such cases.

Figure 1: Trimester diagnosis

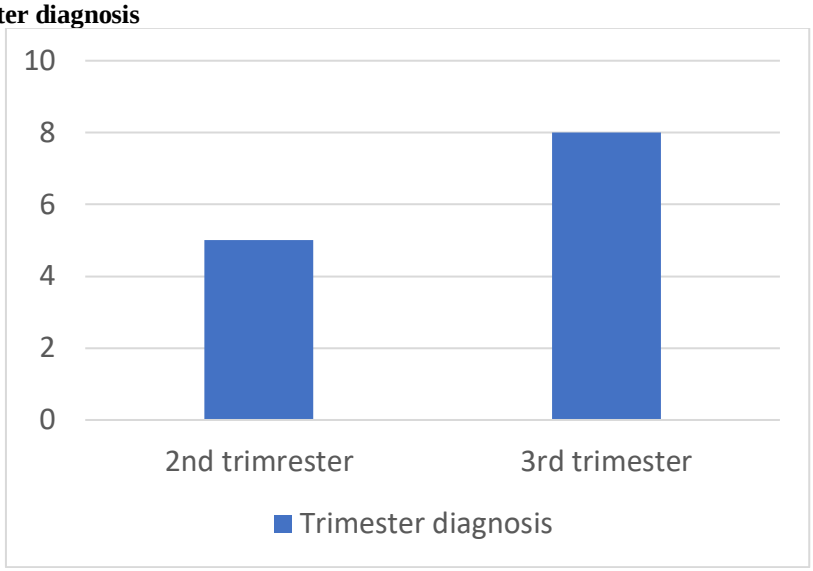
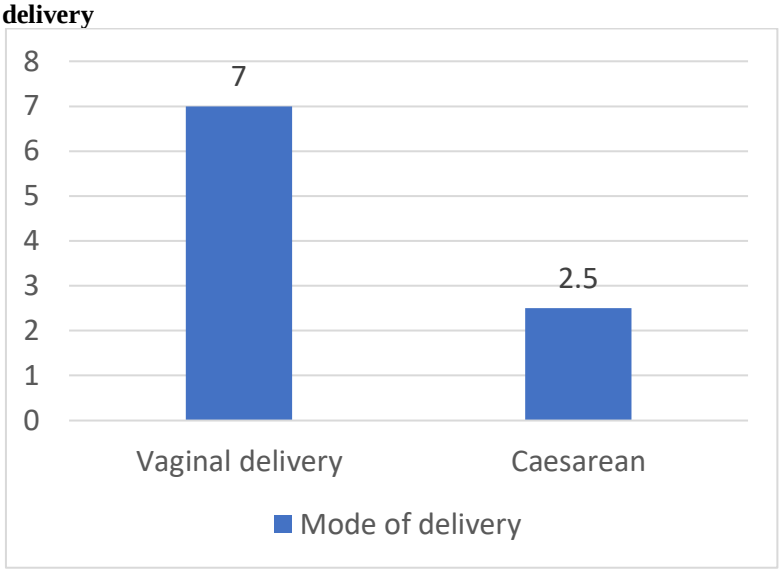


Figure 2: Mode of delivery



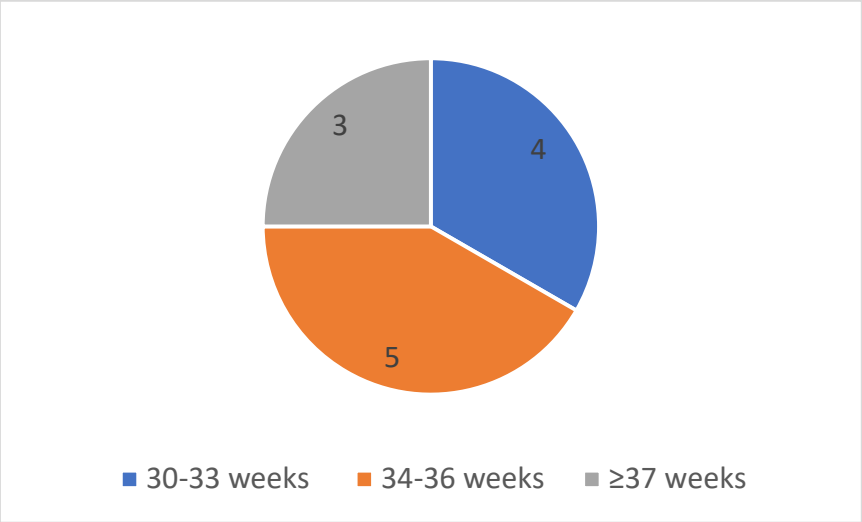
The distribution of gestational age at delivery in the study cohort revealed a varied timeline. Specifically:

- **30-33 weeks:** This gestational age range was observed in 4 cases, indicating that a subset of the study participants underwent delivery during the early preterm period.
- **34-36 weeks:** A total of 5 cases fell within this gestational age range, signifying a group of patients who delivered during the late preterm period.

- **≥37 weeks:** This category encompassed 3 cases, representing patients who carried their pregnancies to term or beyond.

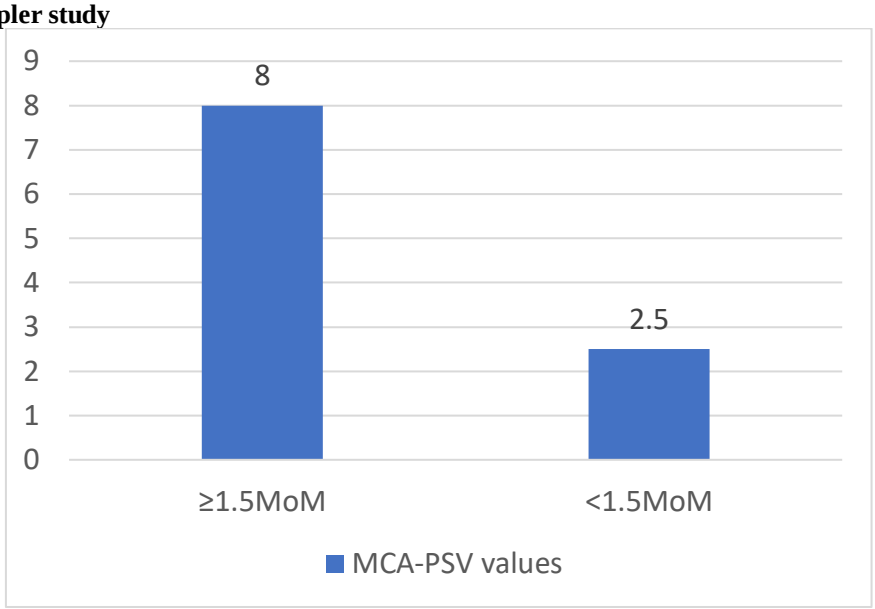
The delineation of gestational age at delivery provides a nuanced understanding of the timing of births within the Rh isoimmunized study cohort. This information is crucial for assessing the potential impact of Rh isoimmunization on pregnancy duration and guiding clinical decision-making regarding the timing of delivery interventions. The distribution across different gestational age groups contributes to the overall characterization of the obstetric outcomes associated with Rh isoimmunization, offering insights that may inform healthcare practices and improve the management of pregnancies affected by this condition.

Figure3: Gestational age at time of delivery



Doppler ultrasound for Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) in the fetus revealed elevated values above 1.5 MoM in 8 cases. This suggests a potential risk of fetalanemia in pregnancies affected by maternal red cell isoimmunization. The findings highlight the sensitivity of Doppler ultrasound in identifying pregnancies at risk, aiding clinicians in making informed decisions for monitoring and interventions to mitigate potential complications.

Figure 4: Doppler study



Post-delivery haemoglobin assessment of the neonates indicated normal values in 3 cases and anaemia in 9 cases, with 2 of them classified as severe anaemia. This suggests a notable incidence of neonatal anaemia associated with maternal red cell isoimmunization. These findings underscore the clinical relevance of monitoring neonatal haemoglobin levels, providing crucial information about the impact of Rh isoimmunization on the hematological status of the newborns. The identification of severe anaemia

emphasizes the potential severity of the condition, warranting careful management and interventions to optimize outcomes for the affected neonates.

Figure 5: Neonatal Hb estimation

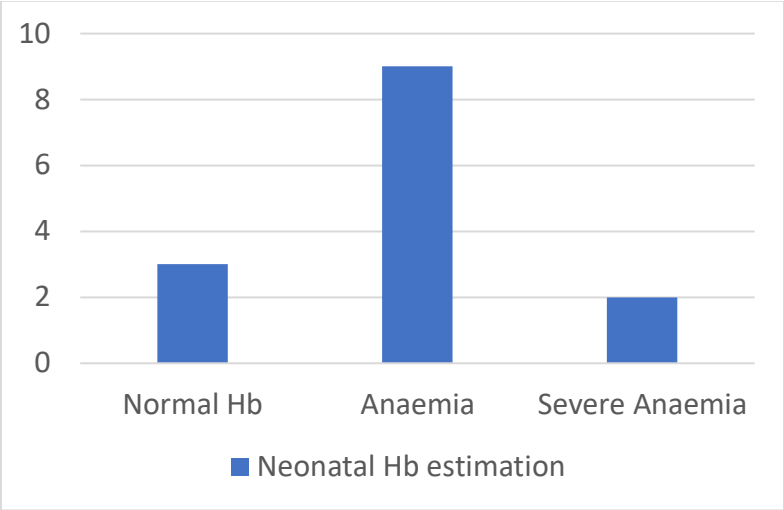


Table1: Haemoglobin cut off levels for anaemia in neonates in 1st week of life

	Hb level
Term babies (≥2.5kg)	17.0
Premature babies(1.2-2.5 kg)	16.4
Small premature babies(<1.2kg)	16.0

The study employed a Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) cutoff of 1.5 Multiples of the Median (MoM) to assess its diagnostic performance in identifying fetalanemia related to maternal red cell isoimmunization. The results revealed promising sensitivity at 88.9%, indicating its effectiveness in detecting cases with fetalanemia. Furthermore, the specificity reached 100%, signifying accurate identification of cases without fetalanemia, with no instances of false positives. The Positive Predictive Value (PPV) of 100% indicates that when MCA-PSV was positive, it consistently
correlated with the presence of fetalanemia. However, the Negative Predictive Value (NPV) of 25% suggests that a negative MCA-PSV result had limitations in ruling out the absence of fetalanemia, potentially resulting in false negatives. These findings underscore the utility of MCA-PSV as a screening tool, emphasizing its strengths and highlighting areas for careful interpretation in the context of maternal red cell isoimmunization.

DISCUSSION

Rh isoimmunization, scientifically termed Rh incompatibility or Rh sensitization, manifests as a unique immunological response during pregnancy. This phenomenon occurs when a woman's immune system reacts to a specific red blood cell antigen inherited from the biological father of the developing fetus. This specific antigen is recognized as the Rh factor, and its introduction into the maternal system triggers an immune response due to its foreign nature.[4]In simpler terms, when there is a disparity in Rh blood types between the mother and the father, such as one being Rh-positive and the other Rh-negative, the potential for Rh isoimmunization arises. In such cases, the mother's immune system perceives the Rh factor as unfamiliar, prompting the production of antibodies against it. This immunological reaction can pose a significant risk, particularly in subsequent pregnancies, as the maternal antibodies may cross the placenta and target the red blood cells of the fetus.The consequences of Rh isoimmunization span a spectrum of severity, ranging from mild to potentially severe, with the potential to impact the health of the unborn baby. Monitoring becomes paramount to assess the development of any complications. To manage and prevent adverse outcomes associated with Rh isoimmunization during pregnancy, healthcare professionals employ various interventions, including monitoring the titers of maternal antibodies, administering anti-D immunoglobulin injections, and closely monitoring the well-being of the fetus through advanced ultrasound techniques. This comprehensive approach aims to safeguard the health of both the mother and the developing fetus, highlighting the importance of vigilant care and timely interventions in cases of Rh isoimmunization.

In this comprehensive study, the focus was on evaluating the efficacy of Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) as a predictive measure for neonatal anemia, particularly in pregnancies at risk due to factors like maternal red cell isoimmunization. The meticulous methodology involved systematic measurements of MCA-PSV in all non-hydropicfetuses, establishing a reference chart with a cutoff at 1.5 Multiples of the Median (MoM) to identify potential deviations indicative of an increased risk of fetalanemia.Following the prenatal assessments, participants underwent various delivery methods—either vaginal delivery or caesarean section—culminating in live births. Subsequently, the focus shifted to the neonates born through these deliveries, forming the basis for further investigation. The assessment of neonatal hemoglobin values played a central role in determining the presence and severity of anemia. This direct correlation between MCA-PSV values obtained during prenatal assessments and actual neonatal hemoglobin concentrations provided a valuable link between prenatal predictions and postnatal outcomes.The study's comprehensive approach involved a meticulous comparison of MCA-PSV values with neonatal hemoglobin concentrations, aiming to establish a direct relationship between the non-invasive prenatal measurements and the actual hematological status of the newborns. This rigorous analysis sought to gauge the effectiveness of MCA-PSV as a reliable predictor of neonatal anemia and its severity, providing insights that could potentially influence clinical practices, especially in managing pregnancies at risk for fetalanemia linked to maternal red cell isoimmunization.The significance of such comparative studies lies in their contribution to ongoing efforts to enhance prenatal diagnostic tools. By refining predictive measures like MCA-PSV, researchers aim to enable prompt and effective interventions when fetal well-being is in jeopardy. The outcomes of this investigation hold the promise of informing and improving the precision of prenatal care, ultimately optimizing outcomes for neonates at risk of anemia.

While Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) has shown efficacy in evaluating fetalanemia before the initial transfusion, its applicability in predicting the necessity for subsequent transfusions is not strongly supported by current data.[5] A notable trend is observed wherein the accuracy of MCA PSV diminishes with each successive transfusion. This phenomenon is ascribed to the increasing presence of donor red blood cells within the fetalcirculation.The transition from predominantly fetalhemoglobin to adult hemoglobin, a consequence of repeated transfusions, induces changes in blood viscosity. This alteration is characterized by a reduction in fetalhematocrit and an increase in red blood cell rigidity, resulting in a decline in blood flow velocity through the fetal circulation. Moreover, adult hemoglobin, compared to fetalhemoglobin, exhibits a diminished capacity to carry oxygen, necessitating a compensatory increase in blood flow to sustain adequate oxygen delivery to the developing tissues.While various parameters have been explored for the assessment of fetalanemia, including the cardio-femoral index, liver length, and spleen perimeter, their additional benefits have not been firmly established. Among these, liver length assessment is commonly employed but is generally considered a supportive rather than a primary tool in the evaluation process. The measurement of the fetal liver, typically conducted in the longitudinal plane at the maximum length of the right lobe, serves as one of the complementary methods to enhance the overall assessment of fetal well-being and anemia.In summary, the limitations associated with the predictive accuracy of MCA PSV for subsequent transfusions underscore the complexity of managing fetalanemia in the context of repeated transfusions. The exploration of alternative parameters reflects ongoing efforts to refine and optimize the multifaceted approach to assessing and managing fetal well-being in pregnancies at risk for anemia.

Severe fetalanemia, a critical condition during pregnancy, necessitates intervention in the form of intrauterine transfusion (IUT) to address compromised blood conditions in the unborn child. This highly specialized procedure involves the direct administration of blood transfusions to the fetus while it is still within the uterus. The precision required for the procedure is facilitated by ultrasound guidance, ensuring accurate cannulation of the umbilical cord.In cases of severe fetalanemia, multiple intrauterine transfusions may be warranted throughout the course of the pregnancy. This strategic approach aims to maintain the fetus within the optimal target range, ensuring its well-being and development.[6] While IUT stands as a crucial and often life-saving intervention, its implementation is not without potential complications, and a careful weighing of benefits and risks is essential.Complications associated with intrauterine transfusion include the risk of infection due to the introduction of foreign materials during the procedure. Fetomaternalhemorrhage, where fetal blood enters the maternal circulation, is another potential concern. The insertion of the cannula into the umbilical cord may lead to cord hematoma, an accumulation of blood outside the blood vessels. Rupture of membranes poses a risk of premature labor, and the procedure itself may trigger preterm birth.Furthermore, the fetal heart may experience increased strain, resulting in cardiac overload, and there is a possibility of fetalbradycardia, a decrease in fetal heart rate. Despite meticulous interventions, fetal loss remains a rare but significant outcome, particularly in situations where severe anemia and procedural intricacies pose considerable challenges.The decision to proceed with intrauterine transfusion is complex, often reserved for situations where the severity of fetalanemia poses a substantial

threat. Close and vigilant monitoring, coupled with expert medical management, is paramount to navigate these potential complications and optimize outcomes for both the expecting mother and the unborn child. The delicate balance between addressing the critical condition of fetalanemia and managing associated risks underscores the intricacies of antenatal care in such high-risk situations.

CONCLUSION

The Doppler study of Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) emerges as a crucial screening procedure for fetalanemia, especially in cases involving Rh alloimmunization. This non-invasive method has effectively supplanted more invasive approaches like amniocentesis and cordocentesis in diagnosing fetalanemia in pregnancies positive for Indirect Coombs' Test (ICT). Our study underscores the significant role of MCA-PSV, suggesting its commendable performance in detecting fetalanemia. It emerges as a reliable indicator, particularly in cases with Rh isoimmunization, demonstrating the potential to minimize the necessity for invasive methods until the point where a definitive treatment, such as intrauterine fetal blood transfusion, becomes imperative.The non-invasive nature of MCA-PSV not only enhances patient comfort but also contributes to a more favorable risk-benefit profile in the management of pregnancies complicated by Rh isoimmunization. By serving as an effective screening tool, MCA-PSV offers a valuable means of assessing fetal well-being without the need for more intrusive procedures until a critical point in the pregnancy. This finding implies a significant advancement in prenatal care, reducing the reliance on invasive techniques and potentially minimizing associated risks.In summary, our study suggests that MCA-PSV stands as a robust and reliable method for detecting and predicting fetalanemia in the context of Rh isoimmunization. The non-invasive nature of this approach makes it a valuable asset in the continuum of care, emphasizing the potential to defer invasive procedures until warranted by the evolving clinical circumstances, particularly when the intervention involves intrauterine fetal blood transfusion. This shift in approach has the potential to optimize the management of Rh isoimmunization cases, offering improved precision in diagnosing and addressing fetalanemia while prioritizing the safety and well-being of both the mother and the unborn child.

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