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Review Article

BLOOD TRANFUSION FOR IRON DEFICIENCY ANEMIA IN PREGNANCIES A LITERATURE REVIEW

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ABSTRACT

Anemia in pregnancy till date is a worldwide phenomenon, it is defined as a low hemoglobin concentration of less than 11.0 g/dL in the first trimester and less than 10.5 or 11.0 g/dL in the second or third trimester. Globally, the commonest cause for anemia in pregnancy is iron deficiency anemia (IDA). Undiagnosed and untreated IDA can have a great impact on maternal and fetal health. In situations of severe anemia, blood transfusion is commonly done in clinical indications. However, some adverse effect due occur after blood tranfusion in pregnancies. This literatur review was conducted to study the benefits of blood transfusion in IDA and the risk of tranfusion reaction compared with the indications of severe anemia.

Keywords: Iron deficiency anemia, Pregnancy, Blood tranfusion.

INTRODUCTION

Anemia is defined as a low red blood cell (RBC)count, a low hematocrit (the proportion of blood volume that is RBCs), or a low hemoglobin concentration(the oxygen carrying protein of RBCs). Hemoglobin concentration is measured in grams per liter orgrams per deciliter. In pregnancy, a hemoglobin concentration of less than 11.0 g/dL in the first trimester and less than 10.5 or 11.0 g/dL in the second or third trimester (depending on the guideline used) is consideredanemia.[1]Center of Disease Control (CDC) defines anemia as pregnancy hemoglobinless than 11 g/dl in the first and third trimester and less than 10.5 g/dl in the second trimester, while World Health Organisation (WHO)defines anemia in pregnancy as Hb values less than 11gm/dl. [2,3] Anemia in postpartum females is defined as Hbless than 10 g/dl by WHO. Table 1 shows WHO classification of severity of anemia in adult females.[3]Iron deficiency anemia (IDA) is one of the causes anemic frequently in pregnancy even in developed countries. IDA indicates that the physiologic adaptations are often insufficient to meet the increased requirements, and iron intake is often below nutritional needs.[4]Undiagnosed and untreated IDA can have a great impact on maternal and fetal health. Indeed, IDA can affect the general wellbeing of the mother and leads to fatigue, pallor, breathlessness, palpitations, headaches, dizziness, and irritability. There is evidence to suggest a significant correlation between the severity of anemia, premature birth and low birth weight, intrauterine growth restriction, low neonatal iron status, preeclampsia, and post-partum hemorrhage. [5,6]Transfusion is commonly done in clinical indications and lowering risk of complications arising due to severe anemia. However, adverse effects due occur during or after transfusion, and they are commonly called transfusion reactions.[7]This literatur review was conducted to study the benefits of blood transfusion in IDA and the risk of transfusion reaction compared with the indications of severe anemia.

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Table 1. Hemoglobin levels to diagnose anemia at sea level.[3]

	Non anemia (g/dl)	Anemia (g/dl)		
		Mild	Moderate	Severe
Non pregnant women (Age > 15 years or above)	≥ 12 or higher	11-11.9	8-10.9	< 8
Pregnant women	≥ 11 or higher	10-10.9	7-9.9	< 7

PREVALENCE OF IDA AND THE CONSEQUENCES IN PREGNANCY

Globally, the commonest cause for anemia in pregnancy is IDA. The Nutrition Impact Model Study, a systematic analysis of 257 population-representative data sources from107 countries, estimated the global prevalence of anemia in pregnancy as 43% in 1995 and 38% in 2011 with the range varying from 17% in developed and 56.4% in developing countries. Etiology of anemia was attributed to ID in 50%of cases in this study.[8] According to Child Health and Epidemiology Reference Group (CHERG), the risk of maternal mortality significantly decreases for every 1 g/dl rise in Hb, however, the association becomes less clear at Hb levels above8–9 g/dl.[9] With respect to neonatal birth weight, both hemoglobin level>11 g/dl and<9 g/dl are associated with 2–3 times increased risk of small for gestational age neonates. The ideal Hb values with respect to prevention of prematurity and LBW lies between 9 to 11.5 g/dl.[9]

DIAGNOSISNG IDA IN PREGNANCY

IDA is characterized by microcytosis, (low MCV<80 fl) and hypochromia (low MCH<27 pg) and blood film may confirm characteristic microcytic cells or pencil cells.[10]While IDA is the commonest cause for decreased MCV, some studies show low MCV is insensitive and up to 40% of pregnant women with true IDA have normocytic indices. Stimulation of erythropoiesis in pregnancy masks the microcytosis of iron deficiency. Moreover, a low MCV, is not specific, for IDA.[11,12]

The gold standard for the diagnosis of iron deficiency has become a low ferritinlevel.[13] Historically, the gold standard for the diagnosis of

iron deficiency was the absence of stainable bone marrow iron. Although obtaining a bone marrow biopsy for the diagnosis of iron deficiency is not only highly impractical, it has been shown to be neither sensitive nor specific when compared with other assays including serum ferritin, serum iron, total iron binding capacity and transferrin saturation levels.[14]Ferritin is a hollow, globular intracellular protein that has the capacity, by crystallization with phosphate and hydroxide ions, to store up to 4,500 ferric (Fe+3) ions and release them as necessary. Small amounts offerritin are released into the circulation where ferritinserves as an iron carrier. Therefore, serum ferritinserves as an indirect measure of total iron body stores. Serum iron is a measurement of the total amount of circulating iron that is bound to either ferritin (10%) or transferrin (90%). Transferrin is a glycoprotein that can bind two ferric ions and transport iron through the body to various tissues including the liver, spleen and bone marrow. Total iron binding capacity is ameasurement of the amount of transferrin's available binding sites. [15]Transferrin saturation is the ratio of serum iron to the total iron binding capacity divided by 100, which represents the percentage of transferrin's iron-binding sites being occupied by iron. A low transferrin saturation is indicative of iron deficiency and can be used in the diagnosis of iron deficiency when iron deficiency is suspected, but ferritin is normal. When ferritin is low, no other laboratory testing may be necessary. [15]However in settings where detailed biochemical evaluation for iron profile is not feasible, a combination of low MCV accompanied by elevated RDW can be used as a sufficient evidence to start iron therapy. A subsequent marked RDW increase occurring early after the initiation of therapy can be used as a surrogate for confirmation of IDA.[16] Sensitivity and specificity of RDW in the diagnosis of IDA in pregnancy has been reported to be between 72–97 and 82–83% respectively.[12]

MANAGEMENT IDA IN PREGNANCY

Management as per the Trimester/Postpartum State The mode of repletion of iron stores in IDA of pregnancy is guided by the severity of anemia, the stage of pregnancy, obstetric risks of hemorrhage (e.g. premature labor, placentapraevia) and non-obstetric maternal comorbidities (hemoglobinopathy, chronic disease etc.). The flowchart depicts our approach to managing IDA in pregnancy depending on the stage and response (Figure 1).[17]

ROLE OF TRANFUSION IN PREGNANCY WITH IDA

Transfusion in pregnancy carries additional risks after tranfusion. The risk may be acute or delayed. Acute transfusion reactions present as adverse signs or symptoms during or within 24 hours of a transfusion. The most frequent reactions are fever, chills, pruritus, or urticarial rashes, which typically resolve promptly without specific treatment or complications. Other signs are occurring in a temporal relationship, such as severe shortness of breath, red urine, high fever, or loss of consciousness, maybe the first indication of a more severe reaction. Transfusion reactions are broadly divided into two types.

Immunologic reactions:

A. Alloimmunization to transfused antigen may not be present on red cells, leukocytes, platelets, or the recipient's plasma. Serological evidence of a delayed transfusion reaction is common; however, these reactions rarely cause clinical symptoms.[18]
B. Haemolytic transfusion reactions occur most commonly in women due to prior sensitization of RBCs during pregnancy. They are of three types:

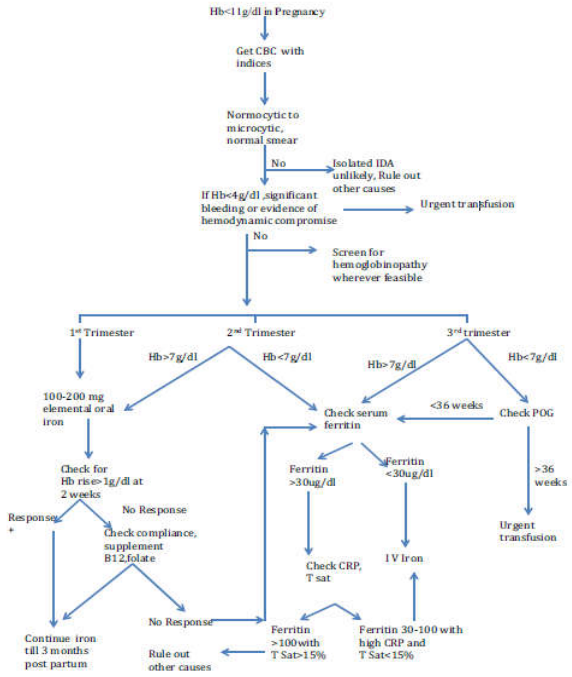

Fig. 1 Approach to IDA in pregnancy. Hb hemoglobin; IDA iron deficiency anemia; CRP C reactive protein; POG period of gestation; Tsat transferrin saturation; IV intravenous.

- Immediate intravascular hemolytic transfusion reactions - Mostly due to ABO incompatibility.
- Delayed hemolytic transfusion reactions- Predominantly extravascular, antibody to Jk and Rh are the usual causes.
- Pseudohaemolytic transfusion reactions- Similar to hemolytic reaction but no incompatibility detected. Drugs, bacterial contamination are the usual causes.

The risk of hemolytic transfusion reactions (HTRs) is approximately 1:70,000 per unit. Acute HTRs occurring during or within 24 hours after administration of a blood product are usually caused by transfusion of incompatible red blood cells (RBCs) and, more rarely, of a large volume of incompatible plasma. Delayed HTRs are caused by a secondary immune response to an antigen on the donor's RBCs.[19]

C. Febrile transfusion reactions due to alloimmunization to the antigen on leukocytes, platelets, and cytokines develop in-vitro. Most febrile non-hemolytic transfusion reactions (FNHTR) to platelets are caused by cytokines that accumulate in the product during storage, probably the result of an incompatibility between leukocytes erythrocyte product and antibodies in the recipient's plasma.
D. Transfusion-related acute lung injury (TRALI) caused by transfusion of antibodies in donor plasma that reacts with recipient granulocytes. Transfusion-related acute lung injury (TRALI) is a syndrome that includes dyspnoea, hypotension, bilateral pulmonary edema, and fever. Two different aetiologies have been proposed. The first is a single antibody-mediated event involving the transfusion of anti-HLA class I and class II or antigranulocyte antibodies into patients whose leukocytes express the cognate antigens. The second is a 2-event model: the first event is the clinical condition of the patient resulting in pulmonary endothelial activation and neutrophil sequestration, and the second event is the transfusion of a biologic response modifier (including lipids or antibodies) that activates these adherent polymorph nuclear leukocytes (PMNs), resulting in endothelial damage, capillary leak, and TRALI.[20]
E. Post transfusion purpura (PTP): It is a rare bleeding disorder caused by alloantibodies specific to platelet antigens. The

antibody against the human platelet alloantigen HPA-1at is responsible for most of the cases. The majority of affected patients are multiparous women who presumably have been previously sensitized during pregnancy. Blood transfusions rarely have been implicated as the primary cause for alloimmunization in PTP.[21]

Non-immunologic reactions:

- Circulatory volume overload may result in pulmonary edema.
- Bacterial contamination of blood and blood products - Various sources of contamination have been suggested, including infection in the donor and invasion of the blood product during the process of collection, preparation, and storage. Frequent clinical manifestations are fever (80%), chills (53%), hypotension (37%), and nausea or vomiting (26%).[22]
- Transfusion-associated viral infection - such as Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human Immunodeficiency Virus (HIV). However, the risk of transmitting HIV, HTLV, HCV, or HBV infection by the transfusion of screened blood is tiny. New screening tests will reduce the risk even further.[23]

The current AABB and the RCOG guidelines suggest a threshold of Hb < 7 g/dl for transfusion and a threshold of < 8 g/dl in patients with pre-existing cardiovascular disease.[24,25]

However in obstetrics, the decision of transfusion should be individualized depending on available alternatives of oral and parenteral iron, present and future risk of hemorrhage, comorbidities like DIC, thrombocytopenia, acuteness of fall in Hb and cardiovascular status. Partial exchange transfusion has not been shown to be superior to transfusion under diuretic cover for patients who present with severe anemia and congestive cardiac failure at term.26Some studies do not recommend the routine use of exchange transfusion except for patients with sickle cell disease. Table 2 summarizes the indications for transfusion in case of ID.

Table 2. Indications of blood transfusion in pregnancy with IDA.[24-26]

Antepartum period	Intrapartum period	Post partum period
1. Pregnancy <36 weeks a. Hb < 4 g/dL with or without signs of cardiac failure or hypoxia b. 5–7 g/dL with presence of impending heart failure, hemodynamic instability or acute hemorrhage	a. Hb <7 g/dL[in labor] [Decision of blood transfusion depends on medical history or symptoms]	a. Anemia with signs of shock/acute hemorrhage with signs of hemodynamic instability
2. Pregnancy >36 weeks a. Hb <7 g/dL even without signs of cardiac failure or hypoxia b. Severe anemia with decompensation or acute hemorrhage with decompensation c. Hemoglobinopathy/ Bone marrow failure syndromes or malignancy	b. Severe anemia with decompensation or acute hemorrhage with decompensation	b. Hb <7 g/dL: Decision of transfusion depends on medical history or symptoms

CONCLUSION

IDA in pregnancy is readily manageable yet an unmet health demand. The management strategy is dependent upon the period of gestation and severity of anemia. However, giving blood transfusion for severe IDA in pregnancy could can cause transfusion reactions and complications, therefore it is important to consider the indications and benefits of transfusion.

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