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Thalassemia and pregnancy complications

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Abstract

Thalassemia is a blood disorder passed down through families (inherited) in which the body makes an abnormal form or inadequate amount of hemoglobin. Hemoglobin is the protein in red blood cells that carries oxygen. The disorder results in large numbers of red blood cells being destroyed, which leads to anemia. This abnormal alpha- to beta-chain ratio causes the unpaired chains to precipitate and causes destruction of red blood cell precursors in the bone marrow (ineffective erythropoiesis) and circulation (hemolysis). Affected individuals with thalassemia have variable degrees of anemia and extramedullary hematopoiesis, which in turn can cause bone changes, impaired growth, and iron overload. Recurrent pregnancy loss (RPL), also known as recurrent miscarriages, is defined by the consecutive loss of two or more pregnancies with the same partner and having no more than one living child. Objective of the current review was to determine the maternal and fetal outcomes of women complicated with thalassemia .Conclusion: There are many changes as complications of thalassemia and the stress of pregnancy can make the symptoms of thalassemia worse . pregnancy in thalassemia should be considered high risk and should always be preceded by a complete preconception assessment.

Keywords: Thalassemia; pregnancy loss; Beta thalassemia; Alpha thalassemia

1. Introduction

Thalassemia is a genetic blood disorder that causes abnormal hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen and is made of two proteins from four α-globin genes and two β-globin genes. A defect in one or more of these genes causes thalassemia. The treatment of thalassemia mostly depends on life-long blood transfusions and removal of excessive iron from the blood stream [1,2]. The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing. Thalassemia is widely found with different variants in different populations. In 2018, the World Health Organization (WHO) reported that at least 5.2% of individuals worldwide were thalassemia carriers, that approximately 1.1% of couples worldwide were at risk of having children with a hemoglobin disorder, and that 2.7/1,000 conceptions were affected [3]. Worldwide, Hb E–b-thalassemia is one of the most frequent hemoglobinopathies. Recurrent pregnancy loss is defined as consecutive pregnancy loss before 20 weeks gestation or fetal weight of 500 g or less .There are numerous factors that may cause (RPL), but the underlying problem often remains undetected .The known causes of RPL include chromosomal and metabolic abnormalities, uterine anomalies, and immunologic factors .Still now the etiology of recurrent pregnancy loss (RPL) remains unclear, but it may be related to a possible genetic predisposition together with involvement of environmental factors [4,5,6].

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2. Etiology of Thalassemia

Thalassemias are caused by an abnormality in the rate of synthesis of the globin chains. This contrasts with the true hemoglobinopathies (e.g., Hb S and Hb C) that result from an inherited structural defect in one of the globin chains that produces hemoglobin with abnormal physical or functional characteristics [7]. Thalassemia inherited as autosomal recessive, to develop thalassemia disease both parents must be affected with or carriers for the disease to transfer it to the next generation. Thalassemia it can caused by mutations or deletions of the Hb genes, resulting in underproduction or absence of alpha or beta chains. There are over 200 mutations identified as the culprits for causing thalassemias. Alpha thalassemia is caused by deletions of alpha-globin genes, and beta thalassemias are caused by a point mutation in splice site and promoter regions of the beta-globin gene on chromosome 11[2]. There are two major types of thalassemia: Alpha (α) - Caused by defect in rate of synthesis of alpha chains. Beta (β) - Caused by defect in rate of synthesis in beta chains.

3. Beta Thalassemia

B-thalassemia is an autosomal recessive disorder more common in people of Mediterranean, Middle Eastern, or Asian descent. The underproduction of β globin chains is most frequently caused by point mutations with single nucleotide substitution or oligonucleotide addition or deletion.116 The β globin gene is on chromosome 11 [8]. The β-thalassemia's are genetic disorders of hemoglobin synthesis characterized by deficient (β+) or absent (β0) synthesis of the β-globin subunit of hemoglobin molecule. Most individuals with thalassemia inherit their disorder as a Mendelian recessive. Heterozygous individuals have mild anemia and microcytosis and are categorized as having thalassemia minor or trait, and homozygous individuals have severe anemia of varying degrees and are characterized as having homozygous β-thalassemia or thalassemia major or intermedia, as discussed in detail below. Much rarer is a dominantly inherited β-thalassemia in which disease occurs in heterozygous individuals because of synthesis of a highly unstable β-globin variant. Usually, the disturbance is only in β-globin synthesis, but rare deletional mutations may remove one or more of the other genes on chromosome 11, resulting in forms of the disease characterized as δβ-, γδβ-, or εγδβ-thalassemia [9,10,11].

4. Alpha-thalassemia

Is the type of thalassemia caused by decreased or absent production of α chain? α-thalassemia is usually caused by gene deletion. In α -thalassemia, the decreased production of a chains can manifest in utero because the α chain is a component of both fetal and adult hemoglobin. To inheritance of alpha thalassemia simultaneous or some genetic factors causing sustain production globin chains, (Hb F) in adults [12].

Hemoglobin H forms when only one normal alpha gene has been inherited. This causes significantly impaired alpha globin production. In the neonatal period, this will cause an excess of gamma, and in adults, this leaves an excess of beta-globin chains. Free alpha chains are insoluble. Both gamma and beta chains are soluble and make homotetramers. Hemoglobin H is made of four beta chains, and Hb Barts is made of four gamma chains. They are, however, unstable and some precipitate within the cell, leading to a variety of clinical manifestations. Hb H in adults can make up to 40% of circulating hemoglobin in affected individuals. This hemoglobin is more susceptible to oxidant injury and has poor oxygen-carrying capacity. Its affinity is ten times more than Hb A. It has an abnormal oxyhemoglobin dissociation curve. This means that it can bind to oxygen but does not deliver it to tissues normally [13].

5. Pathophysiology of thalassemia

Decreased or absent production of a particular globin chain that results in decreased amount of Hb, microcytosis, hypochromia, variable target cells (codocyte), ovalocytes, and basophilic stippling. Unequal production of the α- or β-globin chains which leads to: Imbalance in the α/β ratio. Decreased RBCs survival that is a significant contributor to anemia. Formation of unusual polypeptide combinations to make Hb In β-thalassemia, the unpaired, excess α chains precipitate in RBCs and damage their surfaces, which will be destructed by macrophages in the BM or circulation. The premature death of RBCs in the BM is called ineffective erythropoiesis, although the BM attempts to produce RBCs, but it can't release viable cells to the circulation or the cells that are released are destroyed in the spleen. In β-thalassemia, anemia is developed from ineffective erythropoiesis and increased destruction. β-thalassemia individuals are asymptomatic during fetal life and through approximately 6 months of age, because HbF (α2γ2) is the predominant Hb and switching from γ to β chain didn't occur. Symptoms usually begin to appear between 6 and 24 months of age, after completion of the γ to β switch. The mechanism sees that α thalassemias results in decreased alpha-globin production, therefore fewer alpha-globin chains are produced, resulting in an excess of β chains in adults and excess γ chains in

newborns. The excess β chains form unstable tetramers called hemoglobin H or Hb H of four beta chains. The excess γ chains form tetramers which are poor carriers of O2 since their affinity for O2 is too high, so it is not dissociated in the periphery. Homozygote α0 thalassemias, where numerous γ4 but no α-globin's occur at all (referred to as Hb Barts), often result in death soon after birth [14,15,16,17].

6. Pregnancy during thalassemia

Pregnancy is a period of reproduction during which a woman carries one or more live offspring from implantation of a fertilized zygote in the uterus throughout gestation. There are several physiological changes that occur in pregnancy. Physiology of a normal pregnancy involves major changes in both the coagulation system and Hematological parameters. These changes appear to be related to the development of the uteroplacental circulation and provide a protective mechanism during delivery [18]. Thalassemia during pregnancy could be associated with significant complications to the mother as well as her fetus. Therefore, universal antenatal screening for thalassemia carriers should be implemented in populations having a high prevalence of this condition. To improve survival among children born with thalassemia, there is a requirement for com- bined treatment and prevention program during pregnancy. Preconception genetic counseling is strongly advised for all patients with thalassemia. Among the high-risk parents, the most important method for diagnosis of thalassemia is invasive prenatal diagnosis. Following a standard management plan and close monitoring of the maternal and fetal condition during pregnancy helps in considerably reducing the mortality and morbidity associated with this condition [19]. A retrospective cohort study was conducted Ruangvutilert et al, by on singleton pregnant women affected and unaffected by thalassemia traits who attended an antenatal care clinic and delivered in Siriraj Hospital. Thalassemia status for all subjects was diagnosed by hemoglobin typing and/or DNA analysis. Patient charts were reviewed from January 2007 to December 2018 concluded that thalassemia traits minimally but significantly increase the risk of hypertensive disorders and maternal anemia. In addition, physiological changes during pregnancy may worsen the severity of anemia in the pregnant women with thalassemia traits [20]. Another study conducted by Kuntharee, et al. to determine the maternal and fetal outcomes of women complicated with thalassemia syndrome and find that the thalassemia syndrome, including thalassemia/HbE disease and HbH disease during pregnancy can present unique management challenges and requires close maternal and fetal surveillance. Despite an attempt to keep hemoglobin levels above 7.0 g/dl, the incidence of fetal growth restriction and preterm birth has been relatively high, though maternal complications are rather not divergent from general. Care for such pregnancies should be multidisciplinary, incorporating a maternal–fetal medicine specialist, a genetic counsellor, and a haematologist. Although our patients did not experience cardiac, hemodynamic, hepatic, or kidney deterioration during pregnancy, these complications can occur, which stresses the need for careful monitoring throughout pregnancy [21]. Women with thalassemia major and intermedia are at an increased risk of various maternal complications, such as cardiac failure, alloimmunization, viral infection, thrombosis, osteoporosis, new endocrinopathies, primarily, diabetes mellitus, hypothyroidism, and hypo parathyroid- ism due to the increasing iron burden, etc. In case of Hb Bart's hydrops, maternal complications may include early-onset severe preeclampsia in the antennal period; problems related to the delivery of a grossly hydropic fetus and placenta in the intrapartum period, and primary postpartum haemorrhage in the postpartum period. Also, the fetus may be at an increased risk of growth restriction and hydrops fetalis (due to Hb Bart's). Therefore, it is practical to follow a standard management plan and to closely monitor the maternal and fetal condition in this group of pregnant women. Various treatment options, such as blood transfusion or postpartum prophylaxis for thromboembolism may be indicated. However, since prevention is always better than cure, antenatal screening and an accurate genetic prenatal diagnosis should be preferably achieved during early gestation [17,22,23]. Also, Sutcu et al., reported a patient having repeated pregnancies with nonimmune hydrops fetalis caused by alpha thalassemia and concluded that the parents who are alpha-thalassemia carriers have 25% chance of having of a child with major alpha-thalassemia. Among he hemoglobinopathies, alpha-thalassemia is the most common cause of nonimmune hydrops fetalis. Since the incidence of alpha-thalassemia is reported high both in Turkey (XX) and in Balkan region, genetic counseling for alpha thalassemia should be suggested to patients having fetuses with nonimmune hydrops fetalis. If both parents are carriers, then genetic counseling together with preimplantation genetic investigation should be considered for future uneventful pregnancies [24]. Healthy pregnancy outcomes have become the expectation in women with thalassemia and provided that a multidisciplinary team is available, gestation can be completely safe for both mother and child However, pregnancy in thalassemia should be considered high risk and should always be preceded by a complete preconception assessment. In patients with severe myocardial or liver iron overload, conception should be delayed until after a period of intensive chelation. During pregnancy, a close follow-up of maternal disorders, as well as that of fetus status, is recommended. Pregnancy also seems to be safe in most patients with non-transfusion-dependent thalassemia, but wider and more detailed studies are needed [25].

7. Conclusion

There are many changes as complications of thalassemia and the stress of pregnancy can make the symptoms of thalassemia worse. pregnancy in thalassemia should be considered high risk and should always be preceded by a complete preconception assessment.

Compliance with ethical standards

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Disclosure of conflict of interest

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