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8

Obstetric care for women with thalassemia

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Thalassemia is the commonest monogenic disease and manifests as severe anemia. It is increasingly encountered outside the Mediterranean region, Africa, Middle East, and Southeast Asia because of immigration. Pregnancy, previously uncommon in patients with homozygous β-thalassemia, is encountered increasingly because of improved management and assisted reproduction technology; however, preconceptional problems that include anemia, iron overload, cardiac dysfunction, thromboembolism, alloimmunization, infections, and endocrine and bone disorders, could influence maternal and obstetric outcome. Although, successful pregnancy in thalassemia trait carriers and women with hemoglobin H disease is more common, there is still increased risk of obstetric and perinatal complications. Prenatal diagnosis to exclude fetal homozygous thalassemia and other congenital anomalies, together with close monitoring of the pregnancy, would optimize outcome. Further research is warranted to elucidate the fetal safety of iron chelation therapy and potential effect of pregnancy on long-term maternal health outcome, especially following occurrence of maternal complications.

Epidemiology

The thalassemia syndromes are prevalent in areas where malaria is prevalent. Estimated prevalence varies in different populations, being 16% in Cypriot populations; 3–14% in Thai populations; 3–8% in Indian, Pakistani, Bangladeshi, and Chinese populations; 0.9% in black Caribbean and African populations; and 0.1% among northern Europeans [1]. α-Thalassemia is found in 10–20% in parts of Africa,

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up to 40% in parts of the Middle East, India, China, and Southeast Asia; and 80% in parts of Papua New Guinea and northern India [2]. Because of population movements and migration and interethnic marriages, thalassemia syndromes can now be encountered in many parts of the world, especially the USA [2]. In California, there have been births of children with severe α- or β-thalassemia because prenatal screening or counseling was not provided to the parents [3,4].

Genotype and phenotype

There are four groups of the thalassemia syndromes, namely α-thalassemia, β-thalassemia, hemoglobin (Hb) E syndrome, and coinheritance and compound heterozygotes.

α-Thalassemia

Of the α2- and α1-globin genes on chromosome 16, output from the α2 gene is doubled that of the α1 gene. Hence, the effects of mutation in these two genes are different, and deletional and nondeletional types together make 40 different known mutations [5]. Anemia related to α°-thalassemia (mutation involving both α-globin genes in the same chromosome) is more severe than α^{+}-thalassemia (deletions involving one gene). Large deletions involving the embryonic gene result in severe anemia [6]. Homozygosity for the $-^{SEA}$ deletion of both α-globin genes but not the embryonic gene is the commonest cause of hydrops fetalis. Most of the affected homozygous offspring develop Hb Bart's (γ4) hydrops fetalis, which can also develop in Hb H mutation from three gene deletions. Childhood survivors sustained by chronic transfusion have been reported, and stem cell transplantation could allow long-term survival [5,6].

Hb H disease develops from either deletion of three genes or deletion of two and inactivation of the third gene by a nondeletional mutation, such as Hb Constant Spring, Hb Pakse, or Quong Sze mutation [5]. Nondeletional disease, found in 40–50% of the cases in Thailand, is more severe and may be transfusion dependent, compared with deletional disease, which accounts for up to 83% of the cases in California, Hong Kong and Ontario [7]. Hb H, an unstable tetramer of β-chains (β4) with high oxygen affinity, impairs oxygen delivery. It is oxidized to form intracellular precipitates, disrupts cell metabolism, and impairs membrane function and deformity, leading to shortened cell survival [7]. Anemia is most often related to hemolysis than ineffective erythropoiesis. Hemolytic crisis can result in oxidative stress or infection, and severe anemia can develop in pregnancy especially in the second and third trimesters [5].

β-Thalassemia

If mutation involves both genes on chromosome 11 responsible for the synthesis of β-globin chain, the affected subject has only fetal Hb (Hb F), and manifest as thalassemia major (TM), which requires more than eight red cell transfusions per year, or thalassemia intermedia (TI), which does not require transfusion or infrequent transfusion [4]. Thalassemia trait (or minor) refers to carriers of mutations, with microcytic and hypochromic red cells but only mild anemia. Long-term survival is possible in TM, at the expense of iron overload and its consequences. Menstruation and ovulation are often preserved; thus, spontaneous pregnancy may occur. In women with amenorrhea, hormonal treatment, including ovulation induction and in vitro fertilization (IVF), can result in successful pregnancies. In one series of 100 Greek Cypriot women with TM and TI, there were 152 successful pregnancies and 161 babies [8]. Most of the women who had normal menstrual cycles conceived spontaneously or following ovulation induction, while six underwent sperm donation because their male partners were having thalassemia, and one had ovum donation.

Hemoglobin E Syndromes

Hb E has replaced β-thalassemia as the commonest thalassemia disorder in many regions including coastal North America [9]. The mutation involves the β-globin gene and activates a cryptic mRNA splice site resulting in reduced synthesis of the E-β chain and a thalassemia phenotype, while the weakened