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Thalassaemia in pregnancy

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Thalassaemia is the most common monogenetic disease worldwide. Antenatal screening is effective and simple, and accurate genetic prenatal diagnosis can be achieved in early gestation. Less invasive methods are feasible with ultrasound fetal assessment for alpha-thalassaemia, analysis of circulating fetal nucleic acid in maternal plasma, and pre-implantation genetic diagnosis. Women with thalassaemia major and intermedia are at risk of various maternal complications, such as cardiac failure, alloimmunisation, viral infection, thrombosis, endocrine and bone disturbances. Therefore, it is prudent to adhere to a standard management plan in this group of pregnant women. Close monitoring of the maternal and fetal condition during pregnancy is essential, and various treatments, such as blood transfusion or postpartum prophylaxis for thromboembolism, may be indicated. After birth, resumption of iron chelation and bisphosphonates treatment is needed, and counselling on breast feeding and contraception should be given.

Introduction

Thalassaemia refers to a group of autosomal recessive disorders of haemoglobin synthesis, and consists of two main types: alpha and beta. Both are different from each other epidemiologically, and have different genetic defects, disease manifestation, and, consequently, prenatal diagnosis and management (Table 1). Although its name (in Greek *θάλασσα:* the sea, *αἷμα:* blood) implies its geographic prevalence in the Mediterranean region, the diseases are not restricted to southern Europe

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Table 1
Comparison of alpha and beta-thalassaemia: epidemiology, genetic defects, disease manifestation, and prenatal diagnosis and management.

	Alpha-thalassaemia	Beta-thalassaemia
Genetics		
Number of alleles	4	2
Gene allocation	chromosome 16.	chromosome 11.
Type of genetic defects	Commonly deletion.	Commonly point mutation.
Mode of inheritance	Autosomal–recessive.	Autosomal–recessive.
Epidemiology	More common in south China and Asia.	More prevalent in Mediterranean region.
Screening of carrier status	MCH less than 27 pg and MCV less than 81 fl.	MCH less than 27 pg and MCV less than 81 fl.
Diagnosis of carrier status	Haemoglobin inclusion bodies.	Elevated haemoglobin A2 3.5% or greater and haemoglobin F.
Prenatal diagnosis		
Genetic diagnosis with chorionic villus sampling or amniocentesis	Yes	Yes
Haemoglobin pattern with cordocentesis	Yes	No
Ultrasound surveillance	Yes	No
Non-invasive prenatal diagnosis	No	Possible
Pre-implantation genetic diagnosis	Yes	Yes
Disease manifestation		
Onset	*In utero* since first trimester.	Few months after birth.
Presentation	Cardiomegaly, thick placenta and hydropic changes *in utero.*	Anaemic symptoms during infancy.
Prognosis and treatment	Lethal.	Continuous transfusions or treat with bone marrow transplantation.

MCH, Mean corpuscular haemoglobin; MCV, mean corpuscular volume.

or northern Africa, and can spread through certain ethnic groups in the Middle East and Southern Asia. The estimated prevalence for different types of thalassaemia trait is up to 16% in southern European populations, 10% in Thai populations, and 3–8% in Indian, Pakistani, Bangladeshi and Chinese populations,[1–3] making it the most common monogenetic disease worldwide.[1,4]

Immigration and inter-ethnic marriage has caused this condition to become an important global concern.[5,6] Therefore, the understanding of this group of disorders and its relevance to pregnancy are important to general obstetricians and maternal–fetal medicine subspecialists. This review will be divided into three main parts: (1) basic genetics of the diseases; (2) up-to-date screening and prenatal diagnostic methods currently in use, which have produced advanced, earlier, faster, more accurate, and less invasive diagnostic pathways; and (3) maternal health and management of the mother with thalassaemia major or intermedia.

Basic genetics of thalassaemia

A normal haemoglobin molecule consists of a central non-protein haem group surrounded by an assembly of four globin protein chains. The structure of these protein subunits is arranged in a tetramer structure, and its constituents varies from the embryonic to the adult life. During the embryonic stage, it is made of two zeta subunits and two epsilon subunits (haemoglobin Gower 1: $\zeta_2\varepsilon_2$). Starting from 6–7 weeks of gestation, it switches from zeta to alpha subunits, and from epsilon to gamma subunits, and forms the fetal haemoglobin (haemoglobin F: $\alpha_2\gamma_2$).[7] The structure of the tetramer remains unchanged until a few months after birth, during which the tetramer changes in to the adult form, which is haemoglobin A. Haemoglobin A consists of two alpha subunits and two beta subunits ($\alpha_2\beta_2$), whereas the other form haemoglobin A2, with two alpha and two delta ($\alpha_2\delta_2$), accounts for less than 3.5% of all adult haemoglobin.[8,9] The thalassaemias are classified according to which chain of the globin molecule is affected, and the two major types are alpha-thalassaemia and beta-thalassaemia.[4]