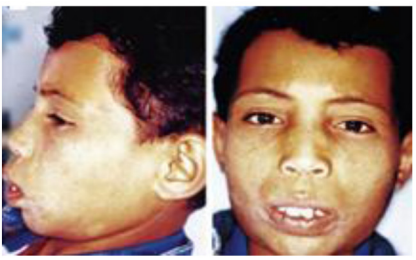
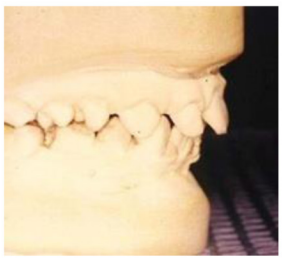
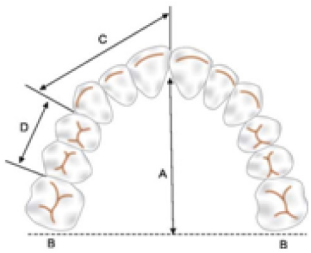
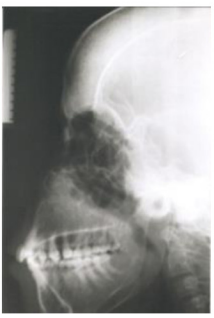
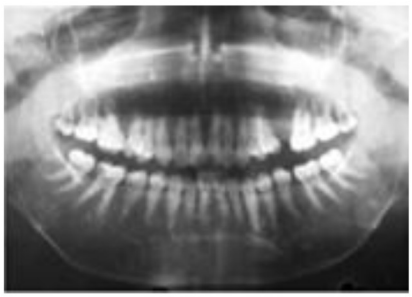
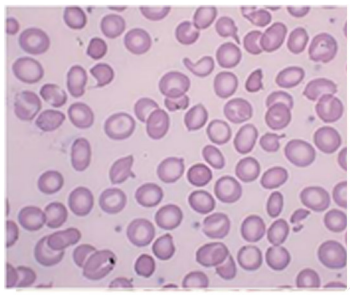
OROFACIAL AND SYSTEMIC FEATURES OF THALASSEMIA MAJOR: MANAGEMENT, AND PREVENTION WITH REFERENCE TO POPULATIONS IN THE ARABIAN GULF

By Faiez N. Hattab

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Orofacial and Systemic Features of Thalassemia Major: Management, and Prevention with Reference to Populations in the Arabian Gulf

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FOREWORD

I am very pleased to write a foreword to this special monograph **"Orofacial and Systemic Features of Thalassemia Major: Management, and Prevention with Reference to Populations in the Arabian Gulf "**, by Dr. Faiez N. Hattab, a friend and colleague for more than 30 years. Thalassemia is a growing global public health problem with severe social impact in which few data are available in the populations of the Arabian Gulf region. This monograph provides an outstanding source of current information on thalassemia focusing on practical clinical approaches to the features, physiopathology, complications and management of the disease. It will provide valuable assistance to dental and clinical practitioners, especially those working in multiracial communities.

Nasser Fouda
Senior Consultant of Periodontics
UAE

PREFACE

Thalassemia is one of the most common genetic diseases in the world. In high incidence areas, particularly Mediterranean and Middle Eastern countries, it presents a major public health and social challenge. This monograph updates dental and orofacial characteristics of thalassemia major. The clinical, radiographical, and odontometric features are also presented. Pathogenesis, systemic complications, morbidity and mortality, management, and prevention methods are discussed. Furthermore, guidelines for optimal dental care are also presented. The monograph contains the following key topics: introduction, epidemiology, consanguinity, pathophysiology, clinical and hematologic diagnosis, genetic testing, dental and orofacial features, literature review, mode of treatment, morbidity and mortality, diet and nutrition, cost of treatment, prevention, dental care, and genetic disorders in Arabian Gulf populations and among Arabs. Dental and orofacial characteristics include (i) maxillofacial deformities; (ii) dental caries and periodontal status; (iii) tooth size and dental arches dimensions; (iv) occlusion; (v) dental development;(vi) physical growth. The monograph contains 95 pages, 16 colored photographs, 15 radiographs, 4 drawings, 4 tables, and 2 plates. I hope this work will be helpful to dental and medical students, practitioners, and health educators, to update their knowledge about the nature of the disease.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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I would like to thank Mr. Najwan F. Hattab for excellent proofreading the monograph.

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ABSTRACT

Thalassemia is a group of hereditary hemoglobinopathies. It is one of the most common genetic disorders worldwide, presenting major public health and social challenges in high incidence areas. Thalassemia is inherited in an autosomal recessive manner. It is manifested as chronic hemolytic anemia, which is caused by partial or complete lack of the synthesis of alpha- or beta-globulin chains that form hemoglobin. Thalassemia major (TM) is associated with the most serious clinical changes and life-threatening risk and is characterized by the triad of chronic anemia, ineffective erythropoiesis, and iron overload. Anemia can be treated with regular blood transfusions, but this life-saving therapy results in a "second disease" due to iron accumulation in the body tissues. Iron overload is the main cause of morbidity and mortality. The oral and maxillofacial features of TM are protruding frontal and malar bones, thinning of the mandibular inferior cortex, small maxillary sinuses, maxillary hypertrophy, and flaring of the maxillary anterior teeth. Dental complications of TM include dental caries, periodontal disease, reduction in tooth size, teeth spacing, short and narrow dental arches, delayed tooth development, malocclusion. This monograph discusses the epidemiology, pathophysiology, clinical manifestations, radiological characteristics, dental care, management and complications. Guidelines for dental care are presented and stratiges of thalassemia prevention are reviewed.

Keywords: Clinical features, Complications, Consanguinity, Epidemiology, Management, Pathophysiology, Prevention, Thalassemia.

INTRODUCTION

The term thalassemia is derived from the Greek "Thalassa" (sea) and "haima" (blood), as the disorder was first identified in the Mediterranean area. Thalassemia refers to a group of inherited hemolytic anemia disorders that involve defects in the synthesis of hemoglobin (Hb). Normal red blood cells (RBCs) each contain approximately 300 million molecules of Hb. In adults, there are three main types of Hb molecule: HbA, which on average represents around 96% of the Hb; HbA2, which is approximately 3%, and HbF, which is approximately 1%. Each HbA molecule consists of four globin chains, two α alpha and two β beta, associated with the central heme group of porphyrin ring and ferrous iron (Fig. **1a**) that can reversibly bind one oxygen molecule. The α chain has 141 amino acids and the β chain has 146 amino acids, arranged in a definite order. Mutation in globin genes

(11p15.5) causes a defect in the formation of α- or β-polypeptide. Alpha thalassemia occurs when one or more of the α-globin genes are affected, while β-thalassemia occurs when both β-globin genes are defective [1-3]. A decrease in the synthesis of globin leads to reduced Hb production, hypochromic microcytic anemia, and dysplastic RBCs (erythrocytes) of deficit Hb content (Fig. **1b**). About 1540 variants of the globin gene sequence have been identified. More than 200 mutations have been identified in β-thalassemia. About 1540 variants of the globin gene sequence have been identified. More than 200 mutations have been identified in β-thalassemia [4]. These mutations can interact to produce a wide range of clinical and hematological phenotypes of variable severity from silent to very severe. The manifestations of thalassemia are regulated by a variety of genetic, racial, and environmental factors [2-5].

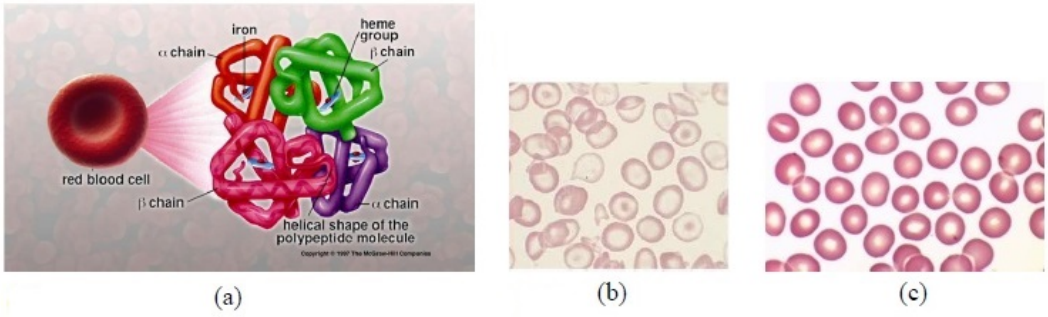

Fig. (1). (a) Normal hemoglobin structure made of heme, α globins, and β globins. **(b)** RBCs in thalassemia major are microcytic, hypochromic (pale), fragmented, and poikilocyte (abnormal shaped). **(c)** Normal RBCs [Source: *Google Images*].

CLASSIFICATION OF THALASSEMIA

According to potential genetic defects and clinical severity, thalassemia is divided into two main diseases: α-thalassemia and β-thalassemia. It is also divided into transfusion-dependent and non-transfusion-dependent thalassemias. This

classification is based on whether the patient requires regular blood transfusions to survive or not. Thalassemia covers α-thalassemia, β-thalassemia, and combinations of the two. Due to the differences in chain production and severity of symptoms, both α- and β-thalassemia are divided into minor or major, in addition to a variety of intermediates.

Alpha Thalassemia

Alpha-globins production is regulated by four α-genes. Alpha-thalassemia is usually caused by a reduction (α+) or completely abolished (α°) globin chains production by the affected allele. The carrier state can either be α+ trait (α-thalassemia 2) or be α°-trait (α-thalassemia 1). It is one of the most common Hb genetic abnormalities, caused by one or more deletions or mutations in the four α-globin gene copies. α-thalassemia is characterized by a decrease in the amount of normal Hb, so there is insufficient oxygen in the body tissues. Affected individuals are suffering from RBCs deficiency, weakness, fatigue, yellowing of the skin, and complications of anemia. This form of the disease is widespread in tropical and subtropical regions. The more genes are affected, the less α-globin is produced. There are at least 4 different types of α-thalassemia, classified according to the number of genes affected and to the pathologic severity, including:

●Silent carrier (1 gene affected). People who have mutations in only one α-globin gene are silent carriers. They usually have normal Hb levels and RBC index with no signs or symptoms. DNA analysis is the only method to identify a silent carrier.

● Alpha thalassemia trait (2 genes affected, also called α-thalassemia minor). In this form, only one α-globin gene is dysfunctional, the RBCs are mildly microcytic, hypochromic, decrease in mean corpuscular volume. It is an asymptomatic carrier state but can be associated with mild chronic anemia that does not respond to iron supplements. Carriers usually do not require any treatment.

●Hemoglobin H disease (3 genes affected). This form of α-thalassemia is most common in people of Southeast Asian and Mediterranean descent. In this disease, the production of α-globin chains is significantly reduced, resulting in excessive β chains (HbH disease, also known as α-thalassemia intermedia). It can cause mild to moderate anemia, which is characterized by microcytic hypochromic hemolytic anemia, mild jaundice, splenomegaly, and bone deformities. For HbH disease, only occasional blood transfusions are usually required. Iron overload during the course of blood transfusions must be treated with iron chelators.

SUBJECTS AND METHODS

Dental and orofacial features of TM was evaluated on 54 Jordanian subjects, 31 males and 23 females aged 5.5 to 18.3 (mean 11.6 ± 3.2) years. A thalassemia-free matched by age and gender served as a control group. Family histories revealed that 41% of the patients were the offspring of first-cousin marriage, 32% of second-cousin marriages, and 27% of distantly related or unrelated parents. The average number of siblings per family was 6.1. One-third (31%) of siblings had TM. Clinical, radiographic, and odontometric examinations were carried out to assess changes caused by this disorder. The subjects were examined for oro-maxillofacial features, dental caries, oral hygiene and periodontal status, tooth crown size, dental arch dimensions, dental development, and physical growth. The ethical approval of the study was obtained from the Research Committee of the Jordan University of Science and Technology, and the parental consent of all participants.

Dental Caries

The sample was divided into four age groups: 6-7, 8-9, 12-14, and 15-18 years old. Teeth were examined for dental caries using plane mouth mirror and sickle-shaped dental probe under standard operating illumination. Before the examination, the teeth were gently dried by compressed air. Dental caries were determined and expressed by dmft (decayed, missing, filled, teeth) for primary teeth and DMFT for permanent teeth, according to the WHO criteria. A tooth is recorded as sound if there is no evidence of treated or untreated clinical caries. A tooth with white spots or stained pits or fissures in the enamel that catch the explorer but not have detectably softened floor is considered sound. The criterion for the diagnosis and recording of caries is when a lesion in a pit/fissure, or on a smooth tooth surface, has a detectably softened floor, undermined enamel, or softened wall. A tooth with a temporary filling is included in this category. On proximal surfaces, the explorer has entered the lesion. All questionable lesions are regarded as sound. The rules for determining deft or DMFT scores include:

- No tooth counted more than once. It is either decayed, missing, filled, or sound. Restoration with recurrent decay is counted decayed.
- Teeth lost due decayed or teeth badly decayed is counted missing.
- A tooth that has several restorations is counted as one ‘F' tooth.
- Only, carious cavities are considered as ‘D', the initial lesions (white spots. stained fissures, *etc*.) are not considered as ‘D'.

The Student's t-test was used to determine the statistical differences between the average dmft and DMFT between males and females and between the test group and the control group [24]. The level of significance chosen was $P< 0.05$.
The Silness-Löe Plaque Index is used to assess oral hygiene. The plaque accumulation on the surface of the six indexing teeth [12, 16, 24, 32, 36, 44] was evaluated using a mouth mirror and explorer. Each of the four surfaces of the teeth (buccal, lingual, mesial, and distal) is given a score from 0 to 3 as follows:

- Score 0: No plaque.
- Score 1: A film of plaque adhering to the free gingival margin and adjacent areas of the tooth. Dental plaque can only be seen *in situ* after applying a disclosing solution or using a probe on the surface of the tooth.
- Score 2: Moderate accumulation of soft deposits in the gingival pocket and/or on the tooth and gingival margin, which can be seen with the naked eye.
- Score 3: Abundance of soft matter in the gingival pocket and/or on the tooth and gingival margin.

Periodontal Status

Simplified Oral Hygiene Index (OHI-S) is composed of the combined Debris Index and Calculus index, which was used to evaluate oral hygiene status. The OHI-S on the six surfaces of the indexing tooth was checked. Calculus deposit was determined by placing a dental explorer into the distal gingival crevice and drawing it subgingivally to the mesial contact area. TheOHI‑S criteria(index and grade) are as follows:

- Score 0 (zero): No soft debris/calculus.
- Score 1: (up to 1.2); soft debris/supragingival calculus cover less than one-third of the tooth surface.
- Score 2: (1.3–3.0); soft debris/supragingival calculus cover one-third of the tooth surface.
- Score 3: (3.1–6.0); soft debris/supragingival calculus cover more than two-thirds of the tooth surface or a continuous heavy band of subgingival calculus around the cervical portion of the tooth (Fig. **4**). Periodontal status and oral hygiene were assessed using a plane mouth mirror, sickle-shaped explorer, and periodontal probe with William’s markings (1-3,5,7,8-10 mm). The periodontal pocket (probing pocket depth, PPD) was assessed by measuring the distance from the free gingival margin to the bottom of the sulcus [25] (Fig. **5**).

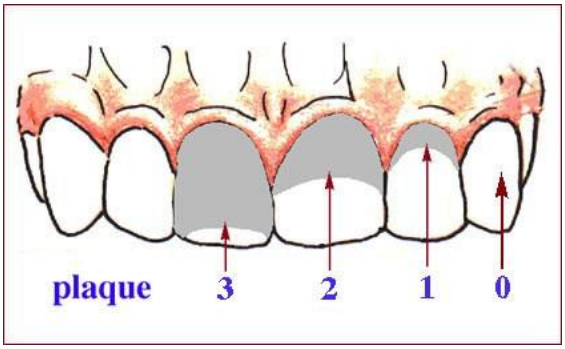

Fig. (4). Criteria for scoring plaque.

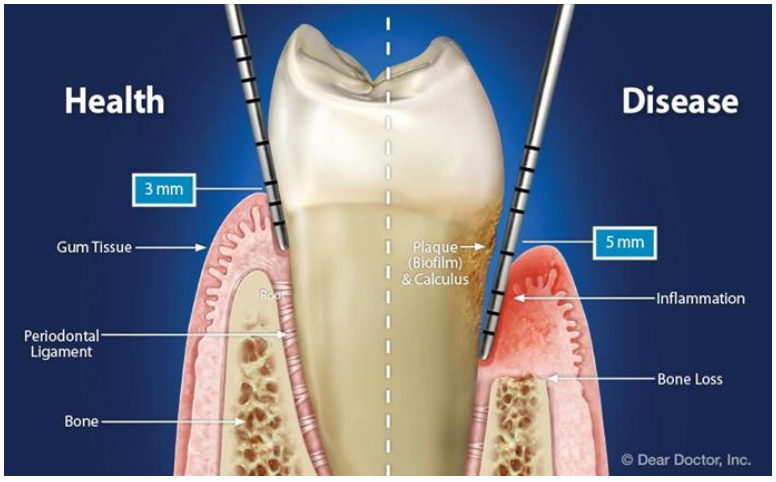

Fig. (5). Periodontal probe (Williams probe, 1 to 10 mm marking) to assess periodontal pocket-depth. Note the inflamed gingiva. [By Dr. Mario A. Vilardi. From: https://www.deardoctor.com/articles/understanding-periodontal-pockets]. Google Images.

Gingivitis was assessed for the six index teeth using the criterion of the gingival index (GI) of Löe and Silness (1963). The index teeth examined were the maxillary right first molar (# 16), maxillary right central incisor (# 11), maxillary left first molar (# 26), mandibular left first molar (# 46), mandibular left central incisor (# 41), and the mandibular right first molar (# 36). The gingival index to score gingival health is as follows:

- Score 0: Normal gingiva.
- Score 1: Mild inflammation—a slight change in color, slight edema. No bleeding on probing.

RESULTS

Oro-maxillofacial Features

In TM, the oro-maxillofacial features are the result of bony changes due to ineffective erythropoiesis, and the formation of erythroid mass with bone expansion. These changes are characterized by bossing forehead and cheekbone, saddle nose, maxillary protrusion, flaring of the maxillary anterior teeth, increased overjet and open bite, lip incompetence, and malocclusion [32,33]. Of the 54 TM patients, 33% had an almost normal appearance (Grade 1, Plate **2a**), 26% had mild changes (Grade 2, Plate **2b**), and 16.7% had a 'chipmunk face' (Grade 3, Plate **2c**).

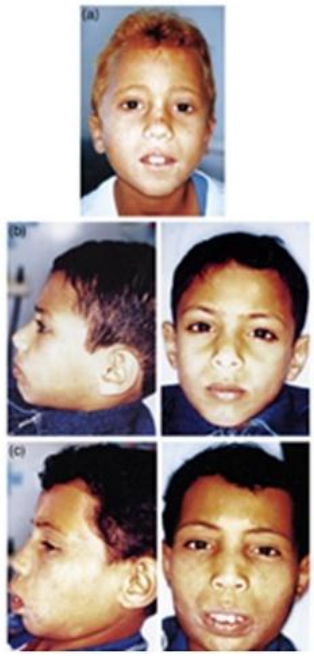

Plate 2. Grades of maxillofacial deformities in TM children.

Grade 1a: Slight depression of the nasal bridge and minor maxillary overgrowth.

Grade 2b: The frontal and cheek (malar) bones are slightly prominent; the upper jaw is barely enlarging; the bridge of the nose is depressed and the eyelids are swollen.

Grade 3c: Forehead (frontal bone) bossing; prominent cheekbones (malar bones), saddle nose; gross maxillary overgrowth; protrusive maxillary anterior teeth; lip

incompetence; excessive overjet; giving a "chipmunk" appearance, and a tendency of eye slanting and flaring of nose alae [32].

Table 1. Prevalence of orofacial TM features in different population groups.

TM sample	**Jordanian[25]**	**Iranian [36]**	**Indian [37]**
Sample size, % and (n)	**54**	**119**	**72**
Frontal bone bossing	61.1 (33)	--	--
Saddle nose	59.2 (32)	34.0 (40)	56.9 (41)
Lip incompetence	51.8 (28)	47.9 (57)	80.6 (58)
Discolored teeth	44.4 (24)	--	--
Dental and jaw pain	40.7 (22)	--	--
Pallor oral mucosa	38.9 (21)	26.9 (32)	22.2 (16)
Headache	29.6 (16)	--	--
Increased overjet	25.9 (14)	--	--
Maxillary protrusion	24.9 (13)	49.7 (149)	60.5 (72)
Chipmunk faces	16.7 (9)	34.7 (104)	--
Nasal airway problem	16.7 (9)	--	--
Lower lip paresthesia	13.0 (7)	--	--
Parotid gland enlargement	5.6 (3)	--	--

Dental Caries

The mean dmft and DMFT values and their components of the 54 TM patients assigned to the age groups (Table **2**). Females had higher caries experience than males: dmft 7.31 vs 6.54 for the 6–7-year age group and DMFT 6.67 *vs* 5.83 for the 12–18-year-old group. Because the differences did not reach the significance level ($P<0.05$), the data for males and females were combined (Table **2**). No significant difference was found between the dmft and DMFT values. The main contributor to dmft and DMFT scores is tooth decay, which accounts for 95.2% of the total dmft and 92.7% of the total DMFT value. Between the ages of 6 and 9, the average dmft for thalassemia patients was 5.82. For 12–14 years old, the DMFT value was 6.57 and 5.95 for 15–18 years old. Compared with the healthy control group, the

incidence of caries in TM patients was significantly higher. Overall, the average DMFT of 15-year-old patients was 6.26, while the DMFT of the control group is 4.84 ($P<0.001$). Only 17.4% of TM children aged 6–9, and 21.4% of those aged 15 years have no caries[24]. Importantly, 36.2% of 6–9-year-old patients and 45.8% of 12–18-year-old patients had 5 or more carious teeth. The average plaque score of TM patients in the 6–11-year-old group was 1.57 ± 0.44 (±SD), and the 1.74 ± 0.57 for 12–18-year-old. The corresponding scores of the healthy control group were 1.43 ± 0.63 and 1.67 ± 0.68, respectively (Table **3**). No significant differences between age groups and gender were found. The overall mean plaque score of the 54 TM patients was 1.67 ± 0.52.

Table 2. Caries experience in primary teeth (dmft) and permanent teeth (DMFT) and their components in the TM age group [24].

Age Group	**Primary Teeth**		**Permanent Teeth**	
(years)	6-7	8-9	12-14	15-18
Decayed	6.59	4.29	6.09	5.33
Missing	0.25	0.18	0.26	0.35
Filled	0.08	0.25	0.22	0.27
Total dmft/DMFT	6.92	4.72	6.57	5.95
(SD)	(4.54)	(3.86)	(4.28)	(3.74)

Table 3. Oral hygiene and periodontal status of TM patients and control group assessed by plaque index (PI) and gingival index (GI) [25].

Age Group (mean ± SD) (years)	**Thalassemic Group (mean ± SD)**		**Control Group**	
	PI	**GI**	**PI**	**GI**
6–11(n = 23)	1.57 ± 0.44	1.30 ± 0.49	1.43 ± 0.63	1.24 ± 0.40
12–18 (n = 31)	1.74 ± 0.57	1.56 ± 0.69	1.67 ± 0.68	1.48 ± 0.61

DISCUSSION

Thalassemia is an autosomal recessive inheritance of chronic hemolytic anemia, which is caused by insufficient or lack of synthesis of α- or β-globin chains due to mutations in the corresponding genes. The first suspicion that a patient has a Hb disorder is seen in a full blood count test. Because iron deficiency anemia shows a very similar picture, it's important to rule it out before diagnosing thalassemia, which can be diagnosed once the iron deficiency has been treated. In the presence of an abnormal full blood count and normal iron status, more specialized tests are required to confirm the diagnosis of thalassemia. Among thalassemia types, TM is associated with the most severe clinical changes and life-threatening risks. In the progressive course of illness, the condition is characterized by iron overload, cardiomyopathy, infection, liver fibrosis and cirrhosis, endocrinopathy, hypersplenism, osteoporosis, growth retardation, and failure of sexual maturation, with typical signs and symptoms of anemia [1-3,5]. TM leads to serious medical, social, psychological, and economic problems for patients and their families as well as budget and care burden for the public health services. The primary treatment for TM involves regular blood transfusions at 3-4 week intervals. This is necessary to maintain Hb at normal levels and treat the anemia. Successful treatment depends on early diagnosis, regular blood transfusion, iron chelation, infection control, and treatment facilities. If given appropriate treatments, many patients in developed countries can survive to the fourth or fifth decade of life [13, 39].

Advances in diagnostic tools and medical care continue to improve the life expectancy and quality of life of TM patients.The way in which the family and the patient come to cope with the disease and its treatment will have a critical effect on the patient's survival and wellbeing. Today, the classic clinical picture of TM is primarily seen in countries with insufficient resources to provide affected individuals with treatment (*e.g.*, regular blood transfusions and iron-chelation therapy). Allogeneic hematopoietic stem cell transplantation was until very recently, the only permanent curative option available for patients suffering from transfusion-dependent β-thalassemia. Gene therapy, by autologous transplantation of genetically modified hematopoietic stem cells, currently represents a novel therapeutic promise byre-establishing effective hemoglobin production. Patients may be rendered transfusion- and chelation-independent and evade the immunological complications that normally accompany allogeneic hematopoietic stem cell transplantation.

LITERATURE REVIEW

Dental and Orofacial Features

The distinctive orofacial features in patients with TM are due to intense hyperplasia of the bone marrow and expansion of the marrow cavity in response to severe hemolytic anemia, chronic hypoxia, and ineffective erythropoiesis.TM oro-maxillofacial changes include:

- bossing of the frontal bone;
- prominence of the malar bone;
- thinning mandibular inferior cortex;
- indiscernible mandibular canal borders;
- altered trabecular pattern;
- obliterated maxillary sinuses;
- enlarged marrow spaces;
- widened diploic spaces;
- reduced dental arches dimensions;
- premaxilla protrusion;
- flaring and spacing of the maxillary anterior teeth;
- teeth discoloration;
- pale oral mucosa;
- lip incompetence;
- faint lamina dura;
- short spiky roots;
- increased overjet and open bite;
- malocclusion (Tables **1** and **2**).

These abnormalities become more prono-unced with age. Generally, if blood transfusion therapy is started in early childhood and the Hb level is maintained at 9–10 g/dL, the orofacial features of TM patients will become minimal.

In TM patients, the impedance of the maxillary antrum pneumatization leads to a smaller antrum, which may be due to the compression caused by the expansion of the maxillofacial bones and hypertrophy of the marrow cavities. The thinning of the mandibular inferior cortex and the reduction or loss of the inferior alveolar canal boundary may be the sequelae of bone marrow expansion, increased bone resorption/erosion, and decreased bone mineral density. The thin mandibular cortex is associated with osteoporosis [40,41]. Overgrowth of bone marrow in the maxillofacial bones may cause lateral displacement of the orbit and eye slanting

(Plate **2c**). Lack of lip seal may be due to maxillary protrusion and proclined maxillary anterior teeth. This leads to mouth breathing and dryness, which exacerbates dental caries and periodontal disease. The pallor of the oral mucosa may arise from the chronic anemia underline the TM. Flaring of nose alae (Plate **2**) is adaptive to air/oxygen hunger caused by the hypoxia of anemia. Dental pain in TM patients may due to pulpal blood vascular infarction/thrombosis, which leads to pulpal necrosis. Painful swelling of the parotid glands and reduced salivary secretions can be a result of iron deposition. Thalassemic patients experience dental and jaw pain, transitory headaches, and lip paresthesia [25, 33].

The orofacial deformities in Jordanian TM patients aged 11.6 ± 3.2 years (Plate **1**) is comparable to those earlier reported by Logothetis *et al.*, [42] on Greek TM patients (mean age10 ± 4) where 32% had a normal appearance, 23% had mild maxillary overgrowth, and 14% had "rodent-like faces." The prevalence of orofacial TM features of Jordanians and other population groups is shown in Table **2**. Elangovanetal. [37] reported that among 72 Indian TM patients (aged 6 to 18 years), 41.7% had a rodent face, 56.9% saddle nose, 80.6% lack of lip seal, 22.2% pale oral mucosa, 18.1% anterior open bite. Radiographic examinations of 50 Indian TM patients showed 82% taurodontism, 56% spiky short roots, 26% faint lamina dura, 50% large bone marrow spaces, 36% obliterated maxillary sinuses, 26% absence of inferior mandibular canal [38] (Table **3**). In a study on 60 Thaiβ-thalassemia major, Wisetsin [43] found that 73% of the patients had thin mandibular cortex, 63% had thickening of the frontal bone and parietal bones, 8% had "hair-on-end" calvarium, and 5% absence of maxillary sinus. Abd - ulla and Husen [44] who examined 50 Iraqi TM patients reported that 68% had enlarged bone marrow spaces, 60% tooth discoloration, 48% Class II malocclusion, 28% saddle nose, 28% thin lamina dura, 24% spiky roots, and 16% taurodont molars (sexes pooled). A study on 300 Iranian TM patients, Salehi *et al.* [45] found that 67% had saddle noses, 49% had a maxillary protrusion, 41% had mucosal discoloration, 34% had rodent face, 20% had teeth spacing, and 8% had an open bite. In addition to genetic and ethnic influences, the significant differences in the frequency of TM manifestations between different studies can also be explained by the severity of the disease, course of treatment, sample size, patients' age, and the diagnostic standards used.

Mandibular Inferior Cortex

Since the change in the width (thickness) of the mandibular inferior cortex is an important feature of TM and related osteoporosis, it needs to be reviewed. Reynolds (1965) reported that the mandibular cortex is considered thin when its

MORBIDITY AND MORTALITY OF TM

The last decades have witnessed advances in understanding the pathophysiology of thalassemia disease and the introduction of novel treatments that improved the clinical outcomes of the disease. Thalassemia-related complications increase the morbidity and mortality of elderly patients, who now live longer than in the past. Complications include anemia, iron overload, infections, cardiomyopathy, pulmonary hypertension, extramedullary hematopoiesis, osteoporosis, thrombosis, splenomegaly, and endocrinopathies [3,5-10]. Iron overload is the main cause of morbidity and mortality related to heart disease, liver and pancreas dysfunction, impaired immune system, endocrinopathy, growth retardation, osteoporosis, and splenomegaly.

Regular blood transfusion is the mainstay of care for people with TM by improving anemia and suppresses ineffective erythropoiesis that leads to compensatory bone marrow expansion and skeletal changes. Blood transfusion can also increase childhood growth and prolong survival. Blood transfusions for children with TM usually begin in the first 2 years of age. Increased gut iron absorption occurs in non-transfused patients as a consequence of increased ineffective erythropoiesis. TM patients who receive irregular blood transfusions usually die before the second or third decade. However, this life-saving therapy is associated with numerous complications "second disease". In treating anemia, the accumulation of iron in the body tissues occurs. Iron overload becomes fatal in the second decade of life if not controlled [9,10,85,86]. The main cause of death is a cardiac failure due to iron overload. Infection is the second most common cause of morbidity and mortality in TM patients, becoming the main cause of death in Western countries [87-89]. Over the years, significant progress has been made in controlling iron-induced heart disease.

The survival and quality of life of patients with β-thalassemia in developed countries have improved markedly in recent decades [39,85,86,89]. Blood transfusion and iron chelation strategies are used to control the disease in the long term and improve the quality of life. In addition, advances in hematopoietic stem cell transplantation technology provide treatment options for certain patients. There is evidence that the survival time of the affected individual who receives regular blood transfusions and appropriate chelation therapy has exceeded 40 years of age [39,85,86]. In developing countries; modest availability of proper medical care, safe and adequate blood transfusions, high therapy cost, and poor compliance to chelation therapy remain major obstacles [12-14]. Early diagnosis and treatment of

thalassemia are essential to limit complications because the pathologic process increases with age.

Iron Overload

In healthy humans there are no controlled mechanisms for the excretion of excess iron, hence body iron is regulated at the sites of absorption, utilization, and recycling. In the physiological state, 1–2 mg of iron is absorbed from food sources daily and the same amount is excreted fecally. Iron overload of body tissues in TM with or without transfusion is fatal if not prevented or adequately treated. For patients who are not receiving transfusions, iron absorption increases several-fold depending on the severity of erythroid expansion [9,10,89]. Regular blood transfusions can double the rate of iron accumulations. Most clinical manifestations of iron loading do not appear until the second decade of life in patients with inadequate chelation. Among patients who received blood transfusions but did not undergo chelation therapy, symptomatic heart disease may appear within 10 years after the initiation of blood transfusion. The burden of transfusion iron overload is related to the frequency, amount, and duration of blood transfusion therapy. Lifelong blood transfusion, chronic hemolysis, and high intestinal absorption of iron can lead to increased iron deposition. This ultimately leads to cardiomyopathy, liver and pancreas dysfunction, and endocrine disorders [3,5,7-9,89]. Other complications of iron overload are hypersplenism, venous thrombosis, osteo-porosis, growth retardation, and failure of sexual maturation due to iron loading in the anterior pituitary [8, 9, 86].

Due to the lack of a mechanism for the human body to excrete excess iron, iron overload occurs in patients who are dependent on regular blood transfusion therapy [4,7,9,10]. According to the recommended blood transfusion protocol for TM, 100-200 mL RBCs per kilogram of body weight per year is equivalent to 0.32-0.64 mg iron/kg body weight/day or 116-232 mg/kg/year. If chelation therapy is not given, iron loading rates of patients' weight 20, 35, or 65 kg are averaging 3.4, 6.2, or 11.3 grams per year. The corresponding daily iron loads were 9.4, 16.8, and 30.9 mg, respectively [9]. Hence, unless chelation therapy is provided, blood transfusion therapy will increase the iron load too many times the normal level. Patients with poor blood transfusion can absorb about 3-5 mg/day or more of iron per day through the intestine, which means that an additional 1-2 grams of iron are absorbed every year [3,5,9]. Poorly transfused individuals can absorb around 3–5 mg/day or more of iron through their gut, Hemolysis and chronic hypoxia can further increase intestinal absorption. Paradoxically, despite the massive increase in the body's iron load, excessive iron absorption still exists.

One unit of blood transfusion (420 ml) contains approximately 200–250 mg of iron, and the human body cannot excrete more than 1–2 mg of iron per day [3,89]. Mainly through the shedding of the epithelial cells from the intestine. Patients who receive 25 units per year (every 2 weeks) will accumulate an average of 5 grams of iron without chelation therapy. In addition to the increasing iron absorption from the gastrointestinal tract. Excessive iron is toxic to human cells and may cause severe and irreversible functional damage. Iron overload eventually leads to the following sequelae: hypogonadism, (35–55% of the patients), cardiomyopathy (11.4%–15.1%), liver disease (21%), hypothyroidism (9–11%), diabetes (6–10%), heart failure (6.8%), arrhythmia (5.7%), hypoparathyroidism (4%), human immunodeficiency virus (1.7%) and thrombosis (1.1%) [3, 86, 90, 91].

Infection

Infection remains one of the major causes of morbidity and mortality in patients with TM. The prevalence of infection in patients with TM varies from 22% to 66% [86-89]. The mechanisms of increased susceptibility to infection in these patients include: (1) impaired chemotaxis and phagocytosis of macrophages and neutrophils, (2) alterations in the T- and B-lymphocytes,(3) decreased the number and activity of natural killer cells, (4) reduced the secretion of immunoglobulin (5) inhibit the function of the complement system [87-89,93,94]. Where infection is suspected, the main reasons to consider are splenectomy; transmission of pathogens by blood transfusion; iron overload; and iron chelation. Splenectomy plays an important role in susceptibility to infections [89,93-95]. The risk of death from infection after splenectomy ranges from 38% to 69% [95-97]. Patients who have undergone splenectomy are at higher risk of massive infection after bacteremia. The most frequent pathogens are *Streptococcus pneumonia, Hemophilus influenza, Klebsiella pneumonia, Neisseria meningitidis, Escherichia coli, and Yersinia enterocolitis* [87,88,93,95]. In the presence of excess iron, many of these organisms increase their virulence. Chronic hepatitis is caused by viral infections that cause hepatitis B and/or hepatitis C.

Overwhelming post-splenectomy sepsis is an emergency and requires immediate antibiotics treatment. Antibiotics include intravenous infusion of Cephalosporin (Cefotaxime, 2 grams every 8 hours or Ceftriaxone, 2 grams every 12 hours) combined with Gentamicin (5–7 mg/kg every 24 hours) or Vancomycin (1–1.5 gram every 12 hours) [96,97]. Children should receive pneumococcal and influenza vaccines after six months of age, and meningococcal vaccination after 2 years of age. Anti-pneumococcal vaccination and prophylactic antibiotics can prevent severe pneumococcal infections in the first 2–4 years after splenectomy. All

MANAGEMENT

At the first presentation, it is essential to obtain the social and medical history of the affected family to assess the pattern of inheritance and to provide counseling on the possible course of the disease, management, and the risk of having further thalassemic children. Management of patients with TM lay under the following headings: (1) Life-long blood transfusion to correct anemia and suppress erythropoiesis. (2) Chelation therapy balances the rate of iron accumulations resulted from a blood transfusion and inhibition of gastrointestinal iron absorption by increasing iron excretion. (3) Splenectomy may be necessary because an overactive spleen(hypersplenism) increases the need for blood transfusion and inhibit chelation therapy to control iron levels. (4) Management of iron overload that causes endocrinopathies, cardiac disease, and osteoporosis. (5) Control the infection caused by hypersplenism or splenectomy. (6) Bone marrow transplantation (BMT). Gene therapy offers a potential cure for β-thalassemia and would represent an ideal alternative to both conventional therapy and BMT [102,118-120]. The survival rate of TM has been significantly improved followed by the judicious use of blood transfusion and effective chelation therapy to control the iron accumulation caused by blood transfusion and associated with severe and lethal effects.

Splenectomy

The main function of the spleen is to filter blood. It has a variety of auxiliary functions in the body, including removing microorganisms and antigens from the bloodstream, removing old or damaged blood cells, producing antibodies (mainly immunoglobulin M), and conducting immune responses by detecting pathogens. The excessive function of the spleen in TM can cause splenomegaly, which worsens anemia by reducing the lifespan of the transfused RBCs and intensifies the need for blood transfusions, thus exacerbating the problems caused by iron accumulations. Many TM patients who rely on blood transfusions require splenectomy. The main therapeutic principles of splenectomy are: (1) Prevent the development of extramedullary hematopoiesis (production of blood cells) by increasing hemoglobin levels. (2) Prolong RBCs survival by reducing the number of RBCs removed from circulation. (3) Reduces the need for blood transfusions. (4) Decrease iron overload [9,100-102]. Splenectomy is recommended when: (1). The annual transfusion requirement is greater than 200–220 mL RBC/kg of body weight per year with a hematocrit of 70%. The normal hematocrit levels of children aged 6 to 12 years are 35% to 45%. (2). The annual blood need exceeds 1.5 times those of splenectomized patients [89,102]. Because of the risk of post-splenectomy

infection, splenectomy should delay until the age of 5 years or later [93,97]. Taher *et al.* [97] suggested that splenectomy may reduce the body's ability to scavenge toxic free iron species. The indications for splenectomy among patients with β-thalassemia are becoming increasingly restrictive.

Endocrinopathies

Endocrine dysfunction is a common and serious complication of TM, which requires prompt recognition and treatment. Delayed growth and pubertal development, abnormal gonadal functions, impaired thyroid, parathyroid and adrenal functions, diabetes, and disorderly bone growth are commonly encountered. Early detection and adoption of appropriate blood transfusion regimens, chelation therapy, and treatment of complications are the keys to management. Due to TM hypogonadism (40% to 80% of males), patients suffer from growth retardation, puberty failure, sexual dysfunction, and infertility [3-5,86]. These problems are caused by chronic anemia, excessive iron deposition in the pituitary gland and testes. Iron deposition on gonadotroph cells of the pituitary leads to disruption of gonadotropin, LH (luteinizing hormone), and FSH (follicle-stimulating hormone) production [3,89,106]. Delayed pubertal growth and sexual development may occur despite the timely initiation of iron chelation in early childhood. If pubertal changes have not developed by 13 years of age in females or 16 years of age in males, the use of gonadotropin-releasing hormone and gonadal steroids has been suggested [102]. Because hormonal treatment of pubertal disorders in thalassemia may associate with complications, each patient has to be assessed individually.

Blood Transfusion

Blood transfusion therapy is the main treatment for patients with severe β-thalassemia, usually starting around 2 years of age. Goals include correcting anemia, inhibiting bone marrow activity to produce ineffective erythropoiesis, delaying the development of splenomegaly, inhibiting the intestinal absorption of iron, promoting normal growth, and allowing normal physical activity [2,9,10,89]. In addition, regular blood transfusions can treat the hypoxic symptoms of anemia and maintain Hb levels at 13-14 g/dL after transfusion. Hb after blood transfusion prevents growth disorders, organ damage, skeletal deformities, and allows normal activity and quality of life [89,111,107]. However, Hb greater than 14-15 g/dL after blood transfusion has the risk of high viscosity and stroke. Before the first transfusion, patients' RBCs are typed for Rh and ABO antigens. Parents and first-degree relatives should not be blood donors for these candidates. Hepatitis B

vaccination should be given before transfusion therapy [102]. Currently, there is no vaccine against hepatitis C.

To start a blood transfusion, patients with TM should have severe anemia (Hb<7 g/dL) for more then two weeks. In addition, other factors associated with TM anemia and should be considered are facial changes, poor growth, large extramedullary hematopoietic function, bone expansion, and splenomegaly [3,5,9,107]. The frequency of blood transfusion is usually once every two to four weeks. Generally, the RBCs to be infused should not exceed 15 to 20 mL/kg body weight/day and infused at a maximum rate of 5 mL/kg/hour to avoid a rapid increase in blood volume. A moderate transfusion regimen may reduce iron loading in TM without producing an excessive expansion of erythropoiesis [120,121]. While regular transfusions greatly contribute to the quality and length of life of TM patients, they also leave the body with an iron overload.

Iron Chelation

Iron chelating therapy should be provided to all TM patients who require long-term blood transfusions to reduce iron load and prevent and/or delay complications related to iron deposition in the tissues. Iron chelation therapy doubles the life expectancy of transfusion-dependent TM patients [5,7,9,121]. This therapy balances the rate of iron accumulation in the blood transfusion by increasing iron excretion in the urine and faces. Patients who are pregnant or breastfeeding should avoid chelating agents. Ideally, chelating therapy should be started before clinically iron accumulates. Patients who have received multiple blood transfusions without adequate chelation can also be treated, but they may require an intensive chelation regimen [118]. Since chelating agents remove iron from the heart much slower than iron from the liver, prolonged intensive iron chelation therapy is usually required. The dose of an iron-chelating agent is determined by the presence or absence of cardiac iron overload, the rate of transfusional iron loading, and the body iron burden. The greater the rate of transfusional iron loading, the greater the dose of an iron chelator is needed to control the accumulation of iron. Patients whose iron load exceeds 7 to 15 mg iron per gram of liver are at increased risk of liver fibrosis, diabetes mellitus, and other complications, and require more intensive iron-chelation therapy.

Administration of a chelator usually starts at the age of 2-4 years that requires an infusion of 20- 25 RBC units, and the serum ferritin level is greater than 1000 μg/dL [3,5,9,24]. There are 3 types of iron-chelating agents, namely deferoxamine (Desferal®) parenteral administration and 2-orally administered chelators;

DENTAL CARE

Dental treatment of TM patients requires special attention because the patient may suffer from complications of the disease, such as heart and liver dysfunction, diabetes, weakened immunity, and post-splenectomy infections. Medical history is essential to provide adequate dental treatment and avoid complications due to disease or treatment. Most patients with thalassemia can safely receive routine dental treatment. However, for patients with a severe form of the disease, long-term surgery should be avoided. Prior to conduct an intensive dental procedure, a thorough medical history, and current medical status are required for general health assessment. This should include •Hb level. •chelating agents and other drugs such as antibiotics. •history of splenectomy. •patient prognosis. •life expectancy. Complex surgical treatment is contraindicated if blood transfusion and chelation therapy are not under control. Close contact with the hematology team must determine possible complications during extensive dental treatment and the necessary measures to determine safe outcomes. Treatment should never be initiated during a crisis unless in an emergency situation, and treatment should be designed to decrease infection and discomfort. Dental and medical practitioners and health care professionals, especially those working in multi-ethnic communities, need to understand the nature and source of this disease and its impact on general and oral health.

Patients who undergo splenectomy are susceptible to sepsis. To prevent bacteremia-causing dental treatment, prophylactic preoperative and postoperative antibiotics should prescribe. Any invasive dental procedures in these patients should be performed after a blood transfusion with a hemoglobin level of more than 10 g/dL. Antibiotic prophylaxis similar to that used for the prevention of bacterial endocarditis should be administered. That is, 50 mg/kg of amoxicillin (maximum dose 2 g) one hour before dental work. If the patient is sensitive to penicillin, 20 mg/kg of clindamycin (maximum dose of 600 mg) is the alternative regimen. Some of the medications to avoid are sulfa drugs, chloramphenicol, ciprofloxacin, doxycycline, and aspirin. Paracetamol is a safe alternative to aspirin. The radiographic absence of the inferior dental (alveolar) canal borders in many TM patients should be considered to avoid injury of the inferior alveolar nerve during surgical operations of the posterior mandibular teeth and implant placement. Elective surgery, such as removing asymptomatic teeth, should be avoided. Thalassemic patients are at risk of viral hepatitis due to blood transfusions from donors infected by the Hepatitis C virus. Thus, appropriate precautions should be taken by the dental team when these patients are to be treated.

Dental Caries and Periodontal Disease

Patients with TM are at risk for dental caries and periodontal disease, associated with poor oral hygiene and dental care negligence. Other factors of the high incidence of caries and/or periodontal disease in these patients are reduced salivary flow rate, lower level of salivary immunoglobulin, high count of pathogenic bacteria (Streptococcus mutans in caries and Actinomycetemcomitans in periodontitis), mouth breathing, malocclusion, malnutrition, underlying systemic condition, infection, and impaired immune system. Therefore, patients should be kept under an intensive preventive program with regular follow-up. In some cases, a three-month recall may be necessary. Patients need proper oral hygiene instructions and motivation, including brushing their teeth and using chlorhexidine rinses or gels. For children where manual dexterity is limiting, the use of electric brushes is recommended. Effective prophylaxis, fluoride therapy, and fissure sealant should be applied to minimize the future need for extensive dental procedures. Professional fluoride therapy should be provided at 3 months' intervals and fluoride varnish is the best choice for children under the age of 6 years. Due to the impaired immune function of these patients, the risk of infection after endodontic treatment should be assessed. Primary teeth with infected pulp should be removed, do not try pulp therapy. Extractions should perform under antibiotic coverage.

Orthodontic Treatment

Orthodontic treatment for the TM patient is strictly elective. These patients often have malocclusion or skeletal abnormalities. Correction of proclined maxillary anterior teeth and increased overjet may undertake to improve aesthetics, reduce susceptibility to trauma, avoid gingival inflammation, improve functional capacity and children's self-esteem. Orthodontic treatment should begin as early as possible concentrating on preventive and interceptive approaches. Orthodontic appliances should be appropriately designed to prevent irritation and bacterial infections of soft tissues. Due to the thin cortex and increased bone remodeling, less force should be applied. Because the teeth move faster than normal, it is necessary to closely follow up patients at short intervals between appointments. Smaller tooth size, short and spiky roots, and reduced dental arch dimensions in TM patients should be considered in planning orthodontic treatment. However, the disease may compromise the outcome of the planned treatment.

Anesthesia and Sedation

Most patients with TM can be treated normally using a local anesthetic as long as the dose is limited to one to two cartridges. Because of the possibility of impaired local circulation, a short procedure can be performed using an anesthetic without a vasoconstrictor. If the procedure requires long, profound anesthesia using 2% Lidocaine with vasoconstrictor epinephrine or adrenaline, 1:80,000 (0.012 mg) is preferred. If necessary, nitrous oxide/oxygen can be used. Conscious sedation is a technique in which the use of a drug or drugs produces a state of depression of the CNS, enabling treatment to be administered. Throughout the period of sedation, verbal contact with the patient is maintained.

Nitrous oxide/oxygen (N_2O/O_2) is widely accepted as a behavioral management technique for pediatric dentistry, usually using 30% nitrous oxide and 70% oxygen or 50/50 anesthesia intensity. It is a colorless, odorless gas of sweet smell, non-irritant, causing a feeling of euphoria. It is an effective analgesic/anti-anxiety drug that can cause depression in the central nervous system (CNS) and has little effect on the respiratory system. Nitrous oxide is quickly absorbed, and it can take effect and recover quickly within two to three minutes. It causes minimal impairment of any reflexes, thus protecting the cough reflex. Among other organizations, the American Academy of Pediatric Dentistry (AAPD), recognizes that nitrous oxide/oxygen inhalation sedation is a safe and effective technique to reduce anxiety, produce analgesia, and enhance effective communication between a patient and health care provider. Nitrous oxide is a weak general anesthetic. In general anesthesia, it is used in a 2:1 ratio with oxygen for a more powerful general anesthetic effect.

Midazolam (Versed®) belongs to the sedative class of benzodiazepines. Midazolam is one of the most commonly used drugs for conscious sedation in pediatric dentistry, an aid to behavior management techniques, a drug to manage seizures during dental treatment, and as premedication in general anesthesia. It is a powerful, short-acting hypnotic sedative that can cause drowsiness and reduces anxiety (anxiolytic). It also has anticonvulsant, amnestic (memory loss), and muscle relaxant properties. When taken orally, it is rapidly absorbed in the gastrointestinal tract, producing a peak effect of about 30 minutes, and has a short half-life of 1.5-2.5 hours. The half-life in children is lesser than in adults due to the fact that children have more active liver enzymes. In contrast to midazolam, the half-life of diazepam is 24 to 40 hours. Half-life refers to the time required for the plasma concentration of a drug to decrease to half of its original value. Oral midazolam in

PREVENTION PROGRAMS

Hemoglobinopathies are the most common monogenic disorders in humans, among them thalassemia constitutes a serious medical and public health problem in high prevalence regions. Hb disorders present a significant health problem in 71% of 229 countries. Over 330,000 affected infants are born annually (83% sickle cell disorders, 17% thalassemias). Hb disorders account for about 3.4% of deaths in children less than 5 years of age [12]. Screening for Hb disorders should form part of basic health services in most countries. Thalassemia is common in countries of the Mediterranean, Southeast Asia, the Middle East, the Indian subcontinent, and North Africa [12-14,139]. Patients with TM placed a burden on the healthcare systems in these countries and brought serious medical, social, and economic problems to the patients and their families. In North America and Northern European countries, the disease is traditionally rare. The flow of migration has led to an increase in the number of patients in the area. However, the COVID-19 pandemic has greatly reduced migration, but its long-term consequences remain to be seen. Although significant progress has been made in the treatment of β-thalassemia, many challenges still need to be overcome before global disease control can be achieved. Preventing the birth of new cases of thalassemia is considered the best way to control the disease. Detecting carriers of thalassemia and informing them of the risk and the possibility of reducing the risk will lead to a decrease in the number of births and deaths of children with the disease.

Implementing appropriate prevention programs, including premarital counseling, is essential for the transition from the treatment of children at risk to the prevention of childbirth. This allows individuals to receive information about their health and the potential health risks of their offspring. Prevention can be achieved through the following methods:

- Population education and awareness,
- Providing genetic counseling to the carriers and parents of children with thalassemia,
- Detection carriers through large-scale screening of high-risk communities,
- Prenatal genetic test [139,140-143].

Effective public education is the first step in any prevention program. The first attempts at large-scale and national prevention programs were adopted by Italian provinces, Greece, Cyprus, and Sardinia from the 1970s. The program is characterized by intensive education of the health personnel and the population at large, including secondary school and university students to raise their awareness

of the disease. It makes use of mass media, posters, and booklets. The information includes the genetics of the disease, the nature of the disease, clinical problems, treatments, complications, and life expectancy. Premarital thalassemia screening was carried out, as part of a school prevention programme. In the above-mentioned countries/regions, educational programs, screening, and genetic counseling for at-risk groups have greatly reduced the number of newborns with TM from 1:250 to 1:4000 [139,140]. The main prevention programs established in many countries in Europe, Asia, and Australia are often drawn from the experience of Sardinia.

If public education is provided, the knowledge and understanding of screening for carriers of thalassemia can be improved. Prior to testing, individual or population should be provided with appropriate information about thalassemia to determine whether to conduct genetic screening at the same time as counseling. Carrier screening is performed after obtaining informed consent. The World Health Organization guidelines (1998), stated that no compulsory genetic testing should be carried out [144]. Several countries, mostly Mediterranean and Arab countries, such as Cyprus, Iran, Saudi Arabia, UAE, Bahrain, Jordan, Palestine, Qatar, and other countries have passed laws that require all couples to be screened for hemoglobinopathies before marriage in order to restrict the spread of the disease. Genetic tests can be applied to individuals in the context of health care, or to populations in the context of public health programs. In many countries with limited resources, screening and prevention programs are not enough, and access to effective treatment is far from universal. Carriers can be detected by Hb electrophoresis and/or high-performance liquid chromatography [3,4,23,145].

Premarital Testing

The premarital screening and genetic counseling program aims to reduce thalassemia births in the following ways: 1. Prevention of at-risk marriages through discouragement during counseling. 2. Reduce or prevent congenital disorders caused by the mother-to-child transmission of genetic or infectious diseases. 3. Alleviates anxiety especially if there is a family history of certain genetic diseases or marriage within relatives. 4. Through proper diagnosis and consultation, the family's financial, physical, and psychological burden can be reduced. It has been suggested that screening can reduce the burden of thalassemia by reducing risky marriages and preventing up to 95% of births [146,147]. The programs can also be divided by timing testing in relation to pregnancy being either pre-pregnancy or in the early stages of pregnancy. There are more options available to a couple if screening has occurred before conception. Couples can decide to terminate their relationship, or they can choose to continue the prenatal diagnosis during the first-

trimester of pregnancy. If the fetus is affected by TM, they can choose to terminate the pregnancy [139,141-143]. Many countries do allow termination of pregnancy due to fetal abnormalities, including China, Cuba, Cyprus, India, Sri Lanka, and South Africa [148]. Iran conducts premarital screening for thalassemia and allows abortion in the first 16 weeks of pregnancy [149]. There are considerable differences in the attitude of people toward screening and for prenatal diagnosis and termination of pregnancy. Cultural, religious, ethical, and legal considerations must be considered in each country. In Muslim-majority countries, the analysis of abortion laws has proven to be a conservative approach. Among 47 countries, 18 countries legally allow abortion only in situations that threaten the life of pregnant women [150].

Strategies for Prevention

The best way to control the disease is to prevent the birth of new cases of thalassemia. In developing countries, there is a need for in-depth education of health professionals and the public in the field of preventive genetics, development of national plans for care and prevention, and the support from health organizations and funding agencies of these initiatives [139,151]. Strategies for prevention include [152]:

• Integrate community counseling and screening programs into primary health care. This requires the education and training of primary health workers.

• Educate the public by updating high school curricula and mass media education activities about local culture and religious beliefs.

• Strengthen human resources by updating medical and nursing college courses related to the practice of human genetics, as well as guidelines on how to deal with common genetic and congenital diseases.

• Initiation of population screening programs and national birth registries.

• Introduce new technologies and strengthen existing genetic services.

Cost of Treatment

Patients with severe β-thalassemia need life-long treatment to prevent and control the clinical consequences of the disease. The cost for the treatment includes a regular blood transfusion, chelation therapy, laboratory tests, and tests of heart,

SUMMARY AND RECOMMENDATIONS

Thalassemia syndrome is a group of inherited hemolytic anemia disorders that involve defects in Hb production. Severeβ-thalassemia (TM) is inherited *via* two mutated genes, one from each parent. It presents in childhood, usually between the ages of six months and one year. Children who do not receive TM treatment will die in their first decade, while those who receive irregular blood transfusions will usually die before the second or third decade. The main treatment for TM is regular blood transfusion at intervals of 2–4 week. This will treat anemia, suppress ineffective erythropoiesis (RBCs formation), enable children to develop, and prolong survival. Coupled with blood transfusions and iron overload, iron chelation is essential in the treatment of TM. Life-long care is needed, and financial support should be provided for appropriate treatment. Nowadays, autologous transplantation of genetically modified hematopoietic stem cells represents a novel therapeutic promise.

Based on current data, the following conclusions and recommendations can be drawn:

1. Patients with TM are at high risk for dental caries and susceptible to periodontal disease. Effective preventive measures should be taken to reduce the need for extensive dental procedures. These include periodic prophylaxis, fluoride application, fissure sealant, and oral hygiene instructions.

2. Reduction in tooth crown size and dental arches in TM patients has an impact on the occlusal relationships. The patient's tooth development and growth patterns are significantly delayed. These changes should be considered in planning orthodontic treatment and orthognathic surgery.

3. In the surgical operation of the mandibular posterior teeth, the lack of imaging of the inferior alveolar canal borders in many TM patients should be considered. Precautions must be taken to avoid damage to the inferior dental nerve.

4. TM patients with acute dental infections/abscesses should receive urgent dental care and antibiotic coverage, especially if they have had a splenectomy.

5. Patients who have had a splenectomy are at high risk of massive infection and bacteremia. Before the invasive procedure, antibiotic prophylaxis used for the prevention of bacterial endocarditis should be instituted.

6. Dental treatment of patients with thalassemia requires special attention, because the patient may suffer from complications of the disease; such as heart and liver dysfunction, infection, diabetes, decreased immunity, and infection. Prior to intensive dental treatment, close contact with the hematology team is required to determine potential complications.

7. The complications of TM increase with age. Early diagnosis and management allow a more favorable prognosis.

8. Successful management depends on regular blood transfusion, iron chelation, infection control, and therapeutic facilities. Compliance with chelation therapy is a key factor in the treatment of iron overload.

9. Children and adults with thalassemia should receive all recommended vaccinations, including influenza, pneumococcal, and meningococcal vaccines.

10. The cost of screening and prenatal diagnostic procedures is much lower than the cost of treating patients with thalassemia. Effective prevention strategies should be implemented in Arab countries.

11. Unless the marriage of thalassemia carriers (especially between relatives) isceased, public education and awareness of genetic diseases are strengthened, and premarital screening, genetic counseling, and prenatal diagnosis are provided, the prevention of thalassemia cannot be achieved.

ARABIAN GULF AND NEIGHBORING COUNTRIES

In the Gulf region, hereditary hemoglobinopathies, especially thalassemia and sickle cell disease, are common, causing great suffering to sick children and an economic burden on the healthcare system. This involves two main factors: (1) The consanguineous marriage, which is associated with a high prevalence of recessively inherited disorders. (2) Marriages at a young age and large family sizes, which increase the number of affected children. Obstacles to prevention and care initiatives include insufficient genetic knowledge in the health sector and a lack of public awareness of genetic risks and the possibility of preventing these disorders. These factors, combined with certain cultural, legal, and religious restrictions, limit the selective abortion of affected fetuses [142,151,152].

Iraq

In Iraq, there are 19 hereditary blood diseases centers, with a total of 13,500 patients. Services are provided free of charge, including regular blood transfusion and iron-chelating therapy. National guidelines for the management and prevention of hemoglobinopathies have been developed. The carrier rate of β-thalassemia in various regions of the country is between 3.7% and 4.5% [14,163,164]. In 2008, a five-year premarital screening, genetic counseling, and prenatal diagnosis (PND) program was implemented to identify carriers of hemoglobinopathies in the Kurdistan region of northern Iraq [163,165,166]. Screening is mandatory by law. A total of 102,554 individuals (51,277 couples) visiting a premarital center in Dohuk province between 2008 and 2012 were screened for carrier status and counselling. The main problems facing the program are the low public awareness of genetic diseases, the high rate of marriage among close relatives, the high cost of PND, and the short time between mandatory testing and actual marriage. In addition, some couples are not convinced by the results of the screening tests provided to them. Data on 198 high-risk couples showed that 90% of them continued their marriage plan, while 15% of married couples decided to receive PND in subsequent pregnancies. The premarital program managed to reduce the affected birth rate by 21% [165].

In Sulaimaniyah Province, a total of 108,264 people (54,132 couples) were screened for hemoglobinopathies. A follow-up survey was conducted on 130 couples suffering from β-thalassemia, and the results showed that almost all (98%) who were diagnosed through premarital screening chose to continue their marriage after counseling. The majority (76%) who underwent PND and had an affected fetus choose to terminate the pregnancy. According to reports, the number of

affected births has been reduced by 65% during the five years of the implementation of the plan [166]. Despite premarital counseling provided, the number of couples who decided to continue with their marriage arrangements is quite similar to that reported in Saudi Arabia (90%) and in India (99%) [166,167].

Saudi Arabia

In Saudi Arabia, a royal decree was passed in 2003 requiring mandatory premarital screening tests, but the decision to marry depends on the couple[10]. A study was conducted as a part of the National Premarital Screening and Genetic Counseling Program, which covered all the individuals who applied for a marriage license during the years 2004 and 2005. Of the total 488,315 individuals screened, 4.2% had a sickle cell trait, and 3.2% had a thalassemia trait [167]. Between 2004 and 2009, blood samples were obtained from the couple for genetic counseling. Among the 1,572,140 men and women examined, 4.5% were positive for sickle cell disease (carriers or cases) and 1.8% were positive for β-thalassemia. At the end of the program, the frequency of at-risk couples was reduced by about 60%, while the frequency of voluntary cancellation of marriage proposals increased by more than 5 times [168]. Between 2011 and 2015, a study was conducted on 12,30,582 people seeking marriage certificates. The results showed that the prevalence of β-thalassemia per 1,000 people was 13.6 (12.9 traits and 0.7 TM) and the incidence decreased from 24.2% in 2011 to 12% in 2015% [169]. Findings suggest that the program's objective of decreasing high-risk marriages needs further improvement of health education for the public, more efforts in counseling high-risk couples, and changes in the strategy of screening timing in regard to marriage plans [167,168].

United Arab Emirates

In the United Arab Emirates (UAE), a decree was issued by Sheikh Hamdan Bin Rashid AI-Maktoum (1994), for establishing a thalassemia center. The health authority launched a nationwide campaign to promote premarital screening under the slogan “Emirate free of thalassemia” by 2012. Premarital screening is mandatory, but the final decision depends on the couples. After consultation, about half of the carrier couples chose to get married, while others decided to separate. Compared with the time before the prevention program was adopted, the number of affected births was reduced by half [17]. Termination of pregnancy with thalassemia is not practiced as a solution for the prevention of thalassemia in the UAE. In an interview of 100 couples about their attitudes toward genetic counseling, Al-Gazali [170] reported that almost half preferred consanguineous

marriages and only 10% agreed with prenatal diagnosis and abortion, while 75% agreed with carrier screening and preconception diagnosis in affected families.

A retrospective study conducted in Ras Al Khaimah showed of the 17,826 individuals screened, 4.0% were positive for hemoglobinopathies and 1.05% had β-thalassemia [171]. Baysal [172] studied the DNA of 472 newborns related to UAE mothers and other age groups. He found that the frequency of β-thalassemia gene in the nationals was 8.3%, one of the highest in the Gulf region, and the gene mutations are more than in countries of the Mediterranean, Europe, Southeast Asia, South America, and North Africa [172]. In conclusion, Al-Gazali (2005) stated that "Effective genetic counseling in this community requires an informed educated population and introduction of carrier screening and preconception diagnosis in affected families" [170].

Oman

According to the Ministry of Health, 75% of patients visiting the healthcare centers suffer from blood-inherited disorders. A survey conducted on 6342 children under 5 years of age, showed that the prevalence of sickle cell trait was 5.8%, and the prevalence of severe β-thalassemia was 2.2% [173]. Another study showed that in the population of 1.5 million in 1995, there were 1757 cases of sickle cell anemia and 243 cases of β-thalassemia major [174]. Umbilical cord blood samples of 7,837 newborns were analyzed for complete blood counts, Hb profile, and liquid chromatography. Results showed that β-globin abnormalities accounted for 9.5% of the samples with 4.8% sickle cell trait, and 2.6% β-thalassemia trait [175].

Bahrain

In 2004, the King of Bahrain announced a law that made pre-marital counseling mandatory. It was also declared that after receiving counselling sessions, the marriage and reproduction choices are left for the couple to decide. A Ten-year study was conducted on 60,000 students in the 11^{th} grade from 1999 to 2008. The blood samples were collected and Hb electrophoresis and high-performance liquid chromatography (HPLC) were used to measure and identify the different types of Hb abnormalities.The average prevalence rates of β-thalassemia trait and TM are 3.5% and 0.032%, respectively, which is slightly lower than those of other Gulf countries [176]. A retrospective study of 1,378 records of 9-month-old infants showed that the most common type of hemoglobinopathy was alpha-thalassemia (18.5%), followed by sickle cell trait 11.6% [177].

GENETIC DISORDERS AMONG ARAB POPULATIONS

The Arab countries in the world are also known as the Arab world, or Arab nations and are comprised of 22 countries that are part of the Arab League and located in Africa and Asia. These nations have a total area of over 5 million square miles (12.9 million square kilometers). The total population of all countries is 423 million. Among these countries, Egypt is the most populous country with a population of more than 90 million. In the area, Algeria is the largest Arab country with a total area of 2,381,750 square kilometers. Bahrain has the smallest area , with an area of only 758 square kilometers. The majority of the citizens of Arab countries follow the religion of Islam. About one-quarter of the world's Muslims are Arabs. Throughout the nations, the adult literacy is under 77%, and the female literacy rates are much lower than that of men[https://worldpopulationreview. com/country-rankings/arab-countries].

The available evidence shows that congenital and genetic diseases are more common in Arab countries than in developed countries and account for a large proportion of infant mortality, morbidity, and disability in these countries [20,189-191]. The Arab population is characterized by large family size, high maternal and paternal age, and a high level of inbreeding with consanguinity rates in the range of 25-60% [19-21]. Certain disorders are common in the Arab world, including haemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency. Different congenital malformations are caused by recessive genes and several inborn metabolic disorders. The increase in the incidence of hereditary diseases is mainly due to higher rates of inherited blood disorders and other autosomal recessive diseases. Among Arabs, the carrier rate of β-thalassemia is 2–15%, α-thalassemia is 2–50%, and sickle cell disease is 0.3–30% [20,190,191]. Arab populations have their "own" genetic disorders, both universal and particular and many of the genetic disorders in Arabs are confined to a country or region [191]. Nearly, one-third of the genetic disorders in Arabs result from congenital malformations and chromosomal abnormalities, which are also responsible for a significant proportion of perinatal and neonatal deaths. High fertility rates together with increased consanguineous marriages in Arab tend to increase the incidence of genetic and congenital abnormalities [20,148,152]. Of the six World Health Organization (WHO) Regions, the highest rate of severe congenital disorders and genetic diseases is found in the Eastern Mediterranean region, with affected children over 65 per 1,000 live births as opposed to 52/1,000 in Europe, North America, and Australia [193]. Of the 5.2 million births in the European Union (EU) each year,

approximately 104,000 (2.5%) will be born with congenital anomalies. Down syndrome accounts for about 8 % of all congenital anomalies.

The first known category of genetic conditions is caused by chromosomal abnormalities. Almost one-third of Arab genetic diseases are caused by chromosomal abnormalities. The most common example is trisomy (triplicate)of chromosome 21 (Down syndrome, DS). According to the WHO, the estimated incidence of DS is between 1 in 1,000 to 1 in 1,100 live births worldwide. In western countries, the incidence of DS is 1.2–1.7 per 1000. A higher incidence rate of DS has been reported in Arab Gulf countries ranged from 1:319 in Dubai to 1:581 in Kuwait [Center for Arab Genomic Studies/Dubai –2013]. Besides the above-mentioned Arab family structure, factors that contribute to DS incidence in this region are the relatively high proportion of births to older mothers, and partial or complete lack of prenatal detection, which can aid parental decisions to terminate pregnancies with DS fetuses. Up to 50% of children with Down's syndrome are born to mothers aged 40 or over. In the US, 67% of pregnancies with DS are terminating. The second category of genetic diseases is caused by major mutations or highly penetrant mutations, called monogenic diseases (single-gene diseases or Mendelian diseases). There are about1,500 single-gene diseases in which genetic defects have been identified [191-194]. A review of the molecular basis of β-thalassemia in various Arab countries revealed that there are 52 mutations, most of which are from the Mediterranean and Asia. The factors that contribute to the etiology of congenital malformation include single-gene disorders, chromosome abnormalities, multifactorial inheritance, and environmental factors [192,195-197].

Monogenic disorders are classified into three main categories: dominant, recessive, and sex (X) linked. They have severe clinical manifestations, high morbidity, and early death. Approximately 30% of children with congenital or genetic diseases may die in infancy, and a similar number of children will have chronic severe disabilities. Autosomal recessive disorders are responsible for a great deal of infant mortality, morbidity, physical and mental handicaps in Arab countries [194-197]. Teebi and Farag (1997), described genetically transmitted diseases among Arabs as follows autosomal recessive inheritance (61%), autosomal dominant (28%), and X-linked traits (6%) [194]. Later, Teebi (2010) [191] compiled a list of syndromes in the Arab population containing 160 syndromes compared with 113 syndromes in 1997. The inheritance of these syndromes is 133 (83%) autosomal recessive, 27 (17%) autosomal dominant, and 5 (3%) X-linked.

Consanguinity itself does not cause genetic disease; it only increases the chance that reproduction will occur between two carriers for the same recessive genetic

diseases. Al-Gazali *et al.* (1997) found that children of consanguineous parents are more likely to enter into consanguineous marriages than children of non-consanguineous parents [196]. Hamamy *et al.* (2007) stated that the offspring of first-cousin parents were significantly more prone to marry their relatives than the offspring of non-consanguineous parents, with rates of 25.3% and 17.1%, respectively [181]. Empirical studies have shown that the incidence of morbidity in first cousin offspring is 7.5% higher than that of offspring from unrelated couples [193]. Birth defects in developing countries are >70/1000 live births, while in Europe, North America, and Australia, birth defects are <52/1000 live births [148]. In the Arabian Gulf countries, congenital malformations are the second leading cause of infant death (2.1–19.2 deaths/1,000 people) compared with the world average (8.3 deaths/1,000 people) [189,191]. Major birth malformations of 7.9/1000, 12.5/1000, and 24.6/1000 were registered in the UAE, Kuwait, and Oman, respectively [20,194,197]. Al-Talabani *et al.* (1998), surveyed 24,233 births in UAE for the presence of major congenital malformations. Of the total births, 401 babies (16.6/1000) had a major malformation, live births (15.6/1000), and stillbirths (135/1000). The perinatal mortality was 406/1000. Classification of 401 malformed infants by mode of inheritance showed the following: chromosomal anomalies (19%), single-gene disorder (24%), multifactorial disorders (26%), sporadic conditions (26%) [198].

The factors leading to the high incidence of congenital and genetic disorders in Arab countries are:

- High fertility rate (1.7–6.6 children born/woman) compared to the world average (2.6 children born/woman).

- High rate of consanguinity marriages, particularly the first-cousin. The risk of birth defects in first-cousin marriages is estimated to be 2–2.5 times the general population rate.

- Services for the prevention and control of genetic disorders are restricted by certain cultural, legal, and religious limitations on selective termination of pregnancy of malformed fetus.

- The rate of children with Down's syndrome in some Arab countries exceeds the 1.2–1.7 per 1000 typical for western countries. This may be related to the relatively high proportion of births to older mothers in the region.

● Insufficient public health measures to prevent congenital and genetic diseases coupled with deficiency in health care before and during the pregnancy [20,152].

Pre-implantation genetic diagnosis is desirable in Arab countries, as it does not involve the decision to terminate the pregnancy. A study in the UAE found that most people are in favor of this type of prevention [199]. The decision to terminate an affected fetus is influenced by a variety of factors, including the country's laws and health system, parental level of education, socioeconomic status, religious and cultural beliefs. Many religions do not prohibit the termination of pregnancy for medical reasons, providing termination be performed in the early pregnancy [152,181,186]. In Islam, the fetus is believed to become a living soul after 120 days gestation, and abortion after that point is viewed as impermissible. Several Arab countries including Saudi Arabia, Jordan, UAE, Bahrain, Kuwait, Qatar, Lebanon, Palestine, and others, allow pregnancy termination within the first 120 days after conception. This can be done if there is no doubt that the fetus is affected by severe malformations and is incompatible with life after birth, or there will be severe disability and suffering that is unsuitable for treatment. It is permitted after 120 days when continuing the pregnancy would risk the mother's life. In these countries, the termination of pregnancy with thalassemia is not practiced due to religious restraints. Only Tunisia and Turkey allow women to have an abortion on demand during the first trimester. In Egypt, the highest Islamic council (Al-Azhar) issued a religious edict permitting unmarried women that are victims of rape access to abortion even after 120 days.

In the United Kingdom, for example, antenatal testing for fetal abnormalities is offered to all pregnant women, but most abnormalities are not detected until after 14 weeks of pregnancy. Screening tests for Down's syndrome can be offered at 11-14 weeks of pregnancy, and a detailed ultrasound examination of the fetus at 18-20 weeks. When an abnormality is detected using ultrasonography or biochemical tests, a woman may choose abortion. This can be performed by either surgical or medical methods. Surgery is safer and preferred by women in the second trimester [BMJ 2013;347:f4165]. Religion plays an important role in a patient's bioethical decision to have an abortion as well as in a country's abortion policy. Roman Catholicism takes a strict anti-abortion position, but this strictness only dates to 1930. Jewish tradition allows for abortion for the sake of the mother because there is no soul in the first 40 days, and even in the latter stages of pregnancy. Buddhist belief in reincarnation, makes Buddhists oppose legal abortion.

CONCLUDING REMARKS

Thalassaemia is one of the most common genetic disorders worldwide and presents significant public health and social challenges in areas where incidence is high. The manifestations of the condition are modulated by several genetic, racial, and environmental factors. Thalassemia is an autosomal recessive inheritance of chronic hemolytic anemia. Among thalassemia types, thalassemia major (TM) is associated with the most severe clinical changes and life-threatening risk. TM leads to serious medical, social, psychological, and economic problems for patients and their families as well as budget and care burden for the public health services. Children with TM have a significantly higher incidence of dental caries and periodontal disease. Only one-fifth have no caries and more than 90% of the patients have gingivitis. The tooth crown size of TM patients is significantly reduced. The maxillary and mandibular dental arches are short and narrow. Patients have skeletal/dental Class II malocclusion. The pallor of oral mucosa and yellowing of the skin are characteristics of underlying chronic anemia.TM children and adolescents suffer from short stature and underweight. Their tooth development is significantly delayed. The orofacial manifestations of TM are numerous and intense. They are due to intense hyperplasia of the bone marrow and expansion of the marrow cavity in response to severe hemolytic anemia, chronic hypoxia, and ineffective erythropoiesis. Regular blood transfusion is the mainstay of care for people with TM by improving anemia and suppresses ineffective erythropoiesis. Manifestations of TM increase with age. Early diagnosis and management allow a more favorable prognosis and minimize complications.

The Arab population has specific genetic diseases. Autosomal recessive genetic diseases are important causes of infant morbidity and mortality, congenital malformations, metabolic disorders, and physical and mental impairments. Hemoglobinopathies, among them thalassemia, are the most common genetic diseases in the Gulf countries. The high consanguinity rate of marriages and large family structure in Arab society are the reasons for the frequent occurrence of autosomal recessive diseases. The best way to control the disease is to prevent the birth of new affected thalassemia cases. Prevention of thalassemia cannot be achieved unless the marriage of thalassemia carriers (especially between relatives) is terminated, public education and awareness of genetic diseases are strengthened, and pre-marital screening, genetic counseling, and prenatal diagnosis are provided. Today, all countries are fighting against the COVID-19 pandemic, and blood-dependent thalassemia patients may face severe blood shortages in their blood

banks due to a shortage of donors. Due to increased exposure in crowded hospitals and weak defense systems, these patients are at risk of contracting COVID-19.

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Faiez N. Hattab graduated from College of Dentistry University of Baghdad in 1968 with a BDS degree. In 1983, he received his Ph.D. (Odont. Dr) degree in cariology from Karolinska Institute, Faculty of Odontology, Stockholm, Sweden. Then worked as a researcher in the department of cariology and conservative dentistry. In 1985, he served as a senior researcher in the department of pediatric dentistry at the Prince Philip Dental Hospital, Hong Kong University. From 1987 to 1992, he became an associate professor, then a chairman of Restorative and Pediatric Dentistry at Jordan University of Science and Technology (JUST), Irbid, Jordan. In 1988, he was invited by the David B. Kriser Dental Center of the New York School of Dentistry to set up a fluoride chemistry laboratory and supervise MSc students. From 1993 to 1995, he worked as a professor of restorative dentistry at the faculty of dentistry of the University for Medical Sciences, Tripoli, Libya, and then as a part-time professor of pediatric dentistry at JUST. From 2000 to 2003, he served as the head of the department of dentistry at the Ministry of Public Health and Senior Consultant of Pediatric Dentistry at Hamad Medical Corporation in Qatar and then did private practice until 2013. He has published over 100 full-length articles, abstracts, and chapters on clinical and basic research in international dental and medical journals. In 2002, he received the E.W. Borrow Memorial Award from the International Association for Dental Research (IADR) designated to promote children's oral health. His main research and clinical publications are on fluorides, dental materials, oral pathology, pediatric dentistry, caries prevention, epidemiology, etc. He is the first person to publish a series of articles on the dental and orofacial characteristics of thalassemia in Jordanians. Dr. Hattab is a member of IADR and the European Organization for Caries Research (ORCA). Since 2015, he has been a visiting professor in Germany.