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Supplementary appendix

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SYNOPSIS OF MAJOR CHANGES

Compared to 2008 consensus - Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference, PMID 18671700:

1. Nomenclature
 - a. Previously classical and non-classical DBA / and clinical remission
 - b. Now DBA syndrome (to account for individuals without anemia, or atypical presentations). Use of ‘treatment-independence’ rather than remission in patients with count normalization.
2. Diagnostic criteria
 - a. Previously diagnostic and supporting (major and minor) criteria
 - b. Now simplified: 1 of 2 diagnostic criteria based on genetics and phenotype
3. Major role of genetics
 - a. Previously 6 genes (*RPS17*, *RPS19*, *RPS24*, *RPL5*, *RPL11*, *RPL35A*), in ~50% patients
 - a. Now 26 genes in ~80% patients and new genetic classification established
2. Hemoglobin prior transfusion
 - a. Previously 8g/dL
 - b. Now ≥ 9 -10g/dL or a higher level at which the patient is asymptomatic, independent of age across life span
3. Steroid treatment – starting rules
 - a. Previously when Hb 9-10g/dL (typically 1-2 weeks after last transfusion)
 - b. Now timing independent of last transfusion
4. Steroid treatment – definition of non-response
 - a. Previously when Hb <8g/dL
 - b. Now when Hb <9g/dL
5. Steroid treatment - maximum maintenance dose
 - a. Previously prednisone 0.5mg/kg per day or 1.0mg/kg alternate days
 - b. Now prednisone 0.3mg/kg per day or 0.6mg/kg alternate days
6. Chelation therapy – starting rules
 - a. Previously when liver iron content 6-7mg/g or ferritin 1000-1500 μ g/l
 - b. Now after 10 transfusions or evidence of iron load (infants: wait until after first failed steroid trial)
7. Chelation therapy – drugs
 - a. Previously deferoxamine and deferasirox
 - b. Now deferoxamine and deferasirox (first line or second line as combination) and deferiprone (third line)
8. Hematopoietic stem cell transplantation – donor choice
 - a. Previously only HLA-matched related (family) donors
 - b. Now addition of HLA-matched unrelated donors as comparable donor choice
9. Toxicity monitoring and surveillance
 - a. Previously general statements
 - b. Now with specific recommendations according to age and therapy status
10. Cancer risk
 - a. Previously rudimentary knowledge not allowing to make recommendations
 - b. Now specific recommendations based on evidence from registries (including new recommendation on colorectal cancer screening starting age 20 years old)

METHODS

Panel composition

An international task force of content experts consisting of 53 representatives from 27 countries who are recognized key opinion leaders in clinical management and diagnosis of DBA and ribosome research was appointed by the leaders of the European DBA (EuroDBA) Consortium and the DBA Registry of North America and met for the first time in person in 2014 in Freiburg, Germany. The panel, consisted of clinical providers collectively caring for >2500 children, adolescents, and adults with DBA syndrome, including pediatric hematologists and oncologists, pathologists, endocrinologists, geneticists, and experts in transfusion medicine, hematopoietic stem cell transplantation (HSCT), iron management, adult medicine, in addition to researchers in ribosome biology and patient group representatives. At the first meeting in 2014, clinically relevant discussion items were selected (see below). After 2 additional meetings in Europe 2015 (Vienna, Austria) and 2017 (Freiburg, Germany), the task force met for a 4th time in the Atlanta USA in 2018 to agree on the final items and develop a final structure of the consensus manuscript. The manuscript was refined through continued discussion at 4 additional virtual meetings between 2019 and 2022 resulting in this international guideline document.

Search strategy and consensus methodology

We sourced all publications on PubMed database (<https://pubmed.ncbi.nlm.nih.gov>) through 30th June 2022, with the relevant search terms (including but not limited to: Diamond Blackfan anemia, congenital hypoplastic anemia, congenital anemia, pure red cell aplasia, bone marrow failure, congenital abnormalities, hematopoietic stem cell transplantation, transfusion, steroids, prednisone, chelators, deferoxamine, deferasirox, deferiprone, iron overload, liver iron content, heart iron, MRI, cancer risk, colorectal cancer, osteosarcoma, MDS, AML, cancer screening, toxicity, long-term management, surveillance) and made use of unpublished observations and updates from participating experts, particularly those from national registries. We took into account the expertise and experience of the participants in addition to published evidence.

The modified Delphi technique employed in this study involved a systematic, multi-round process designed to achieve consensus among an expert panel.¹⁸ At an initial face-to-face meeting, we formed separate working groups focused on diagnosis, therapies, and surveillance in children and adults. In the first Delphi round, we conducted an extensive literature review and synthesis of existing data on the topic, which informed the development of a list containing key discussion items and claims for each working group. Each member of the expert panel independently provided judgments and critiques on each item. In subsequent iterative rounds, we had additional meetings and rediscussed the list items, with the goal of obtaining consensus, defined as >85% agreement on each item. This process continued until consensus was reached on most items. However, there were a few items where agreement remained below the 85% threshold; these areas of non-consensus are transparently acknowledged and discussed in the manuscript. Overall, the modified Delphi technique enabled systematic convergence of expert opinions on this complex topic through structured, iterative data collection and discussion within each focused working group.

Evidence level grading

Both levels of evidence A and B (data from randomized trials, meta-analyses, or large non-randomized studies) are lacking in DBA syndrome. Because of that and due to the rarity of disease, level of evidence C (expert consensus statement, retrospective analyses, and registry data) can be used for guideline development on DBA syndrome. The task force sourced published work (level of evidence C) and made use of expertise and clinical experience of the participants and unpublished observations, in particular those from national registries (level of evidence C).

GENES ASSOCIATED WITH DBA SYNDROME AND GENETIC PHENOCOPIES

Gene symbol	Inheritance	Chromosome location	New protein symbol	Approximate frequency	References
DBA SYNDROME: RIBOSOMOPATHY¹					
Small ribosomal subunit (11 genes)					
<i>RPS7</i>	AD	2p	eS7	< 1%	107
<i>RPS10</i>	AD	6p	eS10	3%	54
<i>RPS15A</i>	AD	16p	uS8	<1%	108
<i>RPS17</i>	AD	15q	eS17	1%	109
<i>RPS19</i>	AD	19q	eS19	25%	110
<i>RPS20</i>	AD	8q	uS10	< 1%	57,111
<i>RPS24</i>	AD	10q	eS24	2.4%	112
<i>RPS26</i>	AD	12q	eS26	6.6%	54
<i>RPS27</i>	AD	1q	eS27	< 1%	113
<i>RPS28</i>	AD	19p	eS28	< 1%	114
<i>RPS29</i>	AD	14q	uS14	< 1%	115
Large ribosomal subunit (13 genes)					
<i>RPL4</i>	AD	15q	uL4	< 1%	116
<i>RPL5</i>	AD	1p	uL18	7%	55
<i>RPL8</i>	AD	8q	uL2	< 1%	117
<i>RPL9</i>	AD	4p	uL6	< 1%	13,54
<i>RPL11</i>	AD	1p	uL5	5%	55
<i>RPL15</i>	AD	3p	eL15	< 1%	32,118
<i>RPL17</i>	AD	18q	uL22	< 1%	15
<i>RPL18</i>	AD	19q	eL18	< 1%	119
<i>RPL26</i>	AD	17P	uL24	< 1%	120
<i>RPL27</i>	AD	17q	eL27	< 1%	113
<i>RPL31</i>	AD	12q	eL31	< 1%	42
<i>RPL35</i>	AD	3q	uL29	< 1%	119
<i>RPL35A</i>	AD	9q	eL33	3%	121
Ribosomal protein chaperones (2 genes)					
<i>TSR2</i>	X	X		< 1%	114
<i>HEATR3</i>	AR	16q		< 1%	59
DBA SYNDROME OTHER²					
<i>GATA1</i>	X	X		< 1%	23,122-124
<i>TP53 (GOF)</i>	AD	AD		< 1%	24,25
CANDIDATE GENES³					
<i>RPS11</i>	AD	19q	uS17	< 1%	47
<i>RPL3</i>	AD	22q	uL3	< 1%	
<i>RPL10</i>	AD	X	uL16	< 1%	
<i>RPL10A</i>	AD	6p	uL11	< 1%	
<i>RPL19</i>	AD	17q	eL19	< 1%	
<i>RPL34</i>	AD	4q	eL34	< 1%	
<i>RPL0</i>	AD	12q	uL10	< 1%	
GENETIC PHENOCOPIES⁴					
<i>ADA2</i>	AR	22q11.1			27,29,43
<i>EPO</i>	AR	7q22.1			26

¹ Bona fide ribosomopathy genes validated functionally (ribosomal biogenesis defect or presence of somatic genetic rescue).

² Genes affecting pathways implicated in DBA syndrome and associated with hyporegenerative anemia.

³ Considered putative due to lack of studies demonstrating impaired ribosomal biogenesis.

⁴ Diseases with different pathomechanisms that can manifest with pure red cell aplasia.

Abbreviations: AD, autosomal dominant; X, X-linked recessive; AR, autosomal recessive; GOF, gain-of-function

COMMON CONGENITAL ABNORMALITIES ASSOCIATED WITH DBA SYNDROME

ORGAN SYSTEM	Frequency, median (range)	FINDINGS
Any type	54.4% (40.6-71.8)	(Including short stature, small for gestational age/intrauterine growth retardation)
Craniofacial and neck	21.6% (14.5-25) <i>Cleft palate: 4.26% (3.5-5.8)</i>	Hypertelorism, microcephaly, micrognathia (Pierre-Robin), microtia, broad flat nasal bridge, epicanthus, cleft lip, cleft palate, shorted/webbed neck, Sprengel deformity, Klippel-Feil deformity, low set ears, prominent ears, low hair line, ptosis, mandibulofacial dysostosis (Treacher-Collins syndrome phenocopy)
Cardiac	11.6% (6.9-15)	Ventricular septal defect, atrial septal defect, coarctation of the aorta, tetralogy of Fallot, bicuspid aortic valve, pulmonary stenosis, anomalous venous return, other complex cardiac defects
Thumb and skeletal	18.5% (17.9-19) <i>Thumbs: 7.6% (6-9.2)</i>	Thumb (absent, atypical, duplex, bifid, triphalangeal), flat thenar eminence, polydactyly, syndactyly, absence of radial artery, acetabular dysplasia, pectus excavatum
Urogenital	10.7% (6.3-19.5)	Absent or horseshoe kidney, duplicated collecting systems, hypospadias, inguinal hernias
Ophthalmological	Rare	Congenital glaucoma or cataracts, strabismus
Skin	Rare	Café au lait spots, congenital nevi, hemangioma, dermatofibroma
Neurodevelopmental	3% (1.3-4.6)	Learning difficulties, mild to severe developmental delay

Data on frequency are from DBA syndrome registry papers cited in the manuscript.

SUMMARY OF CLINICAL FEATURES IN PATIENTS WITH DBA SYNDROME

	INTRINSIC (DISEASE RELATED)	THERAPY RELATED
Hematologic	Macrocytic anemia with reticulocytopenia Leukopenia, neutropenia Thrombocytopenia Thrombocytosis (infants) Hypocellular marrow (mostly in adults, sometimes in children)	Alloimmunization with subsequent increased transfusion requirement Agranulocytosis (DFP)
Immunologic	Lymphocytopenia Decreased B-cell numbers Hypogammaglobulinemia Recurrent infections	Port catheter infections Transfusion-related pathogens Viral infections (steroids) Lymphocytopenia (steroids) Infections: campylobacter and other bacteria (associated with iron overload), yersiniosis, mucor mycosis (exacerbated by DFX)
Endocrinologic	Intrauterine growth restriction Failure to thrive Short stature Congenital abnormalities	>50% patients experience endocrine problems related to steroids and iron overload: <ul style="list-style-type: none"> • Adrenal insufficiency • Sex hormone insufficiency • Growth hormone dysfunction • Hypogonadism • Thyroid and parathyroid problems • Pancreatic insufficiency, diabetes mellitus
Orthopedic	Short stature Congenital abnormalities Osteosarcoma (osteogenic sarcoma)	Osteopenia and bone fractures (steroids)
Hepatic, Urogenital, Cardiac	Congenital abnormalities	Liver toxicity (DFX) Liver cirrhosis (iron) Cardiomyopathy with arrhythmias (iron) Nephrotoxicity, phosphate loss (DFX) Urinary stones (DFX, DFO)
Gastrointestinal	Colitis	Diarrhea, esophagitis, nausea (DFX)
Otolaryngologic, ophthalmologic	Congenital abnormalities	Cataract (steroids, DFX, DFO) Ototoxicity (DFO, DFX)
Neurologic and psychosocial	Developmental delay	High psychosocial burden from chronic illness
Oncologic	Cancer risk: MDS, osteosarcoma, colorectal cancer, and other cancers	Increased risk after HSCT
Obstetric	High risk pregnancies	Infertility (iron overload, HSCT)

Abbreviations: DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; HSCT, hematopoietic stem cell transplantation.

PARVOVIRUS B19 TESTING

In individuals with normal red blood cell turnover, short interruption of erythropoiesis by Parvovirus B19 (B19) infection does not lead to anemia, however in infants and patients with chronic hemolysis or immunodeficiency state, severe anemia can develop. Modern diagnostics of B19 infection usually include the combination of serology (B19 IgG and IgM antibodies in blood) and PCR for B19 DNA in blood or BM. Morphologically, BM aspirates show no mature erythroid precursors and with characteristic giant pronormoblasts at time of acute infection. In infected individuals, the positive rates of parvovirus B19 genome were shown to be significantly higher in the bone marrow (22%) vs. peripheral blood cells (0.8%).¹²⁵ B19V infection is usually self-limited, resolving in days to weeks. However, B19 DNA can be found by PCR in 2% of healthy individuals in the BM (but not in blood) despite seroconversion after previous infection. Thus, persistency of B19 DNA may represent both infectious virus and residual DNA from remote infection.¹²⁶

RECOMMENDATIONS FOR CHELATION THERAPY

	DEFEROXAMINE, DEFERRIOXAMINE (DFO)	DEFERASIROX (DFX)	DEFERIPRONE (DFP)
Indications	First line: DFO or DFX (off label in children <2 years old ¹) Second line: switch between or combine both <ul style="list-style-type: none"> • Start after 10 transfusions or evidence of iron load (transferrin saturation >60%, serial ferritin >500ng/ml) • Infant with DBA: wait until after first failed steroid trial, then start with low dose and close monitoring 		Third line in patients with cardiac iron overload or failure /intolerance to other chelators First line in patients with severe cardiac iron overload or cardiac failure (in combination with DFO)
Formulation	Subcutaneous (SQ) or intravenous (IV): 500mg/vial or 2 g/vial	a) film-coated oral tablet or granules (90, 180, 360mg); b) dispersible oral tablet (125, 250, 500mg)	Oral tablet: 500mg, 1g Oral syrup: 100mg/ml
Standard dose	30-60mg/kg/day (max 30mg/kg/day in children <3 years), as (10-)12h SQ infusion 5-7 days/week or 24h continuous IV infusion	a) 14-28 mg/kg/day b) 20-40 mg/kg/day once daily	75mg/kg/d, 3 times daily Combination with DFO is standard, with DFX possible
Benefits	Longest experience, liver>heart iron removal	Most effective in liver iron removal	Most effective in heart iron removal
Relevant side effects	Ototoxic, skeletal abnormalities	Renal, hepatic, and gastrointestinal toxicity	Agranulocytosis ² , zinc deficiency, arthralgia

¹ Approval status in most countries: DFO first line >3 years old, DFX in 2-6 years old when DFO cannot be used.

² DFP prescription should come from an experienced provider. Patient/primary care team must receive emergency protocol for agranulocytosis and fever (immediate drug cessation, antibiotics, G-CSF if needed).

LONG-TERM MANAGEMENT AND SURVEILLANCE

Children

Major management goals are optimizing physical and cognitive development. Birth defects require by appropriate follow-up. Routine growth monitoring is essential, with an endocrinologist guiding hormone testing and steroid toxicity management (**panel 4**). To improve growth, steroids can be stopped before/during puberty during which transfusions are given. Growth hormone (GH) therapy can effectively treat DBA syndrome-associated growth deficiency¹²⁷ There are no data demonstrating increased cancer risk from GH in DBA syndrome and results from childhood cancer survivors studies are reassuring.^{128,129} The panel agreed that GH is reasonable if needed - either during pubertal growth (i.e., steroid holiday) or earlier. As steroids may impair efficacy of GH, optimal GH use would be with transfusions, although combining with steroids is not contraindicated. Early and aggressive chelation with toxicity monitoring (**panel 5, appendix p 8**) and MRI-based evaluation of iron burden are critical. HSCT has excellent outcomes in DBA syndrome and should be discussed after initial steroid failure (**panel 6**).

Adults

Adult patient care should involve adjusting anemia-directed therapy, monitoring therapy toxicities and comorbidities including cancer predisposition, addressing family planning and pregnancy monitoring, and planning careful transition from pediatric care. Adults with DBA syndrome are at risk for both non-malignant and malignant complications, resulting in a cumulative incidence of death of 23% by age 45 years, as noted in the DBA Registry of North America; mainly of HSCT complications, iron overload, infections, and leukemia/solid tumors.¹³⁰ Treatment-related organ dysfunction is common (**appendix p 6, 10-11**). Adrenal insufficiency and hypogonadism require specific testing. Psychosocial support and comprehensive services enable optimal possible care. Many adults require higher Hb for a healthy daily life and work. Frequent chelator adjustments are needed with long-term chelator toxicity. CBC monitoring to detect early MDS/AML signs is recommended,¹³¹ as is baseline BM assessment before transition to adult care. Colonoscopy is recommended from 20 years old. Associated immunodeficiency (decreased B/NK lymphocyte counts and immunoglobulins)^{132,133} warrants immune parameter monitoring. Increased autoimmunity has not been reported. Regular immunizations are warranted. Genetic counseling and family planning are of concern to adolescents and adults. DBA syndrome has mainly autosomal dominant inheritance, but genetic penetrance and expressivity vary significantly, and no predictions can be made about disease severity in the next offspring. Decreased fertility has not been reported in males with DBA syndrome. In female patients, pregnancy complications occur, requiring expert obstetrical care (for detailed guidelines see ¹³⁴). Iron chelation should be optimized in transfusion-dependent females prior to conception since chelating drugs are contraindicated during pregnancy (although data from pregnant women with thalassemia suggest that chelation with DFO could be considered in severely iron-overloaded women during the last trimester¹³⁵). In a study evaluating 64 pregnancies, vascular-placental complications were noted in 66% of pregnant women with DBA syndrome.¹³⁶ The panel agreed that the nadir Hb should be maintained at ≥ 10.0 -10.5g/dL as recommended for pregnancy in thalassemia¹³⁷. Thus, many patients with DBA syndrome, including those responsive to steroids, will require transfusions during pregnancy. Due to placental vasculopathy, prophylaxis with acetylsalicylic acid may be considered.^{134,136}

COMPREHENSIVE LONG-TERM SURVEILLANCE IN CHILDREN AND ADULTS WITH DBA SYNDROME

Clinical scenario	Surveillance recommendations
HEMATOLOGY	
<p>Any patient (including therapy-independent) Monitor changes in blood counts (Hb, other blood lineages): viral infection, drug induced, MDS/AML</p>	<ul style="list-style-type: none"> • CBC and reticulocyte count at regular intervals (once yearly if therapy-independent) • Bone marrow aspirate if: more severe anemia without explanation, unexpected reticulocytosis, worsening of neutropenia or thrombocytopenia, abnormal cells
<p>Patient receiving steroids Monitor efficacy (Hb and reticulocyte count) and treatment toxicity (see also panel 4) Involve endocrinology</p>	<ul style="list-style-type: none"> • CBC every ~3-4 months in stable patients • LFTs, creatinine, vitamin D levels regularly • Vitamin D and calcium supplementation as needed • Proton pump inhibitors (or H2 antagonists) during initial high dose prednisone therapy, or when symptomatic • Disclose that estrogen-containing oral contraceptives might weaken steroid effect • Steroid toxicity requires repeat endocrine evaluation <ul style="list-style-type: none"> ○ At least yearly testing for diabetes/ metabolic syndrome, bone health (densitometry scan), eye exam (cataract exclusion) ○ Bisphosphonates as therapy option in patients with significant osteoporosis ○ Joint/bone pain must be investigated being mindful of steroid-induced avascular necrosis and risk of osteogenic sarcoma (MRI may be warranted)
<p>Patients on transfusions and chelation Monitor efficacy (nadir Hb before transfusion) and toxicity (see also panel 3 and 5) Patients with poor iron balance</p>	<ul style="list-style-type: none"> • Before every transfusion: CBC with reticulocyte counts, RBC antibodies (if possible) • Ferritin and transferrin saturation trend (i.e., every 1-3 months before transfusion) • Routine transaminases, creatinine, electrolytes (phosphate if on deferasirox) virus serologies • Yearly MRI evaluation or more often according to iron status: <ul style="list-style-type: none"> ○ Liver iron content (LIC) by T2* or R2 ○ Heart iron by T2* • Echocardiography, ECG evaluation every 1 to 3 years according to iron status. Consider Holter monitor for patients with cardiac iron overload. Intensify chelation; consider deferiprone • Pancreas and pituitary glands: specific endocrine tests: fructosamine (instead of HbA1c in transfused patients), TSH, PTH • Growth hormone replacement when indicated • Consultation for medically assisted reproduction • Dose adjustments and combination of two chelators are frequently required, emphasize importance of medication adherence, facilitate networking with patient groups
<p>Patients on deferoxamine Monitor for toxicity: hearing loss, osteopenia, renal lithiasis</p>	<ul style="list-style-type: none"> • Bone densitometry (every 1 to 3 years) • Regular audiometry (at least yearly or more often with dose changes) • Regular eye exam (yearly)

	<ul style="list-style-type: none"> • Regular renal ultrasound surveillance • Higher risk of toxicity in patients with low ferritin
Patients on deferasirox Monitor for toxicity: renal (glomerular or tubular damage including Fanconi syndrome), hepatic toxicity, transaminitis, gastrointestinal issues	<ul style="list-style-type: none"> • Frequent evaluation of liver and kidney parameters. Patients with toxicity: decrease dose • Regular renal ultrasound surveillance • Regular audiometry and eye exam (yearly) • Higher risk of toxicity is possibly present in patients with low ferritin
Patients on deferiprone Monitor for neutropenia/agranulocytosis	<ul style="list-style-type: none"> • Weekly CBC at treatment initiation and during any fever episode, monitor counts often and discontinue deferiprone for any sign of unusual or progressive neutropenia • Patient information & education (medical passport for emergencies with established plan)
For transplanted patients	<ul style="list-style-type: none"> • Standard surveillance recommendations. • Higher cancer risk in DBA syndrome patients must be taken into account
IMMUNOLOGY / INFECTIONS	
Hypogammaglobulinemia, Lymphopenia, recurrent infections	<ul style="list-style-type: none"> • Ig G, A, M levels and lymphocyte subsets (regularly if indicated) • Antibody responses, discuss immunizations and immunoglobulin treatment • For severe T-cell lymphopenia: consider pneumocystis jirovecii pneumonia prophylaxis • Additional prophylaxis and diagnostics according to local standard
Transfusion-related pathogens	<ul style="list-style-type: none"> • Virus testing at least once yearly (hepatitis B/C, HIV)
Vaccinations	<ul style="list-style-type: none"> • No restrictions on vaccines: Hepatitis B vaccine especially in patients receiving transfusions; live vaccines: first dose ideally before start prednisone, following doses after steroid reduction. • Patient with significant hypogammaglobulinemia: measure specific vaccine antibody titers
ONCOLOGY	
Solid tumors, MDS/AML	<ul style="list-style-type: none"> • Patient education, healthy lifestyle (avoid smoking, alcohol, toxins, unprotected sun exposure) • HPV vaccination • Patient adherence to screening procedures as in the general population • Colonoscopy beginning age 20 years, every 5 years or more often if clinically indicated • Bone marrow analysis: consider as baseline in adolescents/ young adults before transitioning to adult care, otherwise in any patient with significant unexplained cytopenia or rise in reticulocytes • Unexplained joint/bone pain: risk of osteogenic sarcoma (low threshold for x-ray / imaging)
FAMILY PLANNING, PREGNANCY	
Genetic risk (transmission)	<ul style="list-style-type: none"> • Patient education and genetic counselling • Discuss medically assisted reproduction for individuals asking for prenatal or pre-implantation diagnostics (according to national legal regulations)
Pregnancies in DBA syndrome: high risk obstetric care required	<ul style="list-style-type: none"> • Intensification of chelation prior planned pregnancy to optimize iron balance • Blood support frequently needed to maintain Hb >10.0-10.5 g/dL during pregnancy • Screening for fetal anemia • Detailed recommendations reviewed elsewhere (reference 136)

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APPENDIX REFERENCES (references 1-106 are in the main document)

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