

Pregnancy in bone marrow failure syndromes: Diamond-Blackfan anaemia and Shwachman-Diamond syndrome

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Summary. Pregnancy in bone marrow failure syndromes has risk to mother and fetus. There are fewer than 30 reports of cases with Diamond-Blackfan anaemia (DBA), and none with Shwachman-Diamond syndrome (SD). We report two DBA and one SD cases. One DBA mother received transfusions intra-partum, and the other only post-partum. Both required caesarean sections (C-sections) for failure of labour to progress and severe pre-eclampsia respectively. Both subsequently resumed pre-pregnancy steroid-induced control of anaemia. ~40% of DBA pregnancies required maternal transfusions; 25% delivered by C-section. The SD

patient also had Ehlers-Danlos (ED) syndrome and urticaria pigmentosa (UP). Her blood counts were adequate until week 38, when the platelet count dropped and a C-section was performed. Pregnancy management in marrow failure disorders requires obstetricians with expertise in high-risk pregnancies, and haematologists with experience with marrow failure syndromes.

Keywords: Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, pregnancy, transfusion, steroids.

Pregnancy is uncommon in patients with bone marrow failure syndromes. This topic was examined in Fanconi's anaemia (FA), in which there is reduced fertility, and increased miscarriages (7/29 pregnancies in 19 FA women), maternal transfusions (nine pregnancies), pre-eclampsia (four cases) and caesarean sections (C-sections) (six deliveries) (Alter *et al*, 1991; Alter & Young, 1998). Pregnancy in Diamond-Blackfan anaemia (DBA) has been reported rarely, and there are no reports of pregnancy in Shwachman-Diamond syndrome (SD). Our experience with pregnancy in two cases of DBA and one of SD suggests that, as in FA, there may be maternal morbidity requiring haematological monitoring, transfusions and C-sections.

METHODS

The medical literature was searched using *Current Contents* and Medline for all cases of DBA or SD who had been pregnant. Review of previous publications led to the

identification of additional cases (Young & Alter, 1994). The diagnosis of DBA was based on a macrocytic or normocytic pure red cell aplasia (autosomal dominant, recessive or sporadic), with usual onset in infancy or early childhood. The diagnosis of SD required pancreatic insufficiency, neutropenia in infancy, and metaphyseal dysostosis in some patients.

CASE REPORTS

Case 1. This patient was a 30-year-old Caucasian primigravida diagnosed as DBA at age 22 years. She had anaemia at 11 years, diagnosed as 'thalassaemia trait' due to elevated Hb F, and was transfused at 20 years for Hb 5 g/dl with varicella. Bone marrow examination at age 22 showed erythroid hypoplasia. Usual Hbs were ~8–9 g/dl, MCVs ~95 fl and Hb F 3–6%, on 5 mg alternate-day prednisone. At 25 years thymectomy was performed for a large normal thymus. At 27 years red cell adenosine deaminase (ADA) was 3.07 IU/g Hb (normal 0.35–1), consistent with DBA. At 29 years a basal cell carcinoma was removed from her left lower eyelid.

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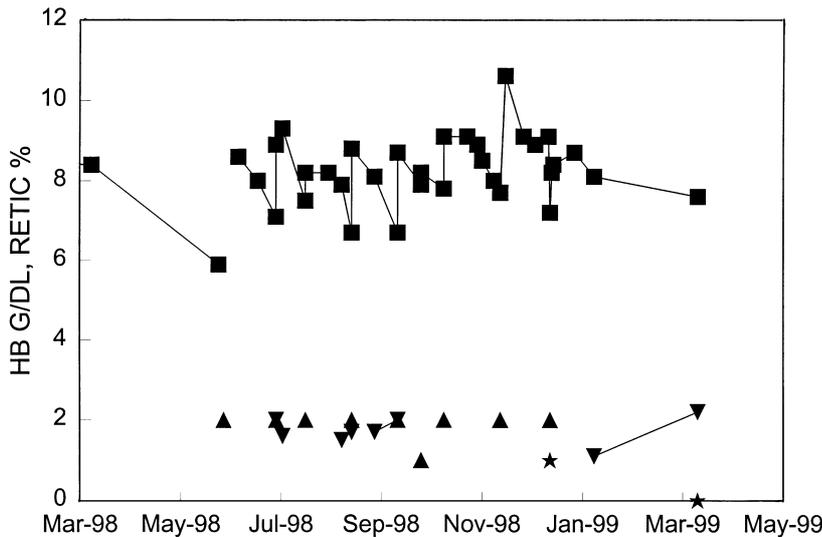


Fig 1. Case 1 blood work: ■, Hb g/dl; ▼, reticulocyte %; ▲, transfusion unit; ★, C-section.

She presented at the University of Texas Medical Branch at 15 weeks gestation, with a singleton gestation by ultrasound. She had short stature (1.48 m), flat thenar eminences, and a borderline midpelvis size with prominent ischial spines. Counselling was provided concerning possible autosomal dominant inheritance of DBA. Hb was 5.9 g/dl, and she received 2 units of packed red blood cells. For fetal well-being and optimal intrauterine growth we chose to maintain maternal Hb >8 g/dl (Fig 1). She required 1–2 units at 3–4-week intervals, totalling 17 units. Fetal growth remained appropriate by clinical examination and ultrasound measurements, without fetal hydrops. Maternal weight gain was 15 kg.

Labour was induced at 40 weeks. A primary C-section was performed for failure of the fetal head to descend into the pelvis due to cephalopelvic disproportion, with delivery of a 3.515 kg normal female with Apgars of 8 and 9 at 1 and 5 min. The baby's Hb was 17.9 g/dl and MCV 111 fl, normal

newborn values. Red cell ADA was 0.43 IU/g Hb (normal). Culture of cord blood mononuclear cells in methylcellulose led to 85 burst-forming units-erythroid, normal for cord (Weinberg *et al*, 1983). The infant did not have DBA.

Case 2. This patient was a 19-year-old Jamaican primigravida who presented to the Joe Di Maggio Children's Hospital at 8 weeks pregnancy, confirmed by beta human chorionic gonadotropin. She had been a 2 kg 38-week product of a non-anaemic healthy primigravida. She had a small ventricular septal defect which closed spontaneously. At 2 months she had presented to Boston Children's Hospital with irritability, tachypnoea, lethargy, thready pulses, thin tea-coloured blood, and Hb 2.5 g/dl, MCV 99 fl, reticulocytes 0.1%, and was resuscitated. Bone marrow examination showed no erythroid precursors, and DBA was diagnosed. She received oral prednisone with intermittent transfusions, and after the first year required only every-other-day prednisone (0.3–1 mg/kg) until adolescence. She was

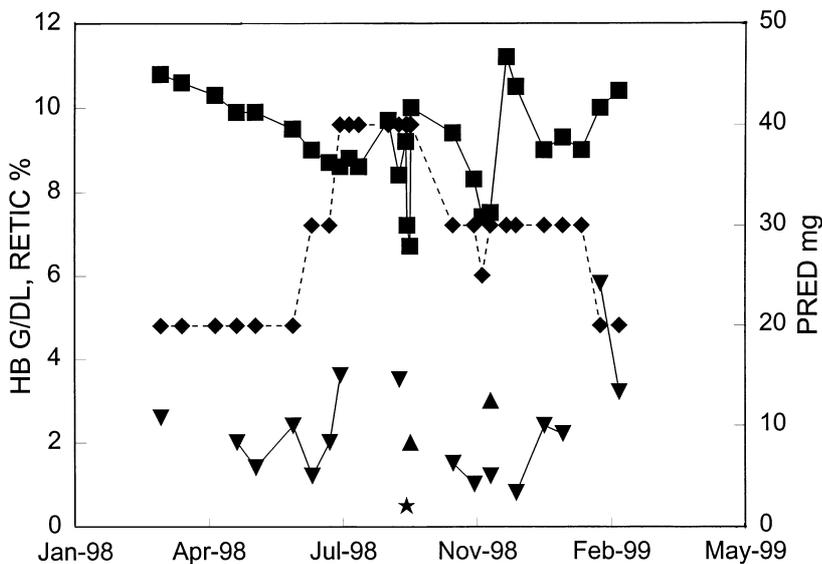


Fig 2. Case 2 blood work: ■, Hb g/dl; ▼, reticulocyte %; ▲, transfusion unit; ◆, prednisone mg; ★, C-section.

off steroids and without follow-up until 1997, when she had shortness of breath, Hb 4.9 g/dl, and received 3 units of blood. Hb was then maintained at ~10 g/dl on 20 mg prednisone on alternate days.

At the beginning of pregnancy Hb was 10.6 g/dl, MCV 103.7 fl, and reticulocyte count 2.6%. It was decided to maintain Hb >9 g/dl to avoid maternal or fetal compromise from anaemia, which required steroid manipulation until the end of the second trimester (Fig 2). At 33 weeks, with acceptable fetal growth, she developed severe pre-eclampsia with blood pressure 162/100, 2–3+ proteinuria and severe headaches. A fetal biophysical profile score was 4/8 due to poor fetal breathing and poor tone. Following two doses of betamethasone and magnesium, an emergency C-section was performed, delivering an appropriate for gestational age 1.765 kg female infant with Apgars of 4 and 8 at 1 and 5 min. The infant required bag and mask resuscitation, and was hospitalized for 15 d for transient tachypnoea, possible sepsis, hyperbilirubinaemia (maximum 135 $\mu\text{mol/l}$) and hypermagnesaemia. Hb was 16 g/dl and MCV 110.9 fl. ADA levels were increased (1.90 IU/g Hb) for the mother and normal (0.38) for the baby.

The mother had a 6 d stay for hypertension, elevated liver enzymes and thrombocytopenia, a mild HELLP syndrome. Hb 6.7 g/dl on day 6 led to a transfusion. She was discharged

on prednisone 30 mg every other day. Weaning to 25 mg every other day 1 month post-partum led to a drop in the Hb to 7.5 g/dl and a further transfusion. 4 months post-partum she reached her pre-pregnancy dose of 20 mg of prednisone every other day.

Case 3. This patient was a 20-year-old Caucasian primigravida with SD referred at 9 weeks gestation (singleton, confirmed by ultrasound). There was a maternal history of childhood urticaria pigmentosa (UP) and Ehlers-Danos (ED) syndrome (believed to be type II), as well as tobacco use. Her younger sister also had SD but neither UP nor ED. The patient had been evaluated at 5 months for failure to thrive and had exocrine pancreatic insufficiency, with an abnormal 72 h faecal fat study, decreased duodenal pancreatic trypsin levels, low fat soluble vitamins A and E, and a neutrophil chemotactic defect. From 6 months to 3 years she had four episodes of pneumonia, recurrent skin infections, impetigo and abscesses, as well as lymphadenitis and otitis media, and was intermittently neutropenic with absolute neutrophil counts (ANCs) of $0.41\text{--}6.432 \times 10^9/\text{l}$. Hip X-rays revealed bilateral metaphyseal dysostosis. Growth was less than the third percentile, leading to adult short stature. From 6 years until teenage she had steatorrhoea, treated with pancreatic enzymes and fat-soluble vitamins. Recent vitamin A and E levels were low: 80 $\mu\text{mol/l}$ (normal

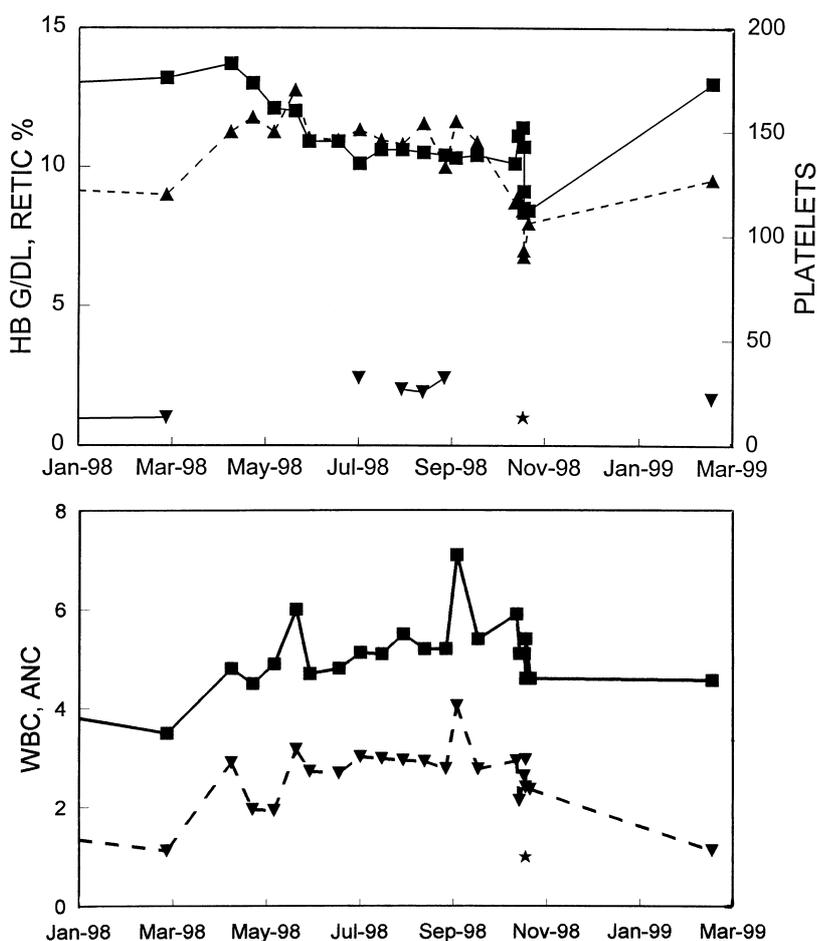


Fig 3. Case 3 blood work. Top: Hb and platelets. ■, Hb g/dl; ▼, reticulocyte %; ▲, platelets, $\times 10^9/\text{l}$; ★, C-section. Bottom: White blood cells. ■, WBC $\times 10^9/\text{l}$; ▼, ANC $\times 10^9/\text{l}$; ★, C-section.

Table I. Pregnancy in DBA.

Babies	No. DBA women	No. pregnancies	No. babies*	M/F babies†	Gestation (weeks)	Mean BW (kg)	No. with low BW	No. C/S	No. spont. abns	No. Txd (% of preg.)	No. Rxd steroids (%)
DBA	15	17	16	9/7	38 (36–40)	2.686 (1.42–3.5)	3	4	1	5 (31)	4 (25)
Normal	10	12	12	3/3	36 (33–40)	2.503 (1.66–3.515)	3	3	0	5 (42)	4 (33)
Total	25	29	28	12/10	38 (33–40)	2.621 (1.42–3.515)	6	7	1	10 (36)	8 (29)
DBA	0	5	5	1/4	36 (32–41)	3.193 (2.02–4.1)	1	4			

DBA: Diamond-Blackfan anaemia; BW: body weight; C/S: caesarean section; Spont. abns: spontaneous abortions; Txd: transfused; Rxd: treated.

*One died. †Sex not stated for some babies.

125–400) and $11 \mu\text{mol/l}$ (normal 12.8–40.6). Serum trypsinogen was $5.5 \mu\text{g/l}$ (normal 17–47). ANCs were $1.1\text{--}2.83 \times 10^9/\text{l}$, Hb $12.7\text{--}13.2 \text{ g/dl}$, MCVs 100–106 fl, and platelet counts $120\text{--}147 \times 10^9/\text{l}$.

As a newborn she had multiple skin spots resembling old bruises and suggestive of UP, followed in childhood by episodes of life-threatening anaphylaxis and elevated serum histamine. The UP slowly burned itself out and she has been asymptomatic since the age of 6 years. She had excessive skin fragility from birth, leaving characteristic 'cigarette paper' scars. Hyperextensible joints, especially wrists, were noted at 6 years, with easy bruisability, and the presumptive diagnosis of ED II was made. She does not have evidence of mitral valve prolapse or aortic valve abnormalities on echocardiogram.

The family was counselled concerning autosomal recessive inheritance for SD. Inheritance patterns for ED and UP were also discussed, and they were informed about pregnancy complications associated with ED. Her weight was 52 kg and height 145 cm, with multiple broad-based scars, and a contracted pelvis by clinical pelvimetry. Pancreatic enzyme therapy was initiated at 21 weeks because of poor maternal weight gain. Hb decreased to $\sim 10 \text{ g/dl}$, consistent with expanded plasma volume during pregnancy. WBC and ANC rose slightly ($>5 \times 10^9/\text{l}$ and $2 \times 10^9/\text{l}$ respectively), less than in a normal pregnancy, and platelet count remained $>120 \times 10^9/\text{l}$ until week 38 (Fig 3). Irregular contractions were noted from 31 weeks, and labour was induced at 38 weeks at a platelet count $<110 \times 10^9/\text{l}$ in the context of ED. A primary C-section was performed for failure of the fetal head to descend due to cephalopelvic disproportion, delivering a 3.175 kg normal male with Apgars 9 and 10 at 1 and 5 min respectively. Tubal ligation was performed. Newborn WBC was $9.9 \times 10^9/\text{l}$, ANC $7.03 \times 10^9/\text{l}$, Hb 19.8 g/dl , MCV 109.5 fl , and platelets $239 \times 10^9/\text{l}$. At 3 months of age his counts were also normal.

The mother's post-partum course was complicated by acute blood loss (Hb 9.1 g/dl which fell to 8.4 g/dl), thrombocytopenia to $90 \times 10^9/\text{l}$, and a small incisional separation. By 4 months post-partum her blood counts were baseline: Hb 13 g/dl , MCV 103 fl , WBC $4.56 \times 10^9/\text{l}$, ANC $1.117 \times 10^9/\text{l}$, and platelets $127 \times 10^9/\text{l}$.

RESULTS AND DISCUSSION

Diamond-Blackfan anaemia

Including the cases discussed here, there have been 25 DBA women reported to have had one or more pregnancies, for a total of 29 pregnancies (Table I). 15 DBA women had 16 children with DBA, and were reported in the context of dominantly inherited DBA; there was also one spontaneous abortion at 8 weeks in this group (Falter & Robinson, 1972; Hamilton *et al*, 1974; McFarland *et al*, 1982; Gray, 1982; Altman & Gross, 1983; Viskochil *et al*, 1990; Hurst *et al*, 1991; Neilson & Khokhar, 1991; McLennan *et al*, 1996; Rogers *et al*, 1997; Ball *et al*, 1996; Escalante *et al*, 1997). 10 DBA women had 12 offspring who did not have DBA (Balaban *et al*, 1985; Rijhsinghani & Wiechert, 1994; Aird *et al*, 1996; Janov *et al*, 1996; Rogers *et al*, 1997; this report). Because of biased reporting of patients whose children were also affected, these data cannot be used to predict the likelihood of a DBA woman having a DBA child.

In a series of 76 cases from Boston, five DBA men and three DBA women had a total of 13 children, three of whom had DBA, and were the offspring of two of the DBA men (Janov *et al*, 1996). The number of DBA adults who had children was not included in a larger series of 127 DBA patients from the U.K., but there were three DBA children who had DBA mothers (Ball *et al*, 1996). Without knowing the denominator, the incidence of dominant inheritance cannot be determined.

Details on the management of the DBA pregnancies are sparse, and the reasons for the treatments are not clear. Prior to the pregnancies, 2/25 DBA women were receiving transfusions, seven were maintained on prednisone, and 10 were known not to be on any treatment; no information was reported for six women. Overall, $\sim 40\%$ of the DBA pregnancies required multiple transfusions, and $\sim 30\%$ continued or added steroids. All steroid-treated patients were also transfused. The decision in our cases to maintain a maternal haemoglobin level of 8–9 g/dl was based on concern that severe maternal anaemia might be detrimental to the fetus, leading to intrauterine growth retardation, preterm delivery, or fetal distress. The literature reports did not identify similar parameters.

The type of treatment during the pregnancy was not correlated with the outcome in the offspring. Two DBA babies had hydrops, one born at 34 weeks who survived, and one at 38 weeks who died. Seven babies were delivered by C-section, four of whom had DBA. The C-sections for DBA babies were done at 34 weeks because of a cordocentesis Hb of 1.6 g/dl (McLennan *et al*, 1996), 37 weeks for maternal hypertension (Neilson & Khokhar, 1991), 38 weeks due to fetal hydrops and bradycardia (Rogers *et al*, 1997), and 40 weeks because of maternal fever (Escalante *et al*, 1997). The C-section reported previously for a non-DBA baby was at 30 weeks for chorioamnionitis in a pregnancy which used an oocyte donor because the DBA mother had premature ovarian failure (Aird *et al*, 1996). The C-sections were indicated in our cases for a failed trial of labour, and for toxemia. The risk appears to be high that the infant of a DBA mother will be small for dates, premature, or require a C-section. There have been no maternal mortalities, despite the apparent morbidities.

Five DBA babies whose mothers were not DBA were diagnosed at birth because of hydrops (Table I) (Freedman, 1985; Visser *et al*, 1988; Scimeca *et al*, 1988; Koenig *et al*, 1989; van Hook *et al*, 1995). Although the reports are incomplete, two were preterm deliveries at 32 and 33 weeks, one was low birth weight of 2.02 kg, and four were delivered by C-section. Thus some of the problems during DBA pregnancies may relate to the anaemia of the DBA baby, rather than of the mother as described in our cases.

Diagnosis of DBA in adults, as in our case 1, is unusual but not unprecedented (Wallman, 1956; Gray, 1982; Balaban *et al*, 1985; Neilson & Khokhar, 1991; Abkowitz *et al*, 1991). In one family reported in the literature where both mother and child had DBA, the mother was diagnosed during her pregnancy at age 22 years (Viskochil *et al*, 1990). Two other adults diagnosed with DBA at 25 and 64 years of age gave histories of normal pregnancies (Balaban *et al*, 1985). Since elevated red cell ADA may identify silent carriers of DBA, it may be worthwhile to test all parents of DBA children (Willig *et al*, 1998).

Prenatal diagnosis of DBA may be offered in candidate families (where either parent has DBA). Fetal blood obtained by cordocentesis prior to 20 weeks gestation could be analysed for Hb, MCV, red cell ADA, and growth of erythroid progenitors, although there are no reports of this approach to prenatal diagnosis of DBA at this time. Since in some families the DBA gene appears to map to 9q13, linkage and mutation analyses may eventually be useful (Gustavsson *et al*, 1997, 1998; Draptchinskaia *et al*, 1999). In practice, ultrasound may detect cardiomegaly and effusions from anaemic hydrops (McLennan *et al*, 1996; Rogers *et al*, 1997), and altered cardiac blood flow velocities may be documented (Visser *et al*, 1988). Affected fetuses may be treated with intrauterine transfusions in order to maintain the pregnancy (McLennan *et al*, 1996).

Shwachman-Diamond syndrome

There is very little information in the literature with regard to adult patients with SD, and none addressing pregnancy. Fewer than 25% of the ~200 reported cases had reached age

16 years or more. Ages at menarche and menopause have not been described, although the former is late and the latter early in FA (Alter *et al*, 1991).

Although pregnancy itself is not a reportable condition, pregnancy in SD merits comment. Features of the syndrome which may complicate pregnancy include pancreatic insufficiency with malabsorption, haematological disorders (neutropenia, anaemia and thrombocytopenia) and short stature and bony abnormalities, such as a contracted pelvis. Since pregnancy in other inherited bone marrow failure syndromes such as FA and DBA was associated with worsening of the haematological status and need for transfusions of blood products (Alter *et al*, 1991), pregnancy in SD also warrants cautious management.

Prior to pregnancy our SD patient had mild neutropenia and mild thrombocytopenia without anaemia but with macrocytosis. The decline in Hb was consistent with normal dilution during pregnancy, but the drop in platelet count at the end was more extreme than seen during normal pregnancy. The WBC and ANC did not demonstrate the expected leucocytosis of a normal pregnancy, but fortunately did not decline, and there were no infectious complications.

The intrapartum manifestations of SD were thus mild decreases in the blood count values, and a failure of adequate weight gain due to the pancreatic insufficiency. Pancreatic enzyme therapy was initiated to enhance the nutritional state of both the mother and the fetus, and the patient demonstrated weight gain, along with appropriate clinical and ultrasound evidence for fetal growth.

Our case was significantly more complicated than straightforward SD, due to maternal ED. The UP was not a concern due to the absence of lesions for many years. ED might have led to serious or even life-threatening haemorrhage at delivery. Fortunately, the C-section and subsequent tubal ligation were performed without sequelae. The infant is presumably a heterozygote for SD, as predicted for an autosomal recessive disorder.

CONCLUSIONS

The pregnant woman with DBA may require transfusions for anaemia, and there is an increased risk of C-section, low birth weight and premature delivery for both DBA and normal babies. Use of oral contraceptives for prevention of pregnancy might not be optimal, since the anaemia of DBA may become worse, perhaps due to marrow suppression by oestrogens (Hamilton *et al*, 1974; Glader, 1987). A single case of a relatively uneventful pregnancy in SD (except for pancreatic insufficiency and a C-section) does not necessarily mean that all SD pregnancies will be haematologically benign. Patients with marrow failure disorders should be managed jointly by maternal fetal medicine obstetricians, gastroenterologists if needed, and haematologists with experience in bone marrow failure syndromes.

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