CASE REPORT

Successful pregnancy following oocyte donation in a patient with Diamond-Blackfan syndrome and premature ovarian failure

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Diamond-Blackfan anaemia (DBA) is a rare congenital condition characterized by profound anaemia associated with an absence of red cell precursors on bone marrow examination. This report represents the first case of pregnancy following egg donation in a patient with DBA and premature ovarian failure. The patient was a 24 year old woman who had been diagnosed with DBA when aged 6 months. Shortly after menarche, the patient became amenorrhoeic and was diagnosed as suffering from premature ovarian failure. She was entered onto an assisted conception programme and conceived after one cycle of egg donation. The pregnancy was characterized by a gradual decline in haemoglobin concentration, reaching a low of 8.1 g/dl, necessitating a single blood transfusion at 29 weeks of gestation. The patient suffered preterm rupture of the membranes at 29 weeks of gestation and was delivered by emergency Caesarean section at 30 weeks of gestation because of chorioamnionitis and breech presentation. Comparing this case with other reports of pregnancy in patients with DBA, our patient suffered a less dramatic fall in haemoglobin concentration and required only a single blood transfusion. It is suggested that because the pregnancy arose from donated genetic material, this may have conferred some protective effect.

Key words: Diamond–Blackfan/oocyte donation/pregnancy

Introduction

Diamond–Blackfan anaemia (DBA) is a rare form of congenital red cell aplasia characterized by progressive normochromic, macrocytic anaemia in infancy, an absent reticulocyte response, markedly decreased to absent bone marrow red cell precursors, with normal marrow cellularity and preservation of other precursor cell lines, and normal peripheral white cell count with normal or slightly increased platelet counts (Diamond and Blackfan, 1938).

Most cases of DBA are sporadic, but in 10–25% of patients there may be a family history of DBA, and possible autosomal recessive and autosomal dominant modes of inheritance have been reported (Viskochil et al., 1990).

There are several associated congenital anomalies with DBA that may be present in up to 50% of cases (Halperin and Freedman, 1989). These include craniofacial abnormalities, prenatal and postnatal growth failure, neck abnormalities, including fusion of the cervical vertebrae (Klippel–Feil syndrome), and congenital elevation of the scapula (Sprengel's deformity). Thumb malformations have also been documented, including triphalangeal thumbs and hypoplasia of the thenar eminence.

Although it is recognized that treatments associated with DBA may cause delayed sexual maturation (Diamond et al., 1961) and growth problems (Halperin and Freedman, 1989), the presence of premature ovarian failure, as far as we are aware, has not been reported previously. There have been few reports of pregnancy in patients with DBA (Hamilton et al., 1974; Rijhsinghani and Weichert, 1994). Here we describe the first case of pregnancy occurring in a patient with DBA that has arisen following oocyte donation.

Case report

The patient was first seen in the oocyte donation clinic in September 1994. At this time she was 24 years old. She had been referred by her general practitioner with a history of primary infertility secondary to premature ovarian failure. She was known to suffer from DBA.

The patient was born at full term via a normal vaginal delivery. She presented at the local children's hospital aged 6 months with extreme pallor. A full blood count showed a haemoglobin concentration of 5.6 g/dl, with other haematological indices being normal. A blood film showed a reticulocyte count of <1%.

Bone marrow examination at this time showed normal cellularity but with an absence of red cell precursors; a diagnosis of congenital red cell aplasia (Diamond–Blackfan syndrome) was made.

Initial management consisted of a top-up blood transfusion followed by prednisolone therapy, which achieved a good haematological response but nevertheless was steroid dependent, with a fall in haemoglobin concentration when her steroid dose was reduced.

Her steroid requirements reduced gradually until, in 1986, steroid therapy was tailed-off completely. Thereafter she maintained acceptable haemoglobin concentrations of 11.0–11.5 g/dl.
The patient commenced normal pubertal development at the age of 12 years with the onset of menarche at the age of 15 years. She menstruated normally for a short while, but developed secondary amenorrhoea and markedly elevated gonadotrophin concentrations, consistent with premature ovarian failure. Laparoscopic assessment of the pelvis revealed streak ovaries but a normal uterus and Fallopian tubes. Further investigations revealed a normal karyotype of 46,XX and an auto-antibody screen was reported to be negative. Thyroid function was also assessed and reported as normal.

She was initially commenced on the combined oral contraceptive pill for hormone replacement purposes (ethinyl oestradiol 30 μg and levonorgestrel 150 μg), and this induced regular withdrawal bleeds. However, in July 1994 this was changed to standard hormone replacement therapy (oestradiol valerate 2 mg and levonorgestrel 75 μg) because of depression.

At the age of 24 years the patient was referred to us for oocyte donation treatment. As much information as possible was sought regarding pregnancies in patients with DBA, including contacting the DBA Registry in both the UK and the USA and discussions with obstetricians interested in medical problems during pregnancy. When all this information was available, the patient was counselled regarding the potential problems posed by the pregnancy. Following counselling, the patient decided to proceed with oocyte donation treatment and when a suitable donor had been found the endometrium was prepared using 6 mg oestradiol valerate for 16 days. An ultrasound scan after 10 days of treatment revealed an endometrial thickness of 10 mm. At 2 days prior to embryo transfer, progesterone therapy was commenced in the form of 400 mg progesterone pessaries twice daily. This combination of oestradiol valerate and progesterone was continued until 14 weeks of gestation. Two embryos were replaced and 2 weeks later a pregnancy test was positive. By 3 weeks following embryo transfer a transvaginal ultrasound scan revealed the presence of a single intrauterine pregnancy with a visible fetal pole but no evidence of fetal heart activity.

Over the following week the patient experienced some painless vaginal bleeding and a further ultrasound scan revealed a viable fetus; there was also a second sac visible at this time though no evidence of a fetal pole. Further scans revealed this second sac to be collapsing and the viable pregnancy to be progressing well. By 9 weeks post-embryo transfer the pregnancy was seen to be progressing normally with no evidence of a second sac and no further vaginal bleeding. The patient was discharged from the oocyte donation clinic and referred for antenatal care.

The patient was seen in the antenatal clinic 11 weeks post-embryo transfer. She remained well and had no further vaginal bleeding. An ultrasound scan revealed a viable pregnancy of a size consistent with the period of gestation. The plan for the remainder of the pregnancy was that she should be seen on a fortnightly basis for haemoglobin estimations, with regular growth scans from 28 weeks of gestation. The patient was also seen regularly throughout the pregnancy by the haematologist who had been responsible for the management of her anaemia. An ultrasound scan performed at 19 weeks of gestation revealed no evidence of fetal abnormality. Serum screening for Down's syndrome was performed at 15 weeks of gestation and the overall risk was calculated to be very low.

Haemoglobin concentration at booking was measured at 11.7 g/dl with normal indices. Thereafter the patient was seen at fortnightly intervals. The haemoglobin concentration was checked at each clinic visit. There was a gradual but progressive fall in the haemoglobin concentration so that at 25 weeks of gestation the concentration was measured at 9.7 g/dl. There had also been a progressive rise in the mean corpuscular volume to 107.3 fl. The serum B12, folate and ferritin concentrations were normal. Although a partial relapse of the DBA could not be excluded, it was thought that most of the fall in the haemoglobin concentration was caused by physiological haemodilution of pregnancy. As the patient was symptomatically well, it was thought that a bone marrow examination and steroid therapy were not indicated at this stage. If the haemoglobin concentration dropped further, the recommendation was to transfuse the patient. Over the next 3 weeks the haemoglobin concentration remained relatively stable.

An ultrasound scan performed at 28 weeks of gestation showed the fetus to be growing well with good liquor volume. At 29 weeks of gestation the patient was admitted to hospital with pre-labour, preterm rupture of the membranes. This was confirmed on examination and the patient was admitted to hospital for observation. Corticosteroids were prescribed to accelerate fetal lung maturity, and daily blood samples were taken to check for signs of developing uterine infection.

By 2 days following admission the haemoglobin concentration had dropped to 8.1 g/dl and the mean corpuscular volume had increased to 108.8 fl. It was decided to transfuse the patient with three units of packed cells. Following this transfusion the haemoglobin concentration rose to 11.2 g/dl, all other haematological indices remaining normal.

By 9 days following admission the patient complained of feeling unwell with backache and period-type abdominal pains. On examination the patient appeared unwell and was pyrexial with a temperature of 38.6°C. The uterus was found to be tender to palpation, with the fetus presenting by the breech; purulent liquor was noted to be draining. Despite no significant rise in the white cell count or C-reactive protein concentrations, a clinical diagnosis of chorioamnionitis was made and a decision was taken to deliver the baby. It was decided to deliver the baby by emergency Caesarean section in view of the combination of breech presentation in association with chorioamnionitis and prematurity. Intravenous antibiotics were commenced and an emergency lower segment Caesarean section was performed. A live male infant weighing 1.66 kg, with Apgar scores of 5 at 1 min and 10 at 5 min, was delivered and transferred immediately to the neonatal intensive care unit. After a short period of ventilation, the infant made good progress and was discharged from the neonatal intensive care unit when aged 5 weeks.

Postoperatively the patient made an uneventful recovery. Haemoglobin estimation prior to discharge was 12.1 g/dl and postnatally the patient remained well. Her haemoglobin concentration 6 weeks post-delivery was 11.3 g/dl.
Discussion

The aetiology of DBA is not fully understood. It was thought initially that DBA may have been caused by the humoral or cellular inhibition of erythropoiesis (Ortega et al., 1975), but these findings have not been confirmed by others (Geller et al., 1975).

It is known that a significant number of patients with DBA have T cell dysfunction with reduced T cell numbers, reduced T4/T8 ratios and a defective lymphocyte-mediated suppression of lymphoproliferation. There is also a large amount of evidence suggesting that erythroid stem cells are intrinsically defective in DBA because they are partly or completely refractory to erythropoietin (Halperin and Freedman, 1989). With regard to where in the cycle of red cell production the problem occurs, it would appear to be at erythroid transition from the colony-forming unit granulocyte, erythrocyte, monocyte, megakaryocyte to burst-forming unit (Tsai et al., 1989).

In terms of treatment for DBA, the mainstay of treatment involves steroid treatments to which >70% of patients are responsive (Alter, 1987). Recurrent blood transfusions are also used frequently, especially to correct severe anaemia and for patients in whom steroids are either ineffective or excessively toxic. Care must be taken to prevent iron overload in patients requiring multiple transfusions.

In the case described, there was no family history of DBA, which would tend to indicate an isolated occurrence, nor were there any associated musculoskeletal abnormalities.

All previous reports of the effect of pregnancy on DBA have commented on the need for multiple transfusions during the pregnancy, with the degree of anaemia being more profound and occurring earlier in the pregnancy than in the case described here (Hamilton et al., 1974; Rijhsinghani and Weichert, 1994). As the pregnancy terminated prematurely at 30 weeks of gestation, it is not possible to say whether more transfusions may have become necessary.

The cause of the relapse of the anaemia occurring during pregnancy is not certain. It is possible that relapses during pregnancy may be immunologically mediated because it is known that patients with DBA have an altered lymphocyte function (Halperin and Freedman, 1989). In the case described, the pregnancy arose following oocyte donation. The use of heterotopic genetic material may have altered the immunological response to the pregnancy and conferred some protective effect to the patient, thus lessening the likelihood of relapse and reducing the severity of the anaemia.

It is possible that the cause of the relapse may be hormonally mediated because relapses on the contraceptive pill have been reported (Hamilton et al., 1974). This would appear unlikely in the case described here because the haemoglobin concentration remained stable despite the long-term use of the oral contraceptive pill and hormone replacement therapy.

The pregnancy in the above case was complicated by premature delivery subsequent to chorioamnionitis following preterm rupture of the membranes. Preterm labour has been described previously in patients with DBA (Rijhsinghani and Weichert, 1994). Although this may be coincidental, more information is needed relating to pregnancy in patients with DBA to assess the full risks of pregnancy in such patients. Hopefully, with the setting up of databases of patients with DBA, such as the Diamond–Blackfan Anaemia Registry (Vlachos et al., 1994), this information will become more readily available.

Because of the risks of severe anaemia to both mother and fetus, it is important that, in any patient with DBA who is planning a pregnancy, their pre-pregnancy haematological status is optimized. Any relapses of the anaemia should be treated with transfusions and steroid therapy if indicated. If these guidelines are followed, from the evidence available thus far, it would appear that the outcome of pregnancy is reasonable in these patients.

It is tempting to suggest that the use of donated oocytes may protect against relapse of the anaemia during pregnancy, although this cannot be based on the outcome of a single pregnancy. More pregnancies will need to be studied to investigate the cause of the relapse during pregnancy, be it immunological or otherwise, before any firm conclusions can be drawn.

References


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