

## Challenges in the management of pregnancy complicated by maternal Diamond Blackfan Anaemia: A case report

Shumaila Tabassum, Fatima Ashfaq Shah, Rachael O'Hare

### Abstract

Diamond Blackfan Anaemia (DBA) is a rare genetic disorder, affecting red blood cells. Pregnancy in women affected by DBA should be managed as a high-risk pregnancy, as it may trigger the relapse of anaemia, and is associated with both maternal and foetal complications. Corticosteroids are the first line of treatment, but a low threshold for blood transfusion should be considered to correct low haemoglobin in pregnancy. An adequate multidisciplinary input and planning is the key to ensure optimal perinatal outcome. We decided to report this case to highlight the implications of pregnancy on DBA and vice versa, taking into consideration the safest approach for the best possible outcomes for the mother and her baby.

**Keywords:** Diamond Blackfan Anaemia. Red blood cell disorder. Blood transfusion. Pregnancy outcome.

**DOI:** <https://doi.org/10.47391/JPMA.1805>

### Introduction

Diamond Blackfan Anaemia (DBA) is a rare autosomal dominant disorder characterised by the failure of bone marrow to produce red blood cells. Approximately 90% of DBA cases are diagnosed during an infant's first year of life and there are often associated physical abnormalities. Treatment of DBA is complex and can range from frequent blood transfusions to steroid regimens and even bone marrow transplants in severe cases. There are few reported cases of successful pregnancies complicated by maternal Diamond Blackfan Anaemia due to the challenges of treatment and associated antenatal complications, including pre-eclampsia, intrauterine growth restriction, miscarriage, and foetal death.

We present the case of a woman with DBA who had a successful pregnancy and delivery which is attributed to the optimisation of management and careful monitoring of her condition by a multi-disciplinary team.

### Case Report

This 33-year-old nulliparous female presented to us in

.....  
Department of Obstetrics and Gynaecology, Yeovil Hospital NHS Foundation Trust, United Kingdom.

**Correspondence:** Shumaila Tabassum. Email: shumaila1910@gmail.com

April 2019 at Yeovil Hospital, Yeovil, United Kingdom, for her obstetric review. She was diagnosed with Diamond Blackfan Anaemia when she was eight months old. She was initially managed with intermittent blood transfusions and eventually required the addition of steroids. From her mid-teens onwards, she was managed with steroids alone, however, several trials to reduce the steroid dose were unsuccessful as it would result in a drop in haemoglobin.

At age 33, she conceived spontaneously and had her first obstetric clinic review at 12 weeks of gestation. At this time, her haemoglobin was stable at 10.6 g/dL on a regimen of Prednisolone 10-15mg on alternate days. She was closely monitored by a multidisciplinary team which comprised a Consultant Obstetrician, Foetal Medicine Unit, Haematologist, Anaesthetist, and a Paediatrician. She remained normotensive throughout the pregnancy and was on low dose Aspirin from 12 weeks onwards until delivery. Weekly ultrasound scans with Doppler were performed from 28 weeks of gestation onwards to monitor the baby who appeared small-for-gestational age with a normal Doppler.

At 21 weeks of gestation, her haemoglobin dropped to 8.0g/dL requiring a transfusion of 2 units Packed Red Cells, following which the haemoglobin corrected to 9.6 g/dL. From 30 weeks of gestation onwards, she received weekly full blood count monitoring and fortnightly Packed Red Cell transfusions to maintain a stable haemoglobin level.

At 38 weeks of gestation, she had a spontaneous onset of labour, and an uneventful vaginal delivery following six hours of uncomplicated labour, giving birth to a healthy boy weighing 5lb 13oz with a birth centile 11. Her post-partum haemoglobin was initially recorded as 12.0g/dl but dropped to 10.0 g/dl on day two requiring a further transfusion of 2 units Packed Red Cells. Post-natal she continued Prednisolone 10 mg (alternate days) with weekly full blood count monitoring. One week post-natal her haemoglobin remained stable at 11.9 g/dL.

The new-born's checks were reassuringly normal, with the baby having unremarkable haematology at birth. Close follow-up was arranged because of the risk of inherited

**Table:** Monitoring of haemoglobin levels and treatment modalities offered at various stages of pregnancy, labour and post-partum.

Timeline	Haemoglobin values (g/l)	Treatment
Pre-pregnancy	>100	Prednisolone 10 mg on alternate days
12-week gestation	106	Prednisolone 10-15mg on alternate days
21-week gestation	80	Transfusion of 2 units Packed Red Cells
30-38 week gestation	76-106 (on weekly blood counts)	Fortnightly transfusion of 2 units Packed Red Cells
Pre-labour	116	Optimum level of haemoglobin
Day-1 post-partum	120	Optimum level of haemoglobin
Day-2 post-partum	100	Transfusion of 2 units Packed Red Cells
Day-7 post-partum	119	Prednisolone 10 mg on alternate days

DBA and the baby was later diagnosed to be unaffected by DBA.

The ongoing outpatient controls of the patient with the haematologist show adequate levels of haemoglobin maintained at the pre-conception doses of steroids, not requiring any further blood transfusion.

## Discussion

Diamond Blackfan Anaemia (DBA) is a rare genetic disorder, with an autosomal dominant inheritance,<sup>1</sup> that was first reported by Josephs in 1936,<sup>2</sup> and later described as a distinct clinical entity by Diamond and Blackfan in 1938.<sup>3</sup> It is characterised by a defect in which erythroid progenitors and precursors are highly sensitive to death by apoptosis, leading to pro-apoptotic erythropoiesis and red cell failure, congenital anomalies, growth failure, and predisposition to cancer.<sup>4</sup> The prevalence of DBA, without ethnic predilection, is estimated to be between 5-7 per million live births, with both sexes equally affected.<sup>5</sup>

The diagnostic criteria for DBA, presented in 1976 by Diamond et al,<sup>6</sup> is still considered the accepted standard. Criteria includes symptomatic anaemia presenting before the first birthday, with near normal, but variable, neutrophil and/or platelet count, lack of reticulocytes, macrocytosis, and normal marrow cellularity with a deficiency of red cell precursor. Certainly, these diagnostic criteria define "classical" DBA; however, the presentation of affected individuals in "non-classical" ways is not uncommon.<sup>7</sup> For example, individuals may present without anaemia, with a mild haematological phenotype (mild normocytic anaemia only), transient neutropenia, or later than one year of age. Based on data from international DBA registries, approximately 50% of DBA patients have one or more congenital abnormalities.<sup>8</sup> Given the unusual presentation of "non-classical" DBA, careful diagnosis is particularly important, especially when reproductive choices are being made. Pre-natal diagnosis is now possible for DBA if a familial mutation has previously been identified by genetic testing, and more

recently, Preimplantation Genetic Diagnosis (PGD) has become available.

With advances in early diagnosis and clinical care, DBA is evolving from an exclusively childhood disorder to a disorder also affecting adults. Improvements in the medical management of pregnant women with DBA have resulted in an increased reproductive potential. However, to date, no prospective data exist that analyses pregnancy in women with DBA. For any

woman with DBA contemplating pregnancy, pre-pregnancy counselling and close monitoring with multi-disciplinary input is the key to achieving successful pregnancy outcomes. A thorough maternal assessment should be performed to identify any co-morbidity that may interfere with the pregnancy, including the presence of blood-borne infections, iron overload, diabetes mellitus, hypothyroidism, or cardiomyopathy. A survey from the French and German registries reviewed 64 pregnancies in 26 women with DBA.<sup>9</sup> Of the 64 pregnancies, 34 (53%) were live births, of which 13 infants were subsequently diagnosed with DBA. Complications were observed in 42 of the pregnancies, and included miscarriage, pre-eclampsia, foetal growth restriction, pre-term delivery, intra-uterine foetal death, and congenital foetal malformations. Interestingly, several of these complications are similar to those seen in Placental Vascular Disease. Although this has never been documented, or directly linked to DBA-related pregnancies, it has been suggested that treatment with aspirin could be of benefit.<sup>9</sup> Given this, foetal well-being should be closely monitored throughout the pregnancy with ultrasound and Doppler to screen for congenital abnormalities including hydrops foetalis, and to assess for potential placental vascular disorder.

Treatment of DBA in pregnancy can be particularly challenging, with corticosteroids remaining the first line treatment. Approximately 80% of DBA patients are responsive to an initial course of steroids.<sup>10</sup> However, steroid-responsive women often experience an increased requirement for steroid in pregnancy or become transfusion dependent. The haemoglobin concentration to be maintained in pregnancy has not yet been established; however, for pregnant women with DBA requiring regular blood transfusions, a maintenance haemoglobin level of 10.0 g/dL has been suggested.<sup>9</sup> The risk of iron overload for those requiring frequent blood transfusions appears as an alarming issue. There are no clear guidelines available on the use of iron chelators in DBA patients and in general, iron chelation therapy during pregnancy remains controversial.<sup>11</sup> However, it

seems reasonable to consider the recommendations from other rare anaemias, such as thalassemia. Hence, iron chelation should be optimised prior to conception since the use of most chelators is contraindicated in pregnancy. However, in pregnant women with severe iron overload, iron chelation should be considered in the third trimester, with a preference for Deferoxamine, based on the data available from pregnant women with thalassemia.<sup>9</sup> Curative treatment can be achieved by haematopoietic stem cell transplantation (HSCT); however, its role is controversial and can only be considered outside the pregnancy.<sup>12</sup>

## Conclusion

Due to the sparsity of available data on pregnancy and DBA, we still lack clear description of risk factors and pregnancy outcomes. Although a substantial data is available on DBA in general, there is a growing concern that not many recent studies can be found in the literature on 'DBA and pregnancy' in particular. The largest prospective study available so far from French and German registry,<sup>9</sup> dates to 2006 and did not consider whether the low dose aspirin had any impact on the placental vascular complications linked to DBA in pregnancy. In our case, the woman was commenced on low dose Aspirin from 12-week gestation and had a reasonably good pregnancy outcome with no evidence of pre-eclampsia, preterm delivery, or stillbirth, and the baby had a birth centile of 11. Our case, therefore, provides a strong recommendation on considering the low dose aspirin in pregnant women with DBA. With multi-disciplinary care, pregnancies can be tolerated well and managed to a successful outcome as highlighted by this case. However, further research into the management of pregnancy complicated by maternal DBA is needed to guide and regulate practice.

**Consent for Publication:** Verbal and written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review on request.

**Disclaimer:** None to declare.

**Conflict of Interest:** None to declare.

**Funding Disclosure:** None to declare.

## References

1. Diamond-Blackfan anaemia. Genetic and Rare Diseases Information Centre (GARD). [Online] [Cited 2021 Jan 26]. Available from: URL: <https://rarediseases.info.nih.gov/diseases/6274/blackfan-diamond-syndrome>.
2. Da Costa L, O'Donohue MF, Dooijeweert B, Albrecht K, Unal S, Ramenghi U, et al. Molecular approaches to diagnose Diamond-Blackfan anemia: The EuroDBA experience. *Eur J Med Genet* 2018; 61: 664-73.
3. Noel CB. Diamond-Blackfan anaemia RPL35A: a case report. *J Med Case Reports* 2019; 13: 185.
4. Vlachos A, Osorio DS, Atsidaftos E, Kang J, Lababidi ML, Seiden HS, et al. Increased prevalence of congenital heart disease in children with Diamond Blackfan Anaemia Suggests Unrecognised Diamond Blackfan Anaemia as a Cause of Congenital Heart Disease in the General Population: A Report of the Diamond Blackfan Anaemia Registry. *Circ Genom Precis Med* 2018; 11: e002044.
5. Diamond-Blackfan anaemia: MedlinePlus Genetics. [Online] [Cited 2021 Jan 26]. Available from: URL: <https://medlineplus.gov/genetics/condition/diamond-blackfan-anemia#diagnosis>.
6. Tyagi A, Gupta A, Dutta A, Potluri P, Batti B. A Review of Diamond-Blackfan Anemia: Current Evidence on Involved Genes and Treatment Modalities. *Cureus* 2020; 12: e10019.
7. Steinberg-Shemer O, Keel S, Dgany O, Walsh T, Noy-Lotan S, Krasnov T, et al. Diamond Blackfan Anaemia: A Nonclassical Patient with Diagnosis Assisted by Genomic Analysis. *J Paediatr Haematol Oncol* 2016; 38: e260-2.
8. Bartels M, Bierings M. How I manage children with Diamond-Blackfan anaemia. *British J Haematol* 2019; 184: 123-33.
9. Taher AT, Iolascon A, Matar CF, Bou-Fakhredin R, de Franceschi L, Cappellini MD, et al. Recommendations for Pregnancy in Rare Inherited Anaemias. *Hemasphere* 2020; 4: e446.
10. Lahoti A, Harris YT, Speiser PW, Atsidaftos E, Lipton JM, Vlachos A. Endocrine Dysfunction in Diamond-Blackfan Anemia (DBA): A Report from the DBA Registry (DBAR). *Paediatr Blood Cancer* 2016; 63: 306-12.
11. Diamantidis MD, Neokleous N, Agapidou A, Vetsiou E, Manafas A, Fotiou P, et al. Iron chelation therapy of transfusion-dependent beta thalassemia during pregnancy in the era of novel drugs: is deferasirox toxic? *Int J Hematol* 2016; 103: 537-44.
12. Diamond Blackfan Anaemia - NORD (National Organisation for Rare Disorders). NORD (National Organisation for Rare Disorders). [Online] [Cited 2021 Jan 20]. Available from: URL: <https://rarediseases.org/rare-diseases/anemia-blackfan-diamond/>.