CASE REPORT

A case series review of patients with Thrombocytopenia and Absent-Radii syndrome (TARS) and their management during pregnancy

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Abstract

Bleeding diatheses due to platelet-related disorders can present challenges to treating clinicians, especially in the context of peri- and post-partum patients in the obstetric setting. Thrombocytopenia and Absent-Radii syndrome (TARS) is an inherited disorder characterized by reduced bone marrow platelet production, skeletal deformities affecting radii and other limbs; cardiac, renal, and other heterogeneous anomalies may occur. It is caused by the co-inheritance of a microdeletion and a nucleotide polymorphism in the R8M8A gene on chromosome 1. Bleeding phenotype is more severe than platelet numbers which might predict especially in infants but improves with age. There is minimal literature regarding the impact of pregnancy and puerperium. We describe the management of three pregnancies in the hematology-obstetrics clinic. As platelet counts normally decrease through pregnancy, close monitoring is required in TARS. No major bleeding was seen antenatally but two required platelet transfusions during labor. No other treatment definitively improves bleeding, although case reports of steroids claim variable success. Tranexamic acid may be helpful, and thrombopoietin agonists represent a potential future option.

Case 1

A 24-year-old woman was referred in her sixth pregnancy with a platelet count of 73x10^9/L (history of 3 miscarriages, 2 terminations of pregnancies). Her only bleeding occurred after orthopedic surgery, requiring blood and platelet transfusions. She remained asymptomatic throughout pregnancy. Her platelet count fell to 40x10^9/L at term. Platelet transfusion was not required, and she had a normal vaginal delivery. Standard measures to minimize trauma to the neonate were instituted, and the cord blood platelet count was 201x10^9/L. Postnatally, there was no excessive bleeding, and 6 weeks later, platelet count was 101.

Case 2

A 23-year-old woman was referred at 6 weeks’ gestation following IVF. She had partial Thrombocytopenia and Absent-Radii syndrome (TARS) with one radius affected. Her platelet count had varied, with occasional drops to single figures, during infections. Booking platelet count was 94x10^9/L. Scans at 16 weeks demonstrated normal radii in the fetus. Her platelet count fell progressively to a level of 31 x10^9/L by 26 weeks, then remaining stable to delivery. A delivery plan outlined precautions for an atraumatic birth, platelet transfusion was given at delivery and the third stage of labor was active managed with intravenous syntocinon.

Case 3

A 32-year-old woman with TARS and seronegative arthritis was referred at 21 weeks’ gestation in her first pregnancy. The baseline platelet count was 70–110x10^9/L. Booking platelet count was 73x10^9/L decreasing to 48x10^9/L at 28 w. A detailed scan at 20 weeks showed no fetal abnormalities.

She was monitored 4-weekly and just prior to delivery had dropped further to 26x10^9/L. Delivery was by elective cesarean at 38 weeks due to breech presentation, covered with two pools of platelets with no abnormal bleeding either peri- or postpartum.

Five years later, she booked at 13 w, with a platelet count of 84x10^9/L, falling to 44x10^9/L by 26 weeks. Unfortunately, the patient contracted streptococcal pneumonia and prematurely ruptured her membranes at 30 + 3 weeks, complicated by antenatal hemorrhage and placental abruption necessitating emergency lower segment cesarean section under general anesthetic. Blood loss was 1100 ml treated with platelet transfusions and tranexamic acid.

Discussion

Bone marrow examination in TARS demonstrates low megakaryocyte numbers with the preservation of other lineages. Ballmaier et al. [1] reported elevation of thrombopoietin in all patients, suggesting reduced receptor sensitivity to TPO. Bleeding phenotype appears out of proportion to platelet count.

Infants have bleeding problems, but platelet count rises rapidly within the first years, reaching near-normal levels in adulthood; exacerbations occur due to various stresses, infection, and diet in addition to pregnancy. Patients often have associated cardiac, renal, and joint problems, and cow’s milk intolerance. Limb abnormalities may be simple radial aplasia or involve skeletal
structure akin to thalidomide. The radial artery is preserved suggesting primary aplasia rather than vascular insufficiency. Skeletal effects are also commonly observed in the legs and feet [2]. Occasionally affected females have urogenital anomalies such as absent uterus [3].

The condition was originally described as autosomal recessive, but more recent work by Klopocki et al. [4] suggested TARS does not fit into standard inheritance pattern on a single gene, and a microdeletion on chromosome 1q21.1 was found in all cases. As also present in 32% of unaffected family members, this suggests that it is necessary but not sufficient to cause the syndrome. Further studies demonstrate that nearly all TARS patients carry single nucleotide polymorphisms in one allele of the RBM8A gene, coded in the 1q21.1 region [5].

The hypothesis is that one causative factor is inherited from each parent, i.e. compound inheritance of a null allele and specific SNP (in the majority of cases). Mutations in other genes have been found as part of a wider spectrum of symptoms but may represent other diseases.

There is little in the medical literature about TARS in pregnancy and its management. In our cases, all three showed a marked reduction in platelet count during pregnancy but with no bleeding complications for the first two. Bleeding in the third case was more likely obstetric rather than due to thrombocytopenia.

However, TARS may present problems for obstetric anesthesia. Thrombocytopenia may prevent safe neuraxial anesthesia. The platelet transfusion guidelines from the British Society of Hematology [6] recommend a minimum platelet count of 80 \( \times 10^9/L \), although lower thresholds may be acceptable in selected patients [7]. Platelet transfusion may be required before neuraxial anesthetic, with confirmation of an acceptable platelet count post transfusion. Consider the possibility of HLA antibodies in pretransfused patients as the availability of matched platelets can take several hours.

Vascular access may be difficult depending on the degree of upper limb deformity; brachial access may even be impossible. Repeated use of veins, e.g. for platelet transfusions, can also present challenges. Upper limb arterial BP monitoring may be difficult, with alternative sites needed.

Other issues include micrognathia, present in 50% cases, which may present difficulty in intubation, as well as cardiac and renal abnormalities, which should be assessed antenatally and prior to delivery.

Two of the women had difficulty conceiving, suggesting a link between TARS and reduced fertility.

Reassuringly, all were managed with platelet transfusions and did not require extreme measures. As a disorder of platelet production, there are few therapeutic strategies to improve the count beyond transfusion. Medications that affect platelet function should be used cautiously, with a risk-benefit ratio of aspirin for prevention of pre-eclampsia and increased bleeding risk. Postpartum use of NSAIDs should be avoided. Tranexamic acid and desmopressin have been used as an adjunctive treatment for bleeding in patients with TARS.

There is one case report of recombinant factor VIIa use in planned surgery in a patient with a bleeding phenotype; however, this unlicensed use of the product is not recommended by the company. Finally, while there is no published evidence at the current time, thrombopoietin receptor agonists may represent potential therapeutic options. There are reports of these agents used in pregnancy for women with refractory ITP, although no data for use in TARS as yet.

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We would be grateful for your consideration of the submitted article. This paper examines the management of pregnancy and specifically, of bleeding, in patients with Thrombocytopenia and Absent Radii Syndrome (TARS). This is a rare syndrome but not so rare as to be irrelevant. There is very little literature on this topic and even less discussion of its management during pregnancy; in addition, there are no consensus guidelines. We have used our experiences with three different patients as well as a thorough search of the existing literature to discuss the expected clinical course and potential therapeutic options. We hope you find this interesting and valuable.

Declaration Of Interest

The authors declare there are no conflicting interests regarding the publication of this article.

Contributorship

BM planned the case series. All three authors contributed to the body of the text. DH wrote the initial draft with both BM and SP adding content as well as revisions.

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