

Case Study: Refractory immune thrombocytopaenia and use of eltrombopag in pregnancy

Dr Laura Butler - Calderdale and Huddersfield NHS Foundation Trust, UK; Dr Lucy McCann - Barts Health NHS Trust, UK; Dr Etienne Ciantar - Leeds Teaching Hospitals NHS Trust, UK; Dr Quentin Hill - Leeds Teaching Hospitals NHS Trust, UK

Background:
Immune thrombocytopaenia (ITP):

- Isolated thrombocytopaenia with an overall prevalence in adults estimated as 9.5 per 100,000¹.
- More common in adult females, and complicates 1-10:10,000 pregnancies.
- A diagnosis of exclusion, with autoimmune disorders and, in pregnancy, gestational thrombocytopaenia considered among differential diagnoses.
- To diagnose: platelet levels need to be less than 100 x10⁹ /l.
- Both platelet destruction and reduced megakaryopoiesis are thought to play a part in causation.
- ITP in pregnancy raises a multitude of considerations antenatally, intrapartum and postnatally. Alongside coexisting factors, mode of delivery requires consideration in relation to anticipated maternal blood loss, but also potential for foetal thrombocytopaenia, particularly in the context of assisted delivery and other intrapartum procedures (e.g. fetal scalp electrodes and fetal blood sampling). Accepted safe platelet levels for administration of regional analgesia is another issue that can significantly change intrapartum management. Venous thromboembolism prophylaxis, and neonatal preparation are also features that require attention and planning.

ITP treatment:

- Dependent on severity.
- In the general population steroids and immunoglobulin treatments are first line and azathioprine second line. Thrombopoietin receptor agonists e.g. eltrombopag and romiplostim have more recently been used, as have biological therapies such as rituximab.
- In pregnancy treatment with steroids and intravenous immunoglobulins (IVIG) is well established with an 80% response rate for both options used separately. Due to placental transfer, treatments such as rituximab are not used in pregnancy.
- Thrombopoietin receptor agonists are not used routinely in pregnancy predominantly due to a lack of data and knowledge. In certain instances of severe, refractory thrombocytopaenia, however, they have been considered.
- Howaidi et al² suggest that eltrombopag and romiplostim have a relatively safe profile. They do however caution that there may be an association between eltrombopag and low fetal birth weight when used in the first and second trimesters though case studies are limited and may contain confounders.

Case:
History

- 28-year-old
- Smoker
- Para 2 (1x caesarean section, 1x vaginal delivery)
- ITP diagnosed in first pregnancy
- Presented at 28 weeks' pregnant with epistaxis, easy bruising and petechiae.
- In both previous pregnancies, responded to IVIG and steroid treatment
- Previous deliveries without significant complications.
- Both babies were diagnosed and treated for thrombocytopaenia

This pregnancy

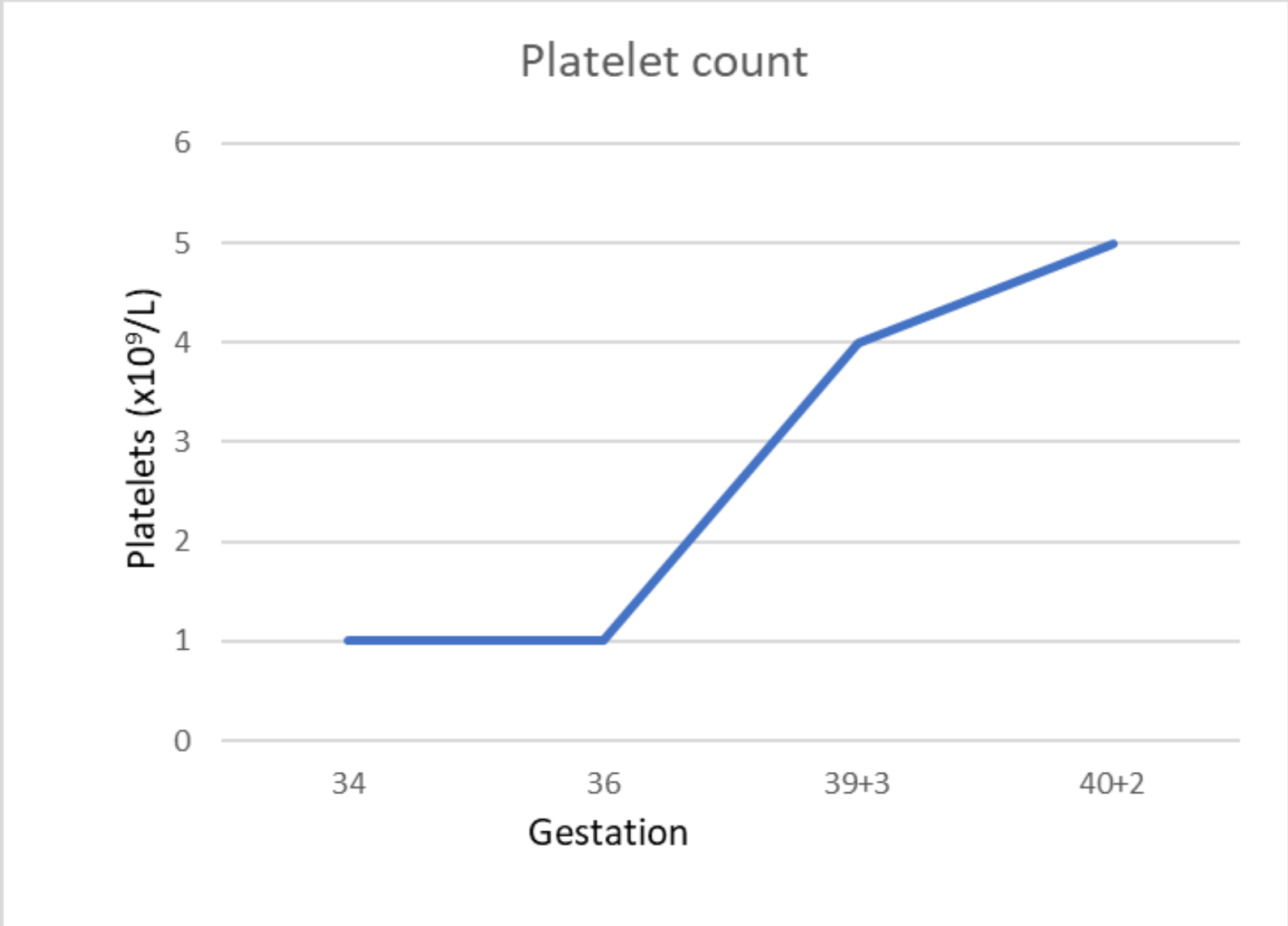
- Unresponsive to steroids, IVIG and platelet transfusions.
- Thiopurine methyltransferase (TPMT) level ADAMTS13 were normal.
- Cytomegalovirus (CMV) and antinuclear antibodies (ANA) were negative.
- **28 weeks'** gestational age - commenced on azathioprine 100 mg/day and prednisolone 10 mg/day.
- **34 weeks'** gestational age - platelet levels were 1x10⁹ /L
- Commenced on 50 mg/day eltrombopag (off licence) alongside the existing dose of azathioprine and prednisolone.
- **36 weeks'** gestational age - platelets remained at 1x10⁹ /L. However, it emerged she had self-discontinued prednisolone and azathioprine and only commenced on eltrombopag one week prior. She was asked to restart azathioprine 100 mg/day with prednisolone 10 mg/day alongside the eltrombopag.
- Subsequently had an Iron infusion
- At **38 weeks**, it was discovered that she had ceased her medications for approximately one week following an episode of vomiting and haematemesis. She re-commenced prednisolone and eltrombopag but declined to take azathioprine due to side effects.
- Eltrombopag dose was up titrated to 75 mg/day. A further dose of IVIG was administered.
- At **39+3 weeks** platelet count was 4x10⁹/L and haemoglobin was 115g/l. She received 250mg methylprednisolone with a plan for platelet transfusion support at time of planned induction at 40+1 weeks.

Labour and delivery

- **40+2 weeks'** gestational age - platelet count was 5x10⁹/l and haemoglobin was 94g/L. Tranexamic acid and platelet transfusions were given during labour and delivery as planned.
- Emergency fully dilated lower segment caesarean section for failure to progress in labour at 40+2 weeks.
- A live female weighing 3659g was delivered, with APGAR Scores of 6/10/10.
- There were no noted neonatal malformations or haemorrhagic episodes, but inflation and ventilation breaths were required. Neonatal immunoglobulins and platelets were given on day 1 of life, and levels were monitored throughout her inpatient stay and she was diagnosed with isoimmune thrombocytopenia.
- Estimated blood loss was 1,500mls.
- Minimal maternal complications during the caesarean section and the patient was discharged two days post-partum.

Post natal

- Re-presented one day post discharge with sepsis and a platelet count of 1x10⁹/L.
- Haematoma was found under the caesarean section scar which was managed conservatively with antibiotics.
- In total, four platelet transfusions were administered throughout her stay plus further immunoglobulins.
- Discharged 10 days later with a platelet count of 4 x 10⁹ /L and a haemoglobin of 100 g/L
- Switched from eltrombopag to romiplostim 3µg per kg weekly alongside completion of her antibiotic course of ciprofloxacin (500 mg BD)
- At a follow-up three weeks postpartum, she had a haemoglobin level of 112 g/L platelet count of 2 x 10⁹ /L after missing a dose of romiplostim.



Discussion:

This case clearly demonstrates the difficulties of managing refractory ITP in pregnancy and the aim of optimising patients where possible prior to delivery.

It is unclear why treatments that this patient had responded to in past pregnancies were ineffective this time. Having the option of thrombopoietin receptor agonists gave another avenue of treatment in this refractory case, and did not raise any safety concerns. This is in keeping with other case studies such as that of Desai, Tiwari, & Chauhan³ and provides further evidence that thrombopoietin receptor agonists may be a viable option in treating refractory ITP in pregnancy. If Eltrombopag is the thrombopoietin receptor agonist used, it may have more of a place in third trimester use rather than earlier in pregnancy to mitigate concerns regarding low birth weight, and low birth weight was not a concern for this patient.

Further studies, research and data collection are required to assemble a comprehensive safety profile across all gestations.



References

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