

Four Pregnancies in Two Patients with Essential Thrombocythaemia— A Case Report

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Abstract

Introduction: We report our experience of 4 pregnancies in 2 patients who had essential thrombocythaemia (ET). **Clinical Picture:** Two patients with ET were managed with a variety of therapeutic approaches including the use of low-dose aspirin, plateletpheresis, hydroxyurea and alpha-interferon in the course of their 4 pregnancies. **Treatment and Outcome:** One patient had 2 successful pregnancies despite having platelet counts in excess of $1000 \times 10^9/L$ antenatally. The second patient had an intrauterine fetal death during the third trimester of her first pregnancy but had a successful second pregnancy. **Conclusion and Clinical Implications:** Management of ET in pregnancy is still very much individualised. The impact of various treatment modalities on the pregnancy outcome remains to be proven but a favourable pregnancy outcome is possible.

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Introduction

Essential thrombocythaemia (ET) is a rare myeloproliferative disease which manifests with an elevated platelet count. It presents predominantly in the middle-aged population, occurring slightly more frequently in women than men.¹⁻⁵ The median age of diagnosis is approximately 60 years and as many as 20% of patients are diagnosed before age 40.⁶ With the advent of automated platelet counting, ET is being recognised in a greater numbers of patients. In fact, almost one third of patients with ET are discovered incidentally.^{3,7,8} The remainder present with either vasomotor disturbances (headaches, dizziness, acral dysesthesia, erythromelalgia, visual symptoms, livedo reticularis) or thrombohaemorrhagic manifestations.⁵ In addition, the clinical course is characterised by frequent miscarriages⁹ and, rarely, transformations into acute myeloid leukaemia (AML) or myelofibrosis with myeloid metaplasia.⁴

Any treatment decision in a patient with ET must take into consideration the fact that life expectancy in this disease is nearly normal¹⁰ and the treatment themselves are not without risk. The morbidity of treatment versus disease must be weighed separately for each individual patient

according to the risk factors. This is to enable the clinician to arrive at a decision as to whether to observe carefully or to treat, and to decide which treatment regimen to implement.

ET in pregnant women necessitates joint care by both the haematologist as well as the obstetrician because of both maternal and obstetrical implications. Currently, there is no consensus on the optimal management of ET in pregnancy. Given the rarity of this condition, it is very unlikely that therapeutic options will be subjected to a prospective, randomised control trial to address this issue. In the few available case series and individual case reports, the management of ET in pregnancy has varied from close observation with expectant treatment to the use of platelet lowering agents such as α -interferon. The obstetric outcome also runs a variable course, ranging from early miscarriage to repeated successful pregnancies.

We report our experience in the management of 2 local patients with ET who had 4 pregnancies.

Case Report

Case 1

A 26-year-old primiparous patient presented at 8 weeks amenorrhoea for threatened abortion. An ultrasound scan

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confirmed a viable pregnancy. However, a routine full blood count revealed a platelet count of $1800 \times 10^9/L$ with a normal white blood cell count and haemoglobin. A diagnosis of essential thrombocythaemia was established according to the criteria defined by the Polycythemia Vera Study Group.¹¹ She was jointly managed by a high-risk obstetric team and a haematologist. She underwent twice weekly plateletpheresis in the first trimester. Interferon therapy at the dose of 3 million units thrice per week was instituted in the second trimester and this was continued till delivery. Although the platelet count remained elevated at a median of $1435 \times 10^9/L$ (range, 827 to $2100 \times 10^9/L$) (Fig. 1), the pregnancy course was relatively uneventful. Low-dose aspirin at a dose of 100 mg per day therapy was commenced upon diagnosis of pregnancy and stopped at 36 weeks for its antiplatelet effect. She developed gestational diabetes at 33 weeks but good glycaemic control was achieved on diet alone. Serial ultrasound scans revealed good fetal growth. Umbilical artery Doppler ultrasound was normal. At 38 weeks, induction of labour was performed for oligohydramnios diagnosed on ultrasound. This resulted in a normal vaginal delivery of a healthy male infant weighing 2665 g. The postpartum course was uncomplicated.

Two years later she again became pregnant. The platelet count at the booking visit at 6 weeks gestation was $970 \times 10^9/L$. This pregnancy was again complicated by gestational diabetes requiring only dietary control. Only low-dose aspirin of 100 mg per day was instituted this time until 36 weeks of pregnancy. The pregnancy was again uneventful despite a median platelet count of $986 \times 10^9/L$ (range, 928 to $1075 \times 10^9/L$) (Fig. 1). She went into labour at 38 weeks and delivered a healthy female baby weighing 3300 g.

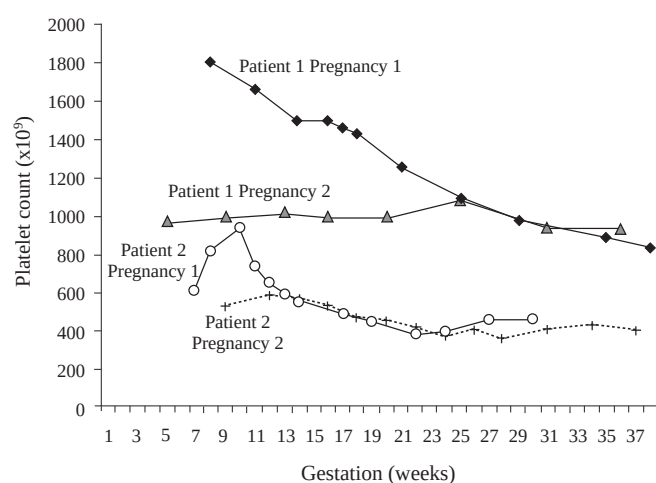


Fig. 1. Antenatal platelet count of the 4 pregnancies.

Case 2

A 30-year-old primipara with a known history of essential thrombocythaemia presented at 7 weeks gestation with an unplanned pregnancy. She conceived while being treated with hydroxyurea 500 mg per day. The platelet count at booking was $805 \times 10^9/L$. Due to the concern of possible teratogenic effects of hydroxyurea, this was discontinued and she was started on twice weekly plateletpheresis. Low-dose aspirin at a dose of 100 mg per day was added. The platelet count was maintained at a median of $430 \times 10^9/L$ (range, 347 to $586 \times 10^9/L$) (Fig. 1). On the 13th week of her pregnancy, the plateletpheresis was discontinued and hydroxyurea 500 mg per day was restarted. The pregnancy was uneventful initially. Ultrasound examination at 20 weeks did not reveal any fetal abnormalities. At 26 weeks, ultrasound scans suggested that fetal growth parameters were along the 5th percentile. However, Doppler studies of the umbilical artery did not reveal any absent or reversed end-diastolic flow indicative of placental insufficiency. Estimation of liquor volume by ultrasound was consistently normal and at 30 weeks, the fetus continued to grow steadily along the 5th percentile. Unfortunately, intrauterine fetal death occurred at 33 weeks. At the time when fetal death occurred, her platelet count was $400 \times 10^9/L$. External examination of the fetus and blood investigations did not reveal any apparent cause for the fetal loss. Karyotyping of the fetus and a postmortem were declined by the parents.

She conceived spontaneously a year later. The platelet count at booking was $531 \times 10^9/L$. In the second pregnancy, hydroxyurea was again discontinued at conception and she was treated with low-dose aspirin at a dose of 100 mg daily. The median platelet count in the first and second trimesters was $523 \times 10^9/L$ (range, 401 to $586 \times 10^9/L$). This platelet count decreased steadily to a median of $397 \times 10^9/L$ (range, 347 to $430 \times 10^9/L$) in the third trimester which is within the normal range. Ultrasound biometry showed good fetal growth initially, which was consistently along the 50th percentile. At 35 weeks, Doppler studies revealed increased umbilical artery resistance and slowing of the fetal growth velocity. Induction of labour was performed at 35 weeks which resulted in the birth of a healthy female baby weighing 1940 g. Aspirin was discontinued a week before the delivery. The platelet count at delivery was $295 \times 10^9/L$. No bleeding complications were sustained in the peripartum or postpartum period.

Discussion

Management of essential thrombocythaemia in pregnancy has been a challenge to the obstetrician and haematologist for decades. Many issues pertaining to indications for treatment, choice of platelet lowering agents and the possible adverse effects of therapeutic agents on pregnancy have not been resolved.

In 2 large case series,^{9,12} it has been found that live births occurred in 55% to 57% of the pregnancies. Fetal loss occurred in 45% of the pregnancies in one series,⁹ mostly during the first trimester. In another series,¹² there was fetal loss in 23% which occurred both during the second and third trimesters. There are conflicting results as to whether pharmacological therapy influences the outcome of pregnancy in ET. However, it is noteworthy that most reports of ET in pregnancy are individual case reports and case series and therefore, there is a potential for significant reporting bias.

Our patient in Case 1 had received the conventional therapy as reported by other case series or single case reports. Her extreme thrombocytosis was discovered incidentally during blood screening test in the first trimester. She did not have any thrombohaemorrhagic complication during the entire pregnancy despite persistent thrombocytosis of above $1000 \times 10^9/L$. Plateletpheresis was used as an interim measure in the first trimester to avoid the use of hydroxyurea or alpha-interferon.

The efficacy of plateletpheresis for ET in pregnancy has not been established. It is effective in rapidly reducing the platelet count in the short term for emergency situations. However, because of the high turnover rate of the platelet, the procedure needs to be done repeatedly, i.e. twice a week. This is inconvenient for both patient and doctor. Griesshammer et al¹³ in their literature review had identified only a few pregnant women with ET that have been treated with plateletpheresis. All the pregnancies resulted in live birth. However, in another series of 34 pregnancies published by Beressi et al,⁹ the benefit of plateletpheresis during delivery could not be substantiated. Plateletpheresis has been recommended to be reserved for patients with major bleeding at platelet counts in excess of $1000 \times 10^9/L$.¹³

Low-dose aspirin, via its inhibition of cyclooxygenase activity and subsequent prevention of thromboxane A_2 production, has been found to be safe and effective in the prevention of thrombotic complications in ET.^{14,15} Because placental insufficiency due to placental thrombosis appears to be the most common pathophysiologic event in ET,³ it is not surprising that aspirin is the most frequently used drug in all published reports. However, the effectiveness of aspirin remains unclear; retrospective study data are equivocal, especially since pregnancy can also be successful in the absence of antiplatelet therapy.³ In addition, a literature review revealed that a decline in platelet count was frequently observed, which was associated with successful pregnancy.¹³ This has been well demonstrated in the our patient in Case 2 during her second pregnancy. Therefore, while aspirin may in fact lead to a higher success birth rate,

no definitive treatment recommendations can be made except that its use should be avoided for at least 1 week prior to delivery to reduce the risk of bleeding complications.¹⁶

Aspirin therapy is well known for potentially causing haemorrhagic complications. This is especially so in ET with a platelet count of above $1000 \times 10^9/L$, in which the disease per se is associated with a paradoxically increased risk of haemorrhage.¹⁷ Under these circumstances, there is no indication for the routine use of aspirin.

Alpha-interferon (IFN) has been used successfully in pregnancy.^{13,18} The advantage of IFN remains in its being non-leukaemogenic and non-teratogenic.¹⁹ However, IFN is expensive and notorious for its associated side effects which are often so severe as to warrant discontinuation of treatment in up to 25% of patients.²⁰ Nonetheless, the excellent safety record so far in terms of pregnancy outcome certainly made it one of the most attractive options.

Cytotoxic agents, such as hydroxyurea and busulphan, are potentially teratogenic and, therefore, should be avoided in the first trimester.¹³ However, in a recent review of the literature on the use of hydroxyurea in ET, AML, chronic myeloid leukaemia and sickle cell disease, there were no reports of fetal malformations in 9 patients exposed to hydroxyurea in the first trimester.²¹ Similarly, no ill effects to the fetus were observed following second and third trimester exposures. Our patient in Case 2 had exposure to hydroxyurea until the time of conception, and this was restarted and continued during her second and third trimester. It remains unclear if the use of hydroxyurea during her first pregnancy had resulted in her intrauterine fetal death.

Anagrelide, an oral imidazoquinazolin agent which has been approved by the Food and Drug Administration in March 1997 for specific use in ET, appears well tolerated.²² However, the safety of anagrelide in pregnancy has not been proven and therefore is not recommended.

In summary, the optimal management of essential thrombocythaemia in pregnancy is still a subject of controversy. Recommendations about treatment and non-treatment should be, as in the non-pregnant individual, made on the basis of several factors, including the risk of thrombohaemorrhagic complications, and the morbidity and side effects of the treatment itself. Low-dose aspirin and alpha-interferon appear to be safe although the impact on the pregnancy outcome remains uncertain. Plateletpheresis may be used as an interim measure to lower an excessively high platelet count in the first trimester of pregnancy to avoid the use of hydroxyurea or alpha-interferon.

REFERENCES

1. Michiels J J, Juvonen E. Proposal for the revised diagnostic criteria of essential thrombocythemia and polycythemia vera by the Polycythemia Vera Study Group. *Semin Thromb Hemost* 1997; 23:339-47.
2. Kutti J, Wadenvik H. Diagnostic and differential criteria of essential thrombocythemia and reactive thrombocytosis. *Leuk Lymphoma* 1996; 22:41-5.
3. Griesshammer M, Bangerter M, VanVliet H H, Michiels J J. Aspirin in essential thrombocythemia: status quo and quo vadis. *Semin Thromb Hemost* 1997; 23:371-8.
4. Tefferi A, Silverstein M N, Hoagland H C. Primary thrombocythemia. *Semin Oncol* 1995; 22:334-40.
5. Fenaux P, Simon M, Caulier M T, Lai J L, Goudemond J, Bauters F. Clinical course of essential thrombocythemia in 147 cases. *Cancer* 1990; 66:549-56.
6. Gruppo Italiano Studio Policitemia. Polycythemia vera: The natural history of 1213 patients followed for 20 years. *Ann Intern Med* 1995; 123:656-64.
7. Chistolini A, Mazzucconi M G, Ferrari A, la Verde G, Ferrazza G, Dragoni F, et al. Essential thrombocythemia: A retrospective study on the course of 100 patients. *Hematologica* 1990; 75:537-40.
8. Tefferi A, Silverstein M N, Pettit R M, Mesa R A, Solberg L A Jr. Anagrelide as a new platelet-lowering agent in essential thrombocythemia: Mechanism of action, efficacy, toxicity, current indications. *Semin Thromb Hemost* 1997; 23:379-83.
9. Beressi A H, Tefferi A, Silverstein M N, Pettit R M, Hoagland H C. Outcome analysis of 34 pregnancies in women with essential thrombocythemia. *Arch Intern Med* 1995; 155:1217-22.
10. Tefferi A, Fonseca R, Pereira D L, Hoagland C. A long-term retrospective study of young women with essential thrombocythemia. *Mayo Clin Proc* 2001; 76:22-8.
11. Murphy S, Peterson P, Iland H, Laszlo J. Experience of the Polycythemia Vera Study Group with the essential thrombocythemia: A final report on diagnostic criteria, survival, and leukemia transition by treatment. *Semin Hematol* 1997; 34:29-39.
12. Cincotta R, Higgins J R, Tippet C, Gallery E, North R, McMahon L P, et al. Management of essential thrombocythaemia during pregnancy. *Aust N Z J Obstet Gynaecol* 2000; 40:33-7.
13. Griesshammer M, Heimpel H, Pearson T C. Essential thrombocythaemia and pregnancy. *Leuk Lymphoma* 1996; 22:57-63.
14. Gruppo Italiano Studio Policitemia (GISP). Low dose aspirin in polythemia vera: a pilot study. *Br J Haematol* 1997; 97:453-6.
15. Van Genderen P J, Mulder P G, Waleboer M, van de Moesdijk D, Miciels J J. Prevention and treatment of thrombotic complications in essential thrombocythaemia: efficacy and safety of aspirin. *Br J Haematol* 1997; 97:179-84.
16. Barbui T, Finazzi G. Clinical parameters for determining when and when not to treat essential thrombocythemia. *Semin Hematol* 1999; 36:14-8.
17. Willoughby S, Pearson T C. The use of aspirin in polycythaemia vera and primary thrombocythaemia. *Blood Rev* 1998; 12:12-22.
18. Delage R, Demers C, Cantin G, Roy J. Treatment of essential thrombocythemia during pregnancy with interferon-alpha. *Obstet Gynecol* 1996; 87:814-7.
19. Elliot M A, Tefferi A. Interferon- α therapy in polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost* 1997; 23:463-72.
20. Lengfelder E, Griesshammer M, Hehlmann R. Interferon-alpha in the treatment of essential thrombocythemia. *Leuk Lymphoma* 1996; 22: 135-42.
21. Diav-Citrin O, Hunnisett L, Sher G D, Koren G. Hydroxyurea use during pregnancy: a case report in sickle cell disease and review of the literature. *Am J Hematol* 1999; 60:148-50.
22. Silverstein M N, Ayalew T. Treatment of essential thrombocythemia with anagrelide. *Semin Hematol* 1999; 36:23-5.