short report
Haematologica 1994; 79:360-363

ESSENTIAL THROMBOCYTHEMIA IN PREGNANCY: REPORT OF FOUR CASES

Franca Radaelli, Mariangela Colombi, Anna Teresa Maiolo

Servizio di Ematologia, Ospedale Maggiore, I.R.C.C.S. Istituto di Scienze Mediche, Università di Milano, Italy

ABSTRACT

We report four pregnancies in four patients with essential thrombocythemia (ET). In two cases pregnancy resulted in spontaneous abortion at 6 and 11 weeks of gestation, respectively. The other two had a full-term, normal delivery; one of them received no therapy during the pregnancy, whereas the other was treated with acetylsalicylic acid from 11 weeks for signs of threatened abortion. No thrombotic or hemorrhagic complications were observed in any of the patients during pregnancy or the post-partum period. We believe that pregnancy in patients with ET represents a risk. Close monitoring is therefore indispensable and antiaggregant therapy might be of benefit.

Key words: essential thrombocythemia, pregnancy, abortion, antiaggregant therapy

Essential thrombocythemia (ET) is a rare clonal myeloproliferative disorder of unknown origin, characterized by abnormal proliferation of bone marrow megakaryocytes and persistent peripheral thrombocytosis.[1] Its main clinical manifestations are a predisposition to hemorrhages and thromboses and functional symptoms such as paresthesias, dizziness, headache, hazy vision and scotomas.[2,3] Although ET is predominantly a disease of middle and old age, with the advent of automated platelet counting, an increasing number of asymptomatic women in childbearing age are found to have ET.[2,4]

Nevertheless, the total number of ET pregnancies in the literature is small. Recurrent abortion and/or fetal growth retardation are frequent complications in women with ET,[5-10] but it is still difficult to define the best therapeutic approach.

For this reason, we consider it useful to report the outcome of four pregnancies in four of the 69 female patients followed by us, 11 (16%) of whom are of childbearing age.

Case reports

All four patients fulfilled the diagnostic criteria of the Polycythemia Vera Study Group[7] and had a normal karyotype.

Patient #1 was diagnosed as having ET at the age 30 in September of 1986 when she presented spontaneous hematomas and severe paresthesias. Her platelet count was 1.9×10^9/L, bleeding time 11 min; platelet aggregation induced by ADP, arachidonic acid and epinephrine was markedly reduced. She was given melphalan 5 mg/day for 5 days a week but this treatment was stopped after 4 weeks because of myelosuppression (hemoglobin 9.5 g/dL, white blood cell count 1.2×10^9/L, platelets 11×10^9/L), which resolved with drug suspension. She became pregnant for the first time in February 1990, 40 months after suspension of cytoreductive therapy, when her platelet count was 850×10^9/L, but she aborted spontaneously at the 6th week of gestation (platelet count 970×10^9/L).

Patient #2 was 32 when ET was diagnosed in July 1988. Her platelet count was 910×10^9/L,

Correspondence: Franca Radaelli, Servizio Autonomo di Ematologia, Centro G. Marcora, Ospedale Maggiore, via F. Sforza 35, 20122 Milan, Italy. Tel. international +39.2.5451365. Fax. international +39.2.5466061.
Received January 27, 1994; accepted April 5, 1994.

Table 1. Hematologic characteristics and outcome of pregnancy in 4 ET patients.

n.	*age*	*pregnancy*	*plt count before pregnancy*	*plt count after pregnancy*	*therapy*	*outcome*	*complications*
1	34	first	850	970	—	SA (6 weeks)	—
2	33	third*	900	900	—	SA (9 weeks)	—
3	37	first	650	670	—	ND	—
4	21	first	680	700	ASA 300 mg/die	ND	—

Plt: platelets; SA: spontaneous abortion; ND: normal delivery; ASA: acetylsalicylic acid.
*The first after ET diagnosis.

bleeding time 5 min. Epinephrine-induced platelet aggregation was notably reduced. The patient was asymptomatic and thus not treated. She had had two normal pregnancies before the diagnosis of ET. Her third pregnancy occurred in January 1991, when her platelet count was 900×10^9/L, and ended in spontaneous abortion at 11 weeks (platelets 850×10^9/L).

ET was diagnosed in patient #3, a 37-year-old woman, in April 1987. She had a platelet count of 700×10^9/L and a bleeding time of 7 min, with spontaneous platelet aggregation and greatly reduced epinephrine-induced platelet aggregation. No treatment was given because she had no symptoms. Her first pregnancy started in October 1988 (platelet count 670×10^9/L); it was uneventful, and she had a full-term normal delivery. Her platelet count was then 950×10^9/L. The baby girl weighed 2950 g and had an Apgar score of 9 at 1 min. The placenta, which weighed 450 g, was without infarctions or hematomas. The post-partum period was normal.

Patient #4 was diagnosed has having ET when she was 21. Her platelet count was 680×10^9/L, bleeding time 6'30", and epinephrine-induced platelet aggregation was markedly decreased. She was asymptomatic and thus was not given therapy. Her first pregnancy occurred in September 1991, when she had a platelet count of 680×10^9/L. When signs of threatened abortion appeared (moderate vaginal bleeding and abdominal pain) at 11 weeks of gestation (platelets 700×10^9/L), treatment with acetylsalicylic acid 300 mg/day was started. The signs regressed completely, the patient remained asymptomatic and the pregnancy was monitored with serial clinical and ultrasound assessments. She had a normal delivery at term when the platelet count was 810×10^9/L. The male infant weighed 3200 g and had an Apgar score of 8 at 1 min. The placenta weighed 365 g and presented rare microinfarctions. The post-partum course was uneventful.

Hematologic characteristics and the outcome of the pregnancies of our patients are summarized in Table 1.

Discussion

Information on pregnancy in ET is still limited and often contradictory. Published data is summarized in Table 2. Some authors report normal pregnancies[11] and others describe an increased incidence of intrauterine death, fetal growth retardation and recurrent spontaneous abortion.[6,9,10] In these latter cases, the presence of numerous acute or chronic placental infarcts, with or without chorionic villous fibrosis, suggests greater thrombotic tendency in these patients that leads to placental ischemia and spontaneous abortion.[5,6,8]

Although these histological findings might justify the use of acetylsalicylic acid and/or heparin, it is difficult to define the best therapeutic approach since only a few cases have been reported in the literature and no controlled studies have been performed.

Furthermore, acetylsalicylic acid may increase the risk of bleeding in ET patients, particularly in those with a history of hemorrhagic events, and there is a lack of significant predictive correlations between laboratory tests and clinical complications.[3] In our patients the most frequent causes of early abortion could be excluded, except for smoking in the case of patient #1.

Table 2. Published data on outcome of pregnancies in patients with essential thrombocytemia.

references	*patients*	*pregnancies*	*treatment received*	*complications*	*outcome*
*Hoagland & Silverstein 1978	1	2	—	—	ND
*Kaibara et al., 1985	2	2	I —	—	IUD 30 weeks
*Bellucci et al., 1986	22				6 SA 2 ND 2 PD
*Falconer et al., 1987	2	7	I → VI — VII plateletpheresis	—	SA GR 34 weeks
*Mercer et al., 1988	2	2	I plateletpheresis II —	— —	ND IUD 36 weeks
*Linares et al., 1988	1	2	—	—	ND
Ferrari et al., 1989	1	1	ASA	abruptio placentae	IUD 27 weeks
Pineo et al., 1991	1	1	ASA	—	GR 38 weeks
Leone et al., 1991	8	10	I ASA II-III DP+HP IV → X —	— —	SA ND 2 SA 5 ND
Beard et al., 1991	6	9	I → IV ASA V ASA+HP VI ASA+plateletpheresis+HP VII → IX —	II leg ulcer — PIH+superficial thrombophlebitis VII incomplete abortion: hemorrhage	ND (I 37 wekks) ND ND VII SA 7 weeks
Petit et al., 1992	1	1	α-IFN	—	ND
Pardini et al., 1993	1	1	α-IFN → ASA	—	GR 37 weeks
Vianelli et al., 1993	1	1	α-IFN	—	Unknown
Frezzato et al., 1993	7	10	—	—	6 ND 1 SA 2 IUD 1 IA
Thronley et al., 1994	1	1	α-IFN+ASA	—	GR 36 weeks

ND: normal delivery; IUD: intrauterine death; SA: spontaneous abortion; PD: premature delivery; GR: growth retardation; HP: heparin; DP: dipyridamole; ASA: acetylsalicylic acid; PIH: pregnancy-induced hypertension; IA: induced abortion; IFN: interferon.
*from Beard et al., 1991.

She smoked 20 cigarettes a day, whereas the other 3 patients were non smokers. The decision not to administer acetylsalicylic acid to patient #1 was based on a history of spontaneous bleeding and a bleeding time of 11 minutes. Patient #2 was not given acetylsalicylic acid because she aborted so early in the pregnancy. In fact, most authors report that placental thrombotic events occur most frequently after the 17th week and therefore they recommend starting antiaggregant and/or anticoagulant therapy at this time.[4,8] Unfortunately, the abortions occurred too soon in patients #1 and #2 to study the histology of the placenta. Our third patient had a complication-free pregnancy and gave birth to a full-term healthy baby without having received any therapy. In the last patient antiaggregant therapy with acetylsalicylic acid was associated with complete resolution of the signs of threatened abortion, and the pregnancy was successful. Unlike other authors,[4] we did not observe a reduction in platelet count after the first trimester, nor did thrombotic or hemorrhagic complications arise during the pregnancy or the post-partum period in any of our patients.

As far as management of patients with a myeloproliferative syndrome during pregnancy is concerned, we feel that the teratogenic risk involved in treatment with cytotoxic drugs (alkylating agents, hydroxyurea), particularly during the first trimester, is too high to justify using them.[12] We have no experience with plateletpheresis, the role of which would seem to be limited to treatment of acute complications.[9,12]

Published data regarding the efficacy and safety of α-interferon (α-IFN) in pregnant women with ET is still limited; however, successful experiences have recently been described. In fact, α-IFN was used in the first trimester in two cases with good results and no ill effects;[13,14] other patients received IFN during the second and third trimesters with favorable results.[15]

Although untreated patients may experience uneventful deliveries,[16] acute or chronic placental infarcts are frequent and are often associated with spontaneous abortions and fetal growth retardation.[5,8,12] For these reasons we believe that pregnancy in patients with ET is a risk, and we think that antiaggregant therapy could be useful in reducing high fetal morbidity and mortality rates. The schedule and the best period for beginning such treatment still needs to be determined.

References

1. Murphy S. Primary thrombocythemia. In: Williams JW, Bentler E, Erslev AJ, Lichman MA, eds. Hematology. New York: McGraw Hill, 1990:232-6.
2. Mitus AJ, Schefer AI. Thrombocytosis and thrombocythemia. Hematol Oncol Clin N Am 1990; 4:157-78.
3. Colombi M, Radaelli F, Zocchi L, Maiolo AT. Thrombotic and hemorrhagic complications in essential thrombocythemia. Cancer 1991; 67:2926-30.
4. Leone G, De Stefano V, D'Addosio D. Trombocitemia essenziale e gravidanza. Haematologica 1991; 76(Suppl 3):365-7.
5. Kaibara M, Kobayashi T, Matsumoto S. Idiopathic thrombocythemia and pregnancy: report of a case. Obstet Gynecol 1985; 65(Suppl 3):185-95.
6. Bellucci S, Janvier M, Tobelem J, et al. Essential thrombocythemias. Clinical, evolutionary and biological data. Cancer 1986; 58:2440-7.
7. Murphy S, Iland H, Rosenthal D, Laszlo J. Essential thrombocythemia: an interim report from Polycythemia Vera Study Group. Semin Hematol 1986; 23:177-82.
8. Snethlage W, Tencate JW. Thrombocythemia and recurrent late abortions: normal outcome of pregnancies after antiaggregant treatment. Case report. Br J Obstet Gynecol 1986; 93: 386-8.
9. Falconer J, Pineo G, Blahey W, Bowen T, Docksteader B, Jadusingh I. Essential thrombocythemia associated with recurrent abortions and fetal growth retardation. Am J Hematol 1987; 25:345-7.
10. Ferrari A, Mazzucconi MG, Martinelli G, Giona F, Paesano R, Pachi A. Pregnancy in a young woman affected by essential thrombocythemia: a case report. Haematologica 1989; 74:115-6.
11. Hoagland HC, Silverstein MN. Primary thrombocythemia in the young patient. Mayo Clin Proc 1978; 53:578-80.
12. Beard J, Hillmen P, Anderson CC, Lewis SM, Pearson TC. Primary thrombocythemia in pregnancy. Br J Haematol 1991; 77:371-4.
13. Pardini S, Dore F, Murineddu M, et al. Alpha-2b-interferon therapy and pregnancy. Report of a case of essential thrombocythemia. Am J Hematol 1993; 43:78-9.
14. Petit JJ, Callis M, de Sevilla AF. Normal pregnancy in a patient with essential thrombocythemia treated with alpha-2b-interferon. Am J Hematol 1992; 40:80.
15. Thornley S, Manoharan A. Successful treatment of essential thrombocythemia with alpha-interferon during pregnancy. Eur J Haematol 1994; 52:63-4.
16. Frezzato M, Ruggeri M, Castman G, et al. Polycythemia vera and essential thrombocythemia in young patients. Haematologica 1993; 78(Suppl 2):11-7.