Original ARTICLE for Thrombosis Research

Title: Essential thrombocythemia as a risk factor for stillbirth

Takeshi Umazume, Takahiro Yamada*, Rina Akaishi, Naoto Araki, Ryutaro Nishida, Mamoru Morikawa, Hisanori Minakami

Department of Obstetrics, Hokkaido University Graduate School of Medicine, Sapporo, 060-8638, Japan

Short running title: Stillbirth by essential thrombocythemia

* Correspondence to Takahiro Yamada, MD, PhD.
Department of Obstetrics, Hokkaido University Graduate School of Medicine,
N15W7, Kita-ku, Sapporo, 060-8638, Japan
Phone: +81-11-706-5941
Fax: +81-11-706-7711
e-mail: taka0197@med.hokudai.ac.jp

Abstract

Introduction: The risk of abortion is known to be high in women with essential thrombocythemia (ET). However, a few studies have focused on the risk of stillbirth among fetuses reaching gestational age compatible with life.

Methods: Review of medical charts of pregnant women with ET who received cares at a single center between January 2003 and June 2013 and the English literature in which more than 20 pregnancies with ET were dealt with regarding outcomes. Outcomes were classified into three categories: spontaneous abortion or preterm delivery before GW 24, stillbirth at and after GW 24, and live birth (LB). Japan national statistics was used to estimate the risk of stillbirth among women with GW 22 or more.

Results: In all nine pregnancies in four women with ET at our hospital, two miscarriages, one stillbirth (intrauterine death at GW 35), and six LBs occurred. There were six reports in the English literature in which a total of 374 pregnancy outcomes were described: 110 miscarriages (29%), 14 stillbirths (3.7% of all 374 pregnancies and 5.3% of 264 pregnancies with GW $\geq$ 24), and 250 LBs (67%) occurred. Japan national statistics between 1995 and 2011 indicated that the risk of stillbirth was less than 0.50% among women with GW $\geq$ 22.

Conclusions: The risk of stillbirth was extremely high among women with ET. More intensified monitoring of fetal wellbeing may be required to improve outcome of pregnancy complicated with ET.

Key words: deep vein thrombosis, essential thrombocythemia, low-dose aspirin, placental abruption, preeclampsia, stillbirth

Introduction

Essential thrombocythemia (ET) is a clonal myeloproliferative disorder characterized by sustained increase in platelet number (> 450×10^9/L) and tendency for thromboembolism. As ET is more common in women and is the most common myeloproliferative disorder in women of childbearing age, its incidence being 0.6 – 2.5/100,000 patients/year, although the median age at diagnosis is 65 – 70 years [1, 2], obstetricians may encounter pregnant women with diagnosed ET.

Most reports suggest that the risk of fetal loss before reaching gestational age compatible with life is several fold higher among women with ET than in the general population [1, 3-7]. Previous review articles dealing with retrospective and prospective cohort studies including single cases or small number of patients [5], case series reports including six or more consecutive patients or at least 10 pregnancies [6, 7] suggested that the risk of fetal loss was high during the second trimester or after fetal maturation compatible with life. However, it is somewhat unclear whether the risk of fetal loss is high among fetuses with gestational week (GW) 24 or more [1-7].

This study was conducted to determine whether the risk of stillbirth at and after GW 24 was higher in women with ET than in the general population.

METHODS

This study was conducted with the approval of the Ethics Committee of Hokkaido University Hospital, a tertiary teaching hospital managing mainly high-risk pregnant women. Medical charts of all pregnant women with diagnosed ET receiving care at Hokkaido University Hospital during the study period between January 2003 and June 2013 were reviewed. In addition, we reviewed reports in the English literature dealing with outcomes of more than 20 pregnancies complicated with ET. Case reports were excluded from the present analysis because of the publication bias inherent in such reports.

Abstraction of pregnant women with ET at Hokkaido University Hospital

A total of nine pregnancies in four women with diagnosed ET were abstracted from the

database of discharge summaries at the Obstetric ward of Hokkaido University Hospital during the study period between January 2003 and June 2013. Medical charts of these women were reviewed focusing on the outcome of pregnancy. All nine pregnancies were booked at their beginning of pregnancies at which time no ominous signs were present regarding pregnancy outcome.

Literature reviewed in this study

Using PubMed (1979 – August 2013), we identified a total of nine reports in the English literature [8-16] concerning the outcomes of pregnancies complicated with ET dealing with a series of more than 20 pregnancies. The search term "essential thrombocythemia and pregnancy" was used. Of the nine reports, two including those by Beressi et al. in 1995 [14] and by Wright and Tefferi in 2001 [15], both at Mayo Clinic, were excluded from the present analysis because a report by Gangat et al. in 2009 [11], also at Mayo Clinic, included patients discussed with in these two reports. Another report by Passamonti et al. [16] was also excluded because the majority of patients had already been described in a previous report by Passamonti [10] in which outcomes of pregnancies were well presented. Thus, pregnant women with ET presented in six reports [8-13], after excluding those presented in three reports [14-16], were considered entirely different populations, without double-counting the same individuals with ET.

The pregnancy outcomes of women with ET presented in these six reports [8-13] were reviewed. Three outcome categories were set in this study: spontaneous abortion, including ectopic pregnancy and preterm delivery before GW 24; stillbirth at and after GW 24; and live birth (LB). Outcome classification was difficult in two of the six reports [11,12]. Three fetal losses were reported to have occurred during the second trimester, but the GWs at which fetal losses occurred were not specified in the report by Gangat et al. [11] in which there was no stillbirth category. These three fetal losses [11] were assumed to have occurred before GW 24 to avoid overestimation of the number of stillbirths at and after GW 24 in this study. In a report by Melillo et al., [12] there were three adverse outcome categories, i.e., spontaneous abortion at GW$\leq$ 12, spontaneous abortion at GW > 12, and stillbirth with no mention of the GW at which stillbirth occurred. We assumed that "stillbirth" in the report by Melillo et al. [12] occurred at or after GW 24 in this study.

Risk estimation of stillbirth among Japanese fetuses at and after GW 22

The Japanese Ministry of Health, Labor, and Welfare releases vital statistics of Japan yearly including the number of infants with live birth and stillbirth [17]. These data allowed us to assess the risk of stillbirth among fetuses at and after GW 22 but not fetuses at and after GW 24.

Results

ET cases at our institution

Of the nine pregnancies receiving care at our hospital, six resulted in live birth, two in miscarriage during the first trimester, and one in stillbirth (intrauterine fetal death at GW 35) (Table 1). All patients were taking low-dose aspirin during pregnancy for treatment of ET. Brief summaries of two pregnancies (Cases 3 and 4) complicated with eclampsia and intrauterine fetal death, respectively, are presented here. Case 3, with a history of two previous uneventful deliveries at GW 40 and 38, was diagnosed as having ET during the third pregnancy. The pregnancy was uneventful until GW 35 while on low-dose aspirin. She developed edema (weight gain 1.3 kg/week) at GW 35 followed by proteinuria (protein to creatinine ratio [mg/mg] of 1.6 in spot urine) at GW 36 and hypertension at GW 37. She gave birth to a healthy female infant, weighing 2344 g with Apgar scores of 8 and 9 at 1 and 5 min, respectively, with an emergency cesarean section for eclamptic convulsions occurring with the induction of labor at GW 37. In Case 4 diagnosed with ET but with no history of thrombosis, the pregnancy was uneventful until GW 35 while on low-dose aspirin at which time fetal death was found. Estimated fetal weight was 1807 g at GW 33. She gave birth to a dead female infant, weighing 1740 g at GW 36 with induced labor. The postpartum course was uneventful and the patient left hospital on postpartum day 2. However, she developed venous thrombosis of sagittal suture sinus in the brain on postpartum day 32 while on low-dose aspirin and died from pulmonary thromboembolism manifested on postpartum day 36.

ET cases in six reports in the literature

Six reports published in or after 2000 presented details of a total of 374 pregnancy outcomes in 231 women (Table 2) [8-13]. Overall live birth rate was 67% (250/374), ranging from 57% (17/30) [8] to 75% (92/122) [12]. The rate of spontaneous abortion,

ranging from 21% [12] to 37% [11,13] was consistently higher than the level of 13.7% among the general population [18]; the overall rate was 29% (110/374). The rate of stillbirth at and after GW 24 was high, occurring in 3.7% (14/374) of all pregnancies and in 5.3% (14/264) of all pregnancies beyond GW 23. Preeclampsia including one eclampsia occurred in 3.5% (13/374) of pregnancies, placental abruption in 1.9% (7/374), and thromboembolic events including one pulmonary thromboembolism in 1.6% (6/374).

Japan national statistics regarding annual number of live births and stillbirths at and after GW 22

The stillbirth rate (per 1000 births including live births and stillbirths) at and after GW 22 decreased from 5.5 to 3.3 over the past two decades (Table 3). Thus, stillbirth at and after GW 22 occurred in approximately one (0.4%) in 250 pregnancies in Japan.

Discussion

This study was conducted to determine whether the risk of stillbirth was higher among women diagnosed with ET, focusing on the outcome of pregnancies that reached mid-gestation in which viable infants are expected; the results indicated that women with ET had a more than 10-fold higher risk of stillbirth after reaching GW 24 compared with the general population.

We experienced one case of stillbirth, occurring at GW 35, among seven ET pregnancies beyond GW 23 (Table 1), raising questions regarding the outcome of viable infants carried by women with ET. This prompted us to search the literature regarding the outcomes of pregnancies complicated with ET. Among six reports dealing with more than 20 pregnancies reviewed in this study [8-13], four reported one to six cases with stillbirth, a total of 14 stillbirth cases (Table 2), occurring at or after GW 24 [8-10,12]. The frequency of stillbirth ranged from 3.8% (1/26) to 26% (6/23) in four reports [8-10,12], and overall stillbirth rate was 5.3% (14/264) among 264 women with GW $\geq$ 24 presented in the six reports [8-13]. As expected based on our experience, stillbirths were rare among women with GW $\geq$ 22 in Japan, accounting for only approximately 0.4% of all births during the past 20 years (Table 3). As prospective risk of stillbirth decreases with advancing gestation [19], the risk of stillbirth is lower in women with

GW ≥ 24 than GW ≥ 22 [19]. Thus, the present study strongly suggested that women with ET had a markedly increased risk of stillbirth compared with the general population (more than 10-fold, 5.3% for women with ET vs. less than 0.4% for the Japanese general population). Incidence of stillbirth in other area/countries are as follows: 0.47% and 0.28% at and after GW 24 for Inuit and non-Aboriginal residents of Quebec in 2000-2009, respectively [20], and 0.17%, 0.19%, 0.20%, 0.22%, and 0.30% at and after GW 32 in 2004 for Finland, Austria, USA, Canada, and Italy, respectively [21].

In an attempt to avoid publication bias, the present study included only case series reports that dealt with more than 20 pregnancies. However, the absolute risk of 5.3% for stillbirth at and after GW 24 in this study was consistent with that of 5.0% at and after GW 28 in a previous review article that dealt with reports including six or more consecutive patients or at least 10 pregnancies [7]. In another review article that dealt with case series reports including six or more consecutive patients, stillbirth risk is 11.3% for fetuses beyond the first trimester [6]. In practice guidelines by the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation, the outcome of pregnancies is described as follows “Overall, 204 of the 461 pregnancies had an unsuccessful outcome (44%), which is about three-fold higher than in the general population” [5]. Fetal loss occurring at and after GW 22 accounts for approximately 15% of all pregnancy loss in Japan [17]. If we assumed that pregnancy loss at and after GW 24 accounted for 15% of all pregnancy loss, stillbirth rate at and after GW 24 would be 6.6% in the Italian study [5]. In a recent review article referring to treatment and outcome of pregnancy [4], it is clearly stated that complications such as intrauterine growth retardation, stillbirth, and preeclampsia occur more frequently in women with ET. Thus, maternity-service providers need to be cognizant that approximately one in 20 fetuses carried by mothers with ET die in utero beyond GW 23.

Although low-dose aspirin was given in all nine pregnancies of four women with ET at our hospital, whether the use of aspirin or cytoreductive agents, such as an interferon α, a recommended agent during pregnancy [4,22,23], can improve pregnancy outcome is uncertain at present [4,22]. However, as aspirin use in pregnancy is safe for both mother and fetus [24], most authors recommend the use of low-dose aspirin unless otherwise

contraindicated [3,4,22]. In addition, anticoagulation therapy is considered for all women with ET for 6 weeks postpartum [22] or with a history of thrombosis or recurrent pregnancy loss [3,4]. Finazzi [22] defines high-risk women as those with previous severe pregnancy complications, such as more than two first-trimester fetal losses or at least one second- or third-trimester fetal loss, birth weight < 5^{th} percentile of gestation, preeclampsia, or stillbirth, and states that low molecular weight heparin throughout all pregnancy is indicated for prophylaxis of deep vein thrombosis and to reduce fetal morbidity in such high-risk women with ET [22]. Maternal death from pulmonary thromboembolism in Case 4 at our hospital may have been avoided with such anticoagulation therapy, although evidence is lacking.

In conclusion, women with ET had a markedly elevated risk of stillbirth at and after GW 24 compared to the general population; the absolute risk of stillbirth was 5.3% among women with ET beyond GW 23 based on a literature review, while its risk is less than 0.5% in most countries. This suggested the possibility that intensified monitoring of fetal wellbeing may improve outcome, although evidence is still lacking.

Conflict of interest statement

All authors declare that they have no financial relationships with biotechnology manufacturers, pharmaceutical companies, or other commercial entities with an interest in the subject matter or materials discussed in this manuscript.

References

1. Fabris F, Randi ML. Essential thrombocythemia: past and present. Intern Emerg Med 2009; 4: 381–8.

2. McNally RJ, Rowland D, Roman E, Cartwright RA. Age and sex distributions of hematological malignancies in the U.K.. Hematol Oncol 1997;15(November (4)):173–89.

3. Valera M-C, Parant O, Vayssiere C, Arnal J-F, Payrastre B. Essential thrombocythemia and pregnancy. Eur J Obstet Gynecol Reprod Biol 2011; 158: 141–7.

4. Beer PA, Erber WN, Campbell PJ, Green AR. How I treat essential thrombocythemia. Blood 2011; 117:1472-82.

5. Barbui T, Barosi G, Grossi A, Gugliotta L, Liberato LN, Marchetti M, Mazzucconi MG, Rodeghiero F, Tura S. Practice guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 2004; 89: 215-32.

6. Elliott M, Tefferi A. Thrombocythaemia and pregnancy. Best Prac Res Clin Haematol 2003; 16: 227 –42.

7. Griesshammer M, Struve S, Harrison CM. Essential thrombocythemia/polycythemia vera and pregnancy: the need for an observational study in Europe. Semin Thromb Hemost 2006: 32 (4 Pt 2): 422-9.

8. Cincotta R, Higgins JR. Christine Tipett C, Gallery E, North R, McMahon LP, Brennecke SP. Management of essential thrombocythaemia during pregnancy. Aust N Z J Obstet Gynaecol 2000; 40: 33-7.

9. Niittyvuopio R, Juvonen E, Kaaja R, Oksanen K, Hallman H, Timonen T, Ruutu T. Pregnancy in essential thrombocythaemia: experience with 40 pregnancies. Eur J Haematol 2004: 73: 431–6.

10. Passamonti F, Randi ML, Rumi E, Pungolino E, Elena C, Pietra D, Scapin M, Arcaini L, Tezza F, Moratti R, Pascutto C, Fabris F, Morra E, Cazzola M, Lazzarino M. Increased risk of pregnancy complications in patients with essential thrombocythemia carrying the *JAK2* (617V>F) mutation. Blood. 2007; 110: 485-9.

11. Gangat N, Wolanskyj AP, Schwager S, Tefferi A. Predictors of pregnancy outcome in essential thrombocythemia: a single institution study of 63 pregnancies. Eur J Haematol 2009; 82: 350–3.

12. Melillo L, Tieghi A, Candoni A, Radaelli F, Ciancia R, Specchia G, Martino B, Scalzulli PR, Latagliata R, Palmieri F, Usala E, Valente D, Valvano MR, Cedrone M, Comitini G, Martinelli V, Cascavilla N, Gugliotta L. Outcome of 122 pregnancies in essential thrombocythemia patients: A report from the Italian registry Am. J. Hematol 2009; 84:636–40.

13. Palandri F, Polverelli N, Ottaviani E, Castagnetti F, Baccarani M, Vianelli N. Long-term follow-up of essential thrombocythemia in young adults: treatment strategies, major thrombotic complications and pregnancy outcomes. A study of 76 patients. Haematologica 2010; 95:1038-40.

14. Beressi AH, Tefferi A, Silverstein MN, Petitt RM, Hoagland HC. Outcome analysis of 34 pregnancies in women with essential thrombocythemia. Arch Intern Med. 1995; 155: 1217-22.

15. Wright CA, Tefferi A. A single institutional experience with 43 pregnancies in essential thrombocythemia. Eur J Haematol 2001: 66: 152-9.

16. Passamonti F, Rumi E, Randi ML, Morra E, Cazzola M. Aspirin in pregnant patients with essential thrombocythemia: a retrospective analysis of 129 pregnancies. J Thromb Haemost 2010; 8: 411–3.

17. Mother's & Children's Health & Welfare Association. Maternal and child health statistics of Japan, Published by Mother's & Children's Health Organization. 2007, 2008, 2009, 2010, 2011, and 2012 editions, Toshihide Ei, Tokyo

18. Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C. A prospective study of early pregnancy loss. Hum Reprod 1996; 11:406-12.

19. Minakami H, Izumi A, Tsukahara T, Tamada T. Stillbirth risk in Japan. Lancet 1993; 341: 1603-4.

20. Auger N, Park AL, Zoungrana H, McHugh N G-L, Luo Z-C. Rates of stillbirth by gestational age and cause in Inuit and First Nations populations in Quebec. CMAJ 2013; 185 : E256-62.

21. Lisonkova S, Sabr Y, Butler B, Joseph K. International comparisons of preterm birth: higher rates of late preterm birth are associated with lower rates of stillbirth and neonatal death. BJOG 2012;119:1630–9.

22. Finazzi G. How to manage essential thrombocythemia. Leukemia 2012; 26: 875-82.
23. Brojeni PY,Matok I, Bournissen FG, Koren G. A systematic review of the fetal safety of interferon alpha. Reprod Toxicol 2012; 33: 265–8.
24. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet.* 2007; 369:1791-8.

Table 1. Outcomes of 9 pregnancies in 4 women with ET receiving cared at Hokkaido University Hospital

Case	GW at birth/ Delivery mode	Fetal sex/ Birth weight (g)	Outcome	Complication
Case 1				
1st pregnancy	40, VD	male, 3180	Live birth	none
2nd pregnancy	10		Miscarriage	none
3rd pregnancy	38, VD	male, 3110	Live birth	none
4th pregnancy	37, VD	male, 3330	Live birth	none
5th pregnancy	6		Miscarriage	none
Case 2				
1st pregnancy	38, VD	male, 3150	Live birth	none
2nd pregnancy	38, VD	male, 3245	Live birth	none
Case 3				
3rd pregnancy*	37, CS	female, 2334	Live birth	Eclampsia
Case 4				
1st pregnancy†	36, VD	female, 1740	Fetal death at GW 35	Thrombosis

CS, cesarean section; GW, gestational week; VD, vaginal delivery

* This case had a history of two uneventful deliveries at GW 40 and 38 before diagnosis of essential thrombocythemia (ET) during her third pregnancy.

† This case developed venous thrombosis of sagittal suture sinus in the brain on postpartum day 32 and died from pulmonary thromboembolism manifested on postpartum day 36.

Table 2. Outcomes of pregnancy in 6 reports of ≥ 20 pregnancies complicated with ET

Author (Ref)	No. of pregnancy /no. of women	Live birth	Spontaneous abortion*	Stillbirth†	Complications¶
Cincotta et al. [8]	30/12	17 (57%)	7 (23%)	6 (20%) [26%]	5PA, 1PE, 1PTE
Niittyvuopio et al. [9]	40/16	25 (63%)	14 (35%)	1 (2.5%) [3.8%]	2PE, 1Ec
Passamonti et al. [10]	96/62	62 (65%)	31 (32%)	3 (3.1%) [4.6%]	5PE
Gangat et al. [11]	62/36	39 (63%)	23 (37%)‡	0 (0.0%)‡	1PE
Melillo et al. [12]	122/92	92 (75%)	26 (21%)	4 (3.3%) [4.2%]	5DVT, 3PE, 1PA
Palandri et al. [13]	24/13	15 (63%)	9 (37%)	0 (0.0%)	1PA
Overall	374/231	250 (67%)	110 (29%)	14 (3.7%) [5.3%]	26 (7.0%)

* Including preterm delivery before gestational week 24 and ectopic pregnancy.

† Stillbirth occurring at GW ≥ 24 (% of all gestations) [% of gestations at GW≥ 24].

¶ Complications occurring in pregnancy including placental abruption (PA), preeclampsia (PE), pulmonary thromboembolism (PTE), eclampsia (Ec), and deep vein thrombosis (DVT).

‡ Including three fetal losses during the 2nd trimester in which gestational age at fetal loss was not specified.

Table 3. Risk of stillbirth among Japanese fetuses at and after gestational week 22

	Number of infants born at ≥ gestation week 22			Stillbirth rate
Year	Live birth	Stillbirth	Overall	(per 1000 births)
1995	1187064	6580	1193644	5.5
2000	1190547	5362	1195909	4.5
2006	1092674	4047	1096721	3.7
2005	1062530	4058	1066588	3.8
2007	1089818	3854	1093672	3.5
2008	1091156	3751	1094907	3.4
2009	1070035	3645	1073680	3.4
2010	1071304	3637	1074941	3.4
2011	1050806	3491	1054297	3.3

This table was based on the data released yearly from the Japanese Ministry of Health, Labor, and Welfare [17].