



Regular Article

Essential thrombocythemia as a risk factor for stillbirth



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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 care 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.

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Introduction

Essential thrombocythemia (ET) is a clonal myeloproliferative disorder characterized by sustained increase in platelet number ($>450 \times 10^9/L$) 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.

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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.

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 ≤ 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

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.

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