



Title	Essential thrombocythemia as a risk factor for stillbirth
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1 **Original ARTICLE for Thrombosis Research**

2

3 **Title: Essential thrombocythemia as a risk factor for stillbirth**

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11 Short running title: Stillbirth by essential thrombocythemia

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19 **Abstract**

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

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

29 **Results:** In all nine pregnancies in four women with ET at our hospital, two
30 miscarriages, one stillbirth (intrauterine death at GW 35), and six LBs occurred. There
31 were six reports in the English literature in which a total of 374 pregnancy outcomes
32 were described: 110 miscarriages (29%), 14 stillbirths (3.7% of all 374 pregnancies and
33 5.3% of 264 pregnancies with $GW \geq 24$), and 250 LBs (67%) occurred. Japan national
34 statistics between 1995 and 2011 indicated that the risk of stillbirth was less than 0.50%
35 among women with $GW \geq 22$.

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

39

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

42 **Introduction**

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

49
50 Most reports suggest that the risk of fetal loss before reaching gestational age
51 compatible with life is several fold higher among women with ET than in the general
52 population [1, 3-7]. Previous review articles dealing with retrospective and prospective
53 cohort studies including single cases or small number of patients [5], case series reports
54 including six or more consecutive patients or at least 10 pregnancies [6, 7] suggested
55 that the risk of fetal loss was high during the second trimester or after fetal maturation
56 compatible with life. However, it is somewhat unclear whether the risk of fetal loss is
57 high among fetuses with gestational week (GW) 24 or more [1-7].

58
59 This study was conducted to determine whether the risk of stillbirth at and after GW 24
60 was higher in women with ET than in the general population.

61

62 **METHODS**

63 This study was conducted with the approval of the Ethics Committee of Hokkaido
64 University Hospital, a tertiary teaching hospital managing mainly high-risk pregnant
65 women. Medical charts of all pregnant women with diagnosed ET receiving care at
66 Hokkaido University Hospital during the study period between January 2003 and June
67 2013 were reviewed. In addition, we reviewed reports in the English literature dealing
68 with outcomes of more than 20 pregnancies complicated with ET. Case reports were
69 excluded from the present analysis because of the publication bias inherent in such
70 reports.

71

72 *Abstraction of pregnant women with ET at Hokkaido University Hospital*

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

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

79

80 *Literature reviewed in this study*

81 Using PubMed (1979 – August 2013), we identified a total of nine reports in the
82 English literature [8-16] concerning the outcomes of pregnancies complicated with ET
83 dealing with a series of more than 20 pregnancies. The search term “essential
84 thrombocythemia and pregnancy” was used. Of the nine reports, two including those by
85 Beressi et al. in 1995 [14] and by Wright and Tefferi in 2001 [15], both at Mayo Clinic,
86 were excluded from the present analysis because a report by Gangat et al. in 2009
87 [11], also at Mayo Clinic, included patients discussed with in these two reports. Another
88 report by Passamonti et al. [16] was also excluded because the majority of patients had
89 already been described in a previous report by Passamonti [10] in which outcomes of
90 pregnancies were well presented. Thus, pregnant women with ET presented in six
91 reports [8-13], after excluding those presented in three reports [14-16], were considered
92 entirely different populations, without double-counting the same individuals with ET.
93 The pregnancy outcomes of women with ET presented in these six reports [8-13] were
94 reviewed. Three outcome categories were set in this study: spontaneous abortion,
95 including ectopic pregnancy and preterm delivery before GW 24; stillbirth at and after
96 GW 24; and live birth (LB). Outcome classification was difficult in two of the six
97 reports [11,12]. Three fetal losses were reported to have occurred during the second
98 trimester, but the GWs at which fetal losses occurred were not specified in the report by
99 Gangat et al. [11] in which there was no stillbirth category. These three fetal losses [11]
100 were assumed to have occurred before GW 24 to avoid overestimation of the number of
101 stillbirths at and after GW 24 in this study. In a report by Melillo et al., [12] there were
102 three adverse outcome categories, i.e., spontaneous abortion at $GW \leq 12$, spontaneous
103 abortion at $GW > 12$, and stillbirth with no mention of the GW at which stillbirth
104 occurred. We assumed that “stillbirth” in the report by Melillo et al. [12] occurred at or
105 after GW 24 in this study.

106

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

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

112

113 **Results**114 *ET cases at our institution*

115 Of the nine pregnancies receiving care at our hospital, six resulted in live birth, two in
116 miscarriage during the first trimester, and one in stillbirth (intrauterine fetal death at
117 GW 35) (Table 1). All patients were taking low-dose aspirin during pregnancy for
118 treatment of ET. Brief summaries of two pregnancies (Cases 3 and 4) complicated with
119 eclampsia and intrauterine fetal death, respectively, are presented here. Case 3, with a
120 history of two previous uneventful deliveries at GW 40 and 38, was diagnosed as
121 having ET during the third pregnancy. The pregnancy was uneventful until GW 35
122 while on low-dose aspirin. She developed edema (weight gain 1.3 kg/week) at GW 35
123 followed by proteinuria (protein to creatinine ratio [mg/mg] of 1.6 in spot urine) at GW
124 36 and hypertension at GW 37. She gave birth to a healthy female infant, weighing
125 2344 g with Apgar scores of 8 and 9 at 1 and 5 min, respectively, with an emergency
126 cesarean section for eclamptic convulsions occurring with the induction of labor at GW
127 37. In Case 4 diagnosed with ET but with no history of thrombosis, the pregnancy was
128 uneventful until GW 35 while on low-dose aspirin at which time fetal death was found.
129 Estimated fetal weight was 1807 g at GW 33. She gave birth to a dead female infant,
130 weighing 1740 g at GW 36 with induced labor. The postpartum course was uneventful
131 and the patient left hospital on postpartum day 2. However, she developed venous
132 thrombosis of sagittal suture sinus in the brain on postpartum day 32 while on low-dose
133 aspirin and died from pulmonary thromboembolism manifested on postpartum day 36.

134

135 *ET cases in six reports in the literature*

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

139 ranging from 21% [12] to 37% [11,13] was consistently higher than the level of 13.7%
140 among the general population [18]; the overall rate was 29% (110/374). The rate of
141 stillbirth at and after GW 24 was high, occurring in 3.7% (14/374) of all pregnancies
142 and in 5.3% (14/264) of all pregnancies beyond GW 23. Preeclampsia including one
143 eclampsia occurred in 3.5% (13/374) of pregnancies, placental abruption in 1.9%
144 (7/374), and thromboembolic events including one pulmonary thromboembolism in
145 1.6% (6/374).

146

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

149 The stillbirth rate (per 1000 births including live births and stillbirths) at and after GW
150 22 decreased from 5.5 to 3.3 over the past two decades (Table 3). Thus, stillbirth at and
151 after GW 22 occurred in approximately one (0.4%) in 250 pregnancies in Japan.

152

153 **Discussion**

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

159

160 We experienced one case of stillbirth, occurring at GW 35, among seven ET
161 pregnancies beyond GW 23 (Table 1), raising questions regarding the outcome of viable
162 infants carried by women with ET. This prompted us to search the literature regarding
163 the outcomes of pregnancies complicated with ET. Among six reports dealing with more
164 than 20 pregnancies reviewed in this study [8-13], four reported one to six cases with
165 stillbirth, a total of 14 stillbirth cases (Table 2), occurring at or after GW 24 [8-10,12].
166 The frequency of stillbirth ranged from 3.8% (1/26) to 26% (6/23) in four reports
167 [8-10,12], and overall stillbirth rate was 5.3% (14/264) among 264 women with GW \geq
168 24 presented in the six reports [8-13]. As expected based on our experience, stillbirths
169 were rare among women with GW \geq 22 in Japan, accounting for only approximately
170 0.4% of all births during the past 20 years (Table 3). As prospective risk of stillbirth
171 decreases with advancing gestation [19], the risk of stillbirth is lower in women with

172 GW \geq 24 than GW \geq 22 [19]. Thus, the present study strongly suggested that women
173 with ET had a markedly increased risk of stillbirth compared with the general
174 population (more than 10-fold, 5.3% for women with ET vs. less than 0.4% for the
175 Japanese general population). Incidence of stillbirth in other area/countries are as
176 follows: 0.47% and 0.28% at and after GW 24 for Inuit and non-Aboriginal residents of
177 Quebec in 2000-2009, respectively [20], and 0.17%, 0.19%, 0.20%, 0.22%, and 0.30%
178 at and after GW 32 in 2004 for Finland, Austria, USA, Canada, and Italy, respectively
179 [21].

180

181 In an attempt to avoid publication bias, the present study included only case series
182 reports that dealt with more than 20 pregnancies. However, the absolute risk of 5.3% for
183 stillbirth at and after GW 24 in this study was consistent with that of 5.0% at and after
184 GW 28 in a previous review article that dealt with reports including six or more
185 consecutive patients or at least 10 pregnancies [7]. In another review article that dealt
186 with case series reports including six or more consecutive patients, stillbirth risk is
187 11.3% for fetuses beyond the first trimester [6]. In practice guidelines by the Italian
188 Society of Experimental Hematology and the Italian Group for Bone Marrow
189 Transplantation, the outcome of pregnancies is described as follows “Overall, 204 of the
190 461 pregnancies had an unsuccessful outcome (44%), which is about three-fold higher
191 than in the general population” [5]. Fetal loss occurring at and after GW 22 accounts for
192 approximately 15% of all pregnancy loss in Japan [17]. If we assumed that pregnancy
193 loss at and after GW 24 accounted for 15% of all pregnancy loss, stillbirth rate at and
194 after GW 24 would be 6.6% in the Italian study [5]. In a recent review article referring
195 to treatment and outcome of pregnancy [4], it is clearly stated that complications such as
196 intrauterine growth retardation, stillbirth, and preeclampsia occur more frequently in
197 women with ET. Thus, maternity-service providers need to be cognizant that
198 approximately one in 20 fetuses carried by mothers with ET die in utero beyond GW 23.

199

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

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

215

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

221

222 **Conflict of interest statement**

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

226

227

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- 297
- 298
- 299
- 300

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				
1 st pregnancy	40, VD	male, 3180	Live birth	none
2 nd pregnancy	10		Miscarriage	none
3 rd pregnancy	38, VD	male, 3110	Live birth	none
4 th pregnancy	37, VD	male, 3330	Live birth	none
5 th pregnancy	6		Miscarriage	none
Case 2				
1 st pregnancy	38, VD	male, 3150	Live birth	none
2 nd pregnancy	38, VD	male, 3245	Live birth	none
Case 3				
3 rd pregnancy*	37, CS	female, 2334	Live birth	Eclampsia
Case 4				
1 st 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

Year	Number of infants born at \geq gestation week 22			Stillbirth rate (per 1000 births)
	Live birth	Stillbirth	Overall	
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].