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Original

Pregnancy Transiently Normalized Platelet Counts in Essential Thrombocytosis

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Background: Outcomes of pregnancies complicated by essential thrombocytosis (ET) are worse than those of normal pregnancies. Aspirin, heparin, and interferon (IFN)-α are well-tolerated during pregnancy and prescribed in accordance with the risk of thrombosis. However, some evidence suggests that platelet count decreases during ET-complicated pregnancies.

Methods: We retrospectively analyzed changes in platelet count in ET-complicated pregnancies.

Results: Platelet count decreased during pregnancy without IFN-α use, and 83% of pregnant women had a platelet count of ≤450×10^9/L. Furthermore, all pregnant women achieved a platelet count of ≤600 ×10^9/L. One the basis of revised IPSET-thrombosis score, risk was classified as low or very low. Aspirin use starting in early pregnancy was associated with a higher rate of successful delivery, even in patients with prior miscarriage.

Conclusions: These findings suggest that platelet counts decrease in selected low-risk and very-low-risk ET-complicated pregnancies and that cytoreductive therapy with IFN-α may be avoidable in some cases. These results should be interpreted cautiously because of the small sample size and retrospective study design.

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Keywords: essential thrombocytosis, platelet, pregnancy, interferon α, aspirin

Introduction

Essential thrombocythemia (ET) is a type of BCR-ABL1–negative myeloproliferative neoplasm (MPN). The vital prognosis of ET is favorable, and the 8-year survival rate as compared with that of the general population is 91% (95% confidence interval [CI]: 84–97%)[1]. Factors that reduce the quality of life of patients with ET include systemic symptoms such as malaise and weight loss and the complications of thrombosis. Thrombosis develops in 34% of patients with ET over 10 years[2]. In particular, myocardial infarction and cerebral infarction are major causes of death in patients with ET. Risk factors for thrombosis include age, history of thrombosis, and cardiovascular risk factors, as well as the *Janus Tyrosine Kinase (JAK)2* V617F gene mutation[3]. The International Prognostic Score for ET (IPSET)-thrombosis[4] stratifies thrombosis onset risk according to these 4 items. Risk-based thromboprophylaxis is of utmost importance in ET treatment. Antiplatelet therapy with aspirin is recommended for patients at low or greater risk, and concomitant cytoreductive therapy is recommended for patients at intermediate or greater risk. The most common age of ET onset is 50s to 60s, but women have a second onset peak in their 30s[5] and often experience pregnancy during the course of illness. The incidence of ET-complicated pregnancy has been reported to be 2.6/100,000 pregnancies/year[6]. As compared with normal pregnancies, ET-complicated pregnancies have higher rates of pregnancy complications such as spontaneous miscarriage and preeclampsia[7].

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The incidence of miscarriage is 10–20% for all pregnancies[8]. In Japan, 4.2% had a history of 2 or more miscarriages, and 0.9% had a history of 3 or more miscarriages[9]. Among recurrent/habitual miscarriages, 13% were caused by abnormal coagulation[10]. Abnormal coagulation and thrombosis during pregnancy cause placental circulatory insufficiency, which leads to preeclampsia and miscarriage[11]. Administering aspirin to women with high-risk pregnancies prevents preeclampsia, miscarriage, and stillbirth and is likely to be particularly effective for patients with thrombosis[12].

The rate of miscarriage in ET-complicated pregnancies is 21–59%, the live birth rate is 41–75%, and outcomes are worse than those of normal pregnancies[13]. One cause of this is placental circulatory insufficiency due to the thrombotic tendencies of ET. IPSET-thrombosis is useful as a model of thrombosis outcomes, but its usefulness during pregnancy is limited. According to the European Leukemia Net (ELN) and British Committee for Standards in Hematology/British Society for Hematology (BCSH/BSH), risk factors for ET-complicated pregnancies include history of maternal arteriovenous thrombosis, history of ET-related bleeding, ET-associated pregnancy complications, severe preeclampsia, placental separation, severe bleeding around the time of childbirth that requires red blood cell transfusion, and persistent, markedly elevated platelet count (≥1,500×10^9/L)[14]. The National Comprehensive Cancer Network (NCCN) defines a high-risk pregnancy as having any history of microcirculatory disturbance or hereditary thrombotic predisposition, history of severe pregnancy complications, age 35 years or older, and elevated platelet count (≥1,000×10^9/L)[15]. Although various risk factors have been proposed, there is no useful prognostic model for ET-complicated pregnancies, and treatment must be evaluated individually.

Antithrombotic therapy is important for the treatment of ET-complicated pregnancies. Aspirin, heparin, and interferon (IFN)-α are well-tolerated during pregnancy and are prescribed in accordance with the risk of thrombosis. Aspirin administration during ET-complicated pregnancy reduces the miscarriage rate[16] and increases the live birth rate[13]. Thus, BCSH/BSH, ELN, and NCCN recommend aspirin administration during ET-complicated pregnancies, regardless of pregnancy risk. There are no prospective studies demonstrating the efficacy of low-molecular-weight heparin, but a retrospective analysis has shown concomitant use with aspirin to be useful[17]. In high-risk ET-complicated pregnancies, cytoreductive therapy with IFN-α is often administered in conjunction with antithrombotic drugs, to control blood cell count. IFN-α is not teratogenic and significantly reduces fetal mortality[13]. Griesshammer et al.[18] considered a platelet count of ≥ 1,000×10^9/L to indicate a high-risk pregnancy and recommended concomitant use of aspirin and IFN-α. However, indications for IFN-α in low-risk ET-complicated pregnancies have not been established. One report suggested that IFN-α should be administered to high-risk patients with concurrent thrombosis, a history of miscarriage, and marked splenomegaly, regardless of platelet count[19]; however, little evidence supports this recommendation.

Platelet count was reported to decrease spontaneously during the course of a normal pregnancy[20]. Furthermore, some reports suggest that platelet count decreases even during the course of ET-complicated pregnancy and that remission is sometimes achieved. ET-complicated pregnancies with thrombocytopenia have a lower risk of complications during pregnancy and delivery[21–23]. If the platelet count spontaneously decreases with pregnancy, then cytoreductive therapy can be avoided in ET-complicated pregnancies. Therefore, we retrospectively analyzed changes in platelet count in women with ET-complicated pregnancies.

Methods

Patients

We retrospectively investigated the pregnancy and delivery histories of 8 patients with ET-complicated pregnancies who delivered at our hospital from 2011 to 2021. All patients consented to participate in a large-scale, multicenter, prospective, observational study on the outcomes of MPNs in Japan. A diagnosis of ET was made according to the diagnostic criteria of the World Health Organization 2016 classification. Thrombosis onset risk was classified using the revised IPSET-thrombosis[24]. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Human Subjects Institutional Review Board (IRB approval number: B-2019-030) of the Nippon Medical School (Tokyo, Japan)[25], and informed consent was obtained from all patients.

Methods for Genetic Diagnosis and Mutation Analysis

Bone marrow or peripheral blood mononuclear cells were used for DNA extraction. Mononuclear cells were collected using a lymphocyte separation solution (Organon, Durham, NC). Genomic DNA was isolated from these cells using the QIAmp DNA Mini Kit (Qiagen,

Hilden, Germany). *JAK2* V617F, *JAK2* Ex12del, and *MPL* W515 L/K gene mutations were analyzed using the mutation-biased polymerase chain reaction (MB-PCR) and the direct sequence method. *CALR* gene mutations were analyzed using the direct sequence method of exon 9[26].

Statistical Analysis

The following definitions were used in the analyses: pre-pregnancy, 365 days before pregnancy to 0 days of pregnancy; first trimester, 0–97 days of pregnancy; second trimester, 98–195 days of pregnancy; third trimester, 196 days of pregnancy to 7 days before childbirth; childbirth, 6 days before childbirth to 27 days after delivery; and after delivery, 28–365 days after delivery. Statistical analyses were performed using Microsoft Excel and IBM SPSS Statistics version 21.0 for Windows (IBM Corp., Armonk, NY, USA). To account for repeated measurements within pregnancies and clustering by individual patients, we applied a linear mixed-effects model with random intercepts. A P-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

The characteristics of the patients are shown in **Table 1**. There were 29 pregnancies in 8 women with ET, and 18 pregnancies were managed until delivery at our hospital. *JAK2* V617F mutation was identified in 5 patients. On the revised IPSET-thrombosis tool, 3 patients were classified as very low risk and 5 patients were classified as low risk. All but 2 of the 8 patients had a history of miscarriage or premature birth; 12 pregnancies resulted in miscarriage and 1 resulted in premature birth. For 5 pregnancies, gestational age was known at the time of miscarriage or premature birth; there were 2 cases each at 7 and 8 weeks and 1 pregnancy resulting in stillbirth at 28 weeks. A total of 15 pregnancies resulted in delivery. Pregnancy complications were observed in 3 pregnancies. One patient had gestational hypertension and 2 had gestational diabetes. A total of 11 pregnancies were spontaneous vaginal deliveries, 2 were caesarian sections, and 2 were unclassified. In 1 pregnancy, fetal malformation was diagnosed after delivery and resulted in the death of the fetus. The other pregnancy involved neonatal transient tachypnea, but recovery was quick. All other babies were healthy.

Use of aspirin could be determined in 24 of the 29 pregnancies: 15 pregnancies involved aspirin use (81–100 mg/day) from the start of pregnancy to the 35th week of pregnancy, and no aspirin was used before pregnancy in 9 pregnancies, as it was before ET diagnosis. Only 3 pregnancies were treated with concomitant low-dose heparin. Of the 15 pregnancies during which aspirin use continued from the time of pregnancy, 14 resulted in delivery, and 1 ended in miscarriage. Additionally, all 9 pregnancies not treated with aspirin before pregnancy culminated in miscarriage or premature birth. Only 1 pregnancy resulted in miscarriage or premature birth despite administration of aspirin during pregnancy (**Table 2**).

Changes in Platelet Count during Pregnancy

We analyzed the course of pregnancy and changes in platelet counts for 12 pregnancies delivered at our hospital for which platelet count data were available. Pre-pregnancy ET treatment included aspirin monotherapy for 7 pregnancies, ruxolitinib (secondary myelofibrosis from ET) in 1 pregnancy, anagrelide in 2 pregnancies, and no treatment for 2 pregnancies. Ruxolitinib and anagrelide were discontinued immediately after confirmation of pregnancy. All patients used aspirin after confirmation of pregnancies, which was continued until 35 weeks of pregnancy. IFN-α was not used during any pregnancy. The mean platelet count before pregnancy was 683.7×10^9/L (95% CI: 622.6–744.7×10^9/L). Platelet count decreased over the course of pregnancy and was ≤600×10^9/L in all cases (**Figure 1**). The value decreased to ≤450×10^9/L in 10 pregnancies. **Figure 2** shows changes in mean platelet count during each pregnancy period. The mean platelet counts before pregnancy and during the first, second, and third trimesters were 760.3×10^9/L (95% CI: 663.6–857.0×10^9/L), 582.1×10^9/L (95% CI: 524.4–639.7×10^9/L), and 465.1×10^9/L (95% CI: 424.9–505.3×10^9/L), respectively. A linear mixed-effects model showed that platelet counts before pregnancy and in the first trimester did not significantly differ (P = 0.713) but significantly decreased from the second trimester onward, reaching the lowest level at delivery (delivery vs Pre, $P < 0.001$). A significant declining trend was observed from pre-pregnancy to delivery (P for trend = 4.23 × 10^{-12}). Postpartum platelet counts were not different from pre-pregnancy levels (P = 0.998), indicating recovery to baseline. Platelet count decreased regardless of the presence of the *JAK2* V617F mutation (**Figure 3**). In patients with the *JAK2* V617F mutation, there was a significant decrease in platelet count from the second trimester to delivery ($P < 0.05$, pre-pregnancy vs. second trimester; $P <$

Table 1 Characteristics of pregnant women with essential thrombocythemia

	Age at pregnancy	Pregnancy history	*JAK2*-V617F	*CALR*	*MPL*	Revised IPSET-thrombosis	Pregnancy risk factor (NCCN)	Pregnancy risk factor (ELN, BCSH/BSH)	Pre-pregnancy treatment	Post-pregnancy treatment	Pregnancy complications	Number of weeks of pregnancy at childbirth	Fetal prognosis
P1-1	44	Five pregnancies (3-1-1-3)	+	Unknown	–	Low-risk	+	+	ruxolitinib*	ASA	None	40	NVD
P1-2	36								ASA	ASA	None	39	NVD
P2-1	28	Two pregnancies (2-0-0-2)	+	Unknown	Unknown	Low-risk	–	–	Anagrelide	ASA	None	41	NVD
P2-2	26								Anagrelide	ASA	None	41	NVD
P3	25	One pregnancy (1-0-0-1)	–	–	Unknown	Very low-risk	–	–	None	ASA	None	40	NVD
P4	32	Two pregnancies (1-0-1-1)	–	–	Unknown	Very low-risk	–	–	None	ASA	Hypertension	37	NVD, TTN
P5-1	35	Five pregnancies (2-0-3-2)	+	–	Unknown	Low-risk	+	+	ASA	ASA	Diabetes	35	CS
P5-2	33								ASA	ASA	None	36	CS, mild neonatal asphyxia, TTN
P6	33	Six pregnancies (4-0-2-4)	+	Unknown	–	Low-risk	+	+	ASA	ASA	None	41	NVD
P7-1	37	Three pregnancies (2-0-1-2)	–	–	–	Very low-risk	+	+	ASA	ASA	None	38	NVD
P7-2	35								ASA	ASA	None	39	NVD
P8	37	Five pregnancies (1-0-4-1)	+	–	Unknown	Low-risk	+	+	ASA	ASA	Diabetes	37	NVD

The pregnancy history shows "(number of full-term births - number of premature births - number of miscarriages - number of live births)".

Pre-pregnancy treatment, post-pregnancy treatment, pregnancy complications, number of weeks of pregnancy, and fetal prognosis are data from pregnancies that reached the delivery stage.

*A Case of Myelofibrosis Secondary to Essential Thrombocythemia.

P1, P2, P5, and P7 had a history of two deliveries at our hospital, with each pregnancy course shown.

NCCN: National Comprehensive Cancer Network, BCSH: British Committee for Standards in Hematology, BSH: British Society for Hematology, ASA: acetylsalicylic acid, NVD: normal vaginal delivery, CS: caesarean section, TTN: transient tachypnea of the newborn.

0.01, pre-pregnancy vs. third trimester). The platelet count in patients without the *JAK2* V617F mutation was significantly lower at delivery than before pregnancy, but there was no significant difference between the pre-pregnancy value and the values for each period of pregnancy.

Change in Platelet Count after Childbirth

The mean platelet count at delivery was 426.7×10^9/L (95% CI: 391.1–462.3×10^9/L), which was significantly lower than that before pregnancy ($P < 0.01$). The mean platelet count after delivery was 829.1×10^9/L (95% CI: 748.7–909.4×10^9/L). The platelet count increased immediately after delivery and reached the pre-delivery level. These trends were observed regardless of the presence of the *JAK2* V617F mutation (**Figure 3**).

Table 2 The impact of acetylsalicylic acid (ASA) on the pregnancy outcome

	Aspirin administration during pregnancy		
	Yes	No	Unknown
Miscarriage	1	8	1
Premature birth		1	
Live birth	14		2

In addition to the above, there were two pregnancies that resulted in induced abortions.

Discussion

In this study, we used the revised IPSET-thrombosis tool to retrospectively analyze the course of 29 low-risk ET-complicated pregnancies of 8 patients, as well as platelet counts during pregnancy in 12 pregnancies that culminated in delivery without IFN-α. In this study, the miscarriage rate and live birth rate of ET-complicated pregnancies were 46.4% and 55.5%, respectively, which were similar to previously reported values and which confirmed that ET complications led to worse pregnancy outcomes. However, 67% of miscarriages were before ET diagnosis, suggesting that antithrombotic therapy was insufficient. According to a prospective survey of MPN-complicated pregnancies in the United Kingdom[6], miscarriage incidence in MPN-complicated pregnancies treated with aspirin from when pregnancy was confirmed was lower than in previous reports[13], 1.3/100 pregnancies (95% CI: 0.04–9.24). In other words, antithrombotic therapy given early in ET-complicated pregnancies might prevent recurrent infertility and perinatal complications. **Table 3** shows the outcomes of reported ET-complicated pregnancies[21,23,27–33]. Of these, only 2 studies did not use IFN-α, as in the present study. Wright and Tefferi[21] reported that aspirin was used in 64% of 14 pregnancies

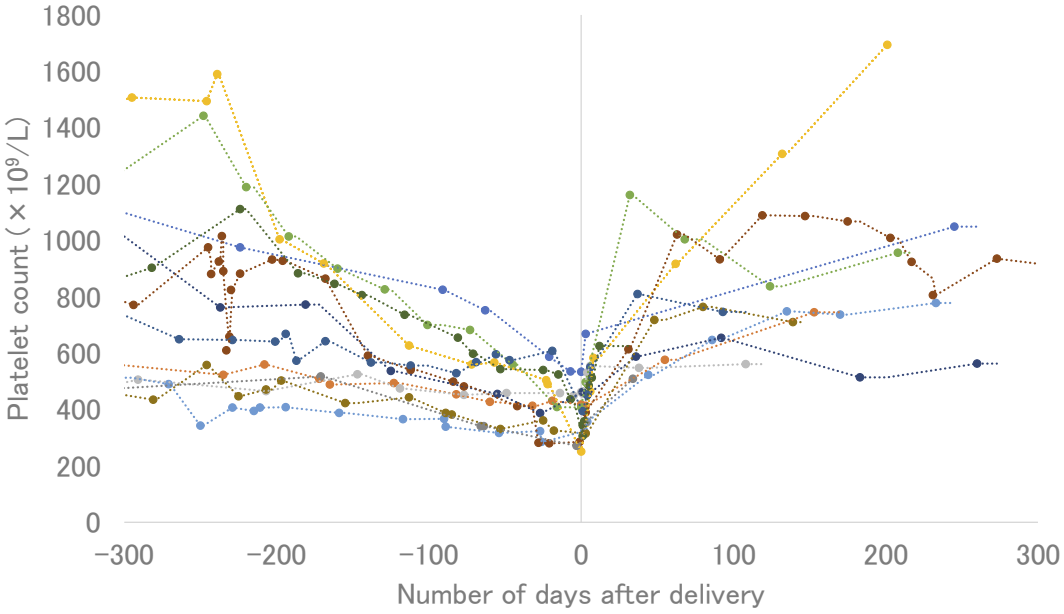

Figure 1 Change in platelet count during pregnancy in ET-complicated pregnancies
The platelet count for each pregnancy is shown. The horizontal axis indicates the number of days, with the date of delivery set to 0. After pregnancy, the platelet count decreased and reached a value of ≤600×10^9/L by delivery in all pregnancies. Platelet counts increased after delivery in all pregnancies.
ET, essential thrombocythemia.

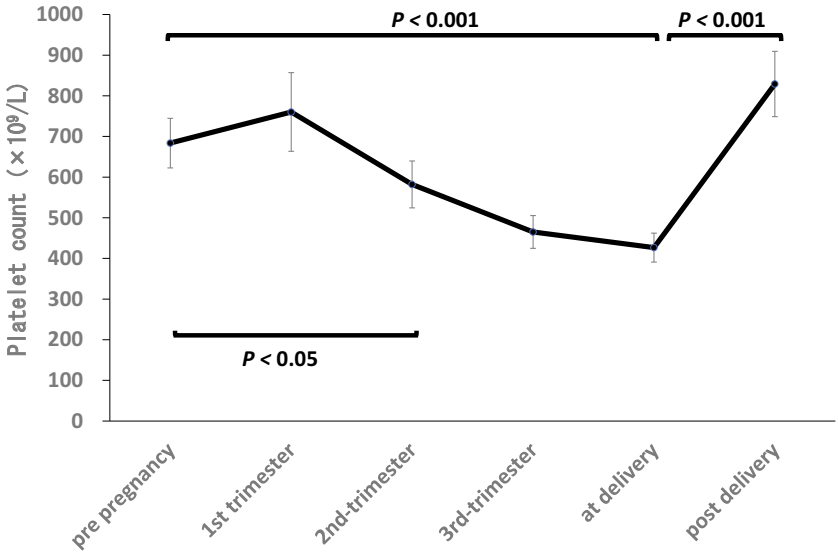

Figure 2 Change in mean platelet count during pregnancy in ET-complicated pregnancies

The mean platelet counts before pregnancy, at each trimester of pregnancy, at delivery, and after delivery are shown. The I bar shows the 95% confidence interval. The platelet count significantly decreased by the second trimester and increased after delivery.

ET, essential thrombocythemia.

that resulted in miscarriage but that it did not necessarily improve outcomes of ET-complicated pregnancies. Bangerter et al.[23] reported that 6 of 17 pregnancies resulted in miscarriage, and these were all in the non-aspirin group, which suggests that aspirin was useful for ET-complicated pregnancies. In our study, excluding 1 premature birth, all pregnancies treated with aspirin from the time of pregnancy culminated in delivery, which suggests that antithrombotic therapy in early pregnancy improves pregnancy outcomes.

In the present ET-complicated pregnancies culminating in delivery, the platelet count decreased over the course of the pregnancy without IFN-α use, and the platelet count was ≤450×10^9/L in 83% of pregnancies. Furthermore, all pregnancies achieved a platelet count of ≤600×10^9/L. These results suggest that pregnancy-related changes in the body environment resulted in a lower platelet count. However, all pregnancies had a very low or low revised IPSET-thrombosis score, so it is possible that only low-risk pregnancies was observed. Furthermore, because the sample size was small, determining if platelet count spontaneously decreases in ET-complicated pregnancies will require accumulation of more cases.

In normal pregnancies, the platelet count decreases over the course of the pregnancy. According to a report by Reese et al.[20], as compared with the mean platelet count of nongravid women (273×10^9/L, 95% CI: 269–276 ×10^9/L), the platelet count of healthy pregnant women significantly decreased from the first trimester (251×10^9/L, 95% CI: 249–253×10^9/L), reaching a nadir at the time of delivery (217×10^9/L, 95% CI: 213–219×10^9/L). The diminished platelet count recovers to that of a nongravid woman (264×10^9/L, 95% confidence interval: 254–274×10^9/L) by 7 weeks after delivery. The mechanism of pregnancy-related thrombocytopenia is thought to be dilution from increased circulating plasma volume, supplementation due to splenomegaly, and supplementation between placental villi. The circulating plasma volume in pregnant women increases from the first trimester, increasing by 40–45% at 32–34 weeks of pregnancy, as compared with nongravid women[34]. This increased circulating plasma volume causes hemodilution and splenomegaly. In late pregnancy, the spleen enlarges by 50–68%, as compared with nongravid women, and platelet supplementation and destruction are accelerated[35,36]. Furthermore, increased circulating plasma volume causes placental enlargement. Platelets are also supplemented between placental villi, which contributes to thrombocytopenia during pregnancy[20]. Thrombocytopenia in ET-complicated pregnancies is triggered by the same mechanism as that in normal pregnancies.

Some studies reported that platelet count decreased

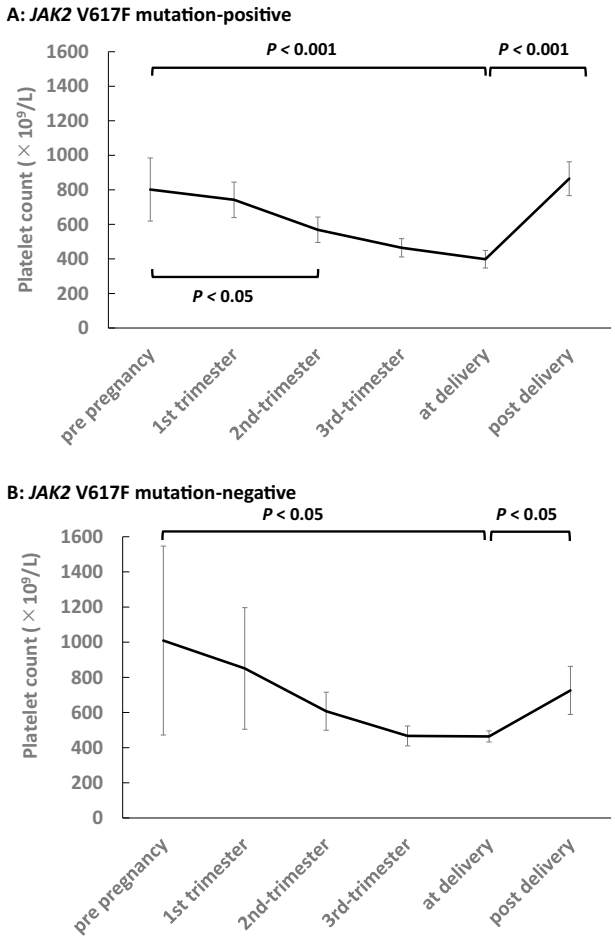

Figure 3 Changes in the mean platelet count during pregnancy in ET-complicated pregnancies, in relation to *JAK2* V617F mutation status

The mean platelet counts before pregnancy, at each trimester of pregnancy, at delivery, and after delivery are shown for *JAK2* V617F mutation-positive cases in Panel A and for *JAK2* V617F mutation-negative cases in Panel B. The I bar shows the 95% confidence interval. The platelet count was significantly lower at delivery than before pregnancy and increased after delivery.

ET, essential thrombocythemia.

over the course of pregnancy in ET-complicated pregnancies (**Table 3**); in most such cases, IFN-α was used as cytoreductive therapy, and it is difficult to evaluate changes in platelet count during pregnancy. Nevertheless, it is noteworthy that platelet count sometimes decreased to the point of remission, even when it exceeded $1{,}000\times10^9$/L during pregnancy. Furthermore, few studies reported a marked decreased in platelet count over the course of pregnancy, even without the use of IFN-α, as was seen in the present study[21,23]. These ET-complicated pregnancies exhibited more severe thrombocytopenia than did normal pregnancies. These results suggest that ET-complicated pregnancies exhibit the mechanism possibly present in normal pregnancies, as well as a factor that reduces platelet count. Turhan et al.[37] reported that clonal hematopoiesis was suppressed during pregnancy and accelerated after delivery in human MPN-complicated pregnancies. This suggests that physiological changes due to pregnancy act on MPN hematopoietic stem cells. Estrogen, which increases during pregnancy, may regulate platelet count. Estrogen acts on hematopoietic stem cells and enhances their turnover[38]. It also induces apoptosis in hematopoietic stem cells with the *JAK2* V617F mutation, although at the in vivo level[39]. However, the effects of estrogen on ET-complicated pregnancies are unclear, and further research is needed.

If the platelet counts of patients with ET decrease spontaneously because of pregnancy, then cytoreductive therapy may be avoided. Although IFN-α is used as a cytoreductive therapy in high-risk ET-complicated pregnancies, it has adverse events, such as depressive tendencies and impaired glucose tolerance. Therefore, if ET is complicated with gestational depression or gestational diabetes, it may not be possible to administer IFN-α, and careful judgment is needed to guide its use. In **Table 3**, only Wright and Tefferi[21] and Bangerter et al.[23] reported a decrease in platelet count without the use of IFN-α, as reported in the present study, but there was no mention of pregnancy risk. In the present study, after excluding 2 patients, 6 patients had a history of miscarriage, and many of them had pregnancy risk factors according to ELN and BCSH/BSH guidelines. Nevertheless, platelet count decreased spontaneously and the course of pregnancy was favorable. Therefore, even in patients with a history of ET-related miscarriage or premature birth, if aspirin is administered pregnancy outcomes may not be as poor as previously reported in selected low-risk populations. Importantly, all patients in this study were classified as low risk or very low risk according to the revised IPSET-thrombosis scores. Therefore, these findings should not be extrapolated to patients at intermediate or high risk, for whom cytoreductive therapy including IFN-α remains an important consideration.

A physiological mechanism for the normalization of platelet levels in ET-complicated pregnancies has not been identified. Clarification of such a mechanism might lead to better assessment of prognosis and new treatments for ET-complicated pregnancies.

This study has several limitations. First, it was a retrospective study with a small sample size at a single center. Second, multiple pregnancies from the same patients were included, which could have introduced intra-

Table 3 Previous research on changes in platelet count during pregnancy in patients with essential thrombocythemia

Year	Type	Patients	Pregnancy	Gene mutation		Treatment during pregnancy		Plt count during pregnancy in patients who were managed by watchful waiting with daily low dose aspirin use*		Plt count during pregnancy in all enrolled in the study**		Reference
2009	Retrospective	92	122	*JAK2* V617F	51%	ASA	76%			818 (603–2,000) at conception	520 (230–1,200) at delivery	27
						IFN-α	16%					
2004	Retrospective	4	9	No data		ASA	44%			650 (310–1,742) at conception	380 (280–875) at delivery	28
						IFN-α	56%					
2004	Retrospective	16	40	No data		ASA	25%			814 (255–1,561) at conception or 1st trimester	574 (376–2,100) at 2nd or 3rd trimester	29
						IFN-α	13%					
						None	68%					
2020	Retrospective	52	121	*JAK2* V617F	56%	ASA	51%			781 (90% CI no data)	336 (90% CI 12.3–393.9)	30
				CALR	12%	IFN-α	13%					
				MPL	0%	None	42%					
2007	Retrospective	62	102	*JAK2* V617F	49%	ASA	62%			601 (266–1,660) at pregnancy	429 (219–2,000) at third trimester	31
						IFN-α	3%					
2001	Retrospective	20	43	No data		ASA	44%	1,106 (400–2,500) at conception	604 (180–3,000) at delivery			21
						IFN-α	0%					
						HU	4%					
						Anagrelide	2%					
						Heparin	2%					
						None	46.5%					
2000	Retrospective	9	17	No data		ASA	35%	785 (600–2,033) at conception	440 (258–1,179) lowest during pregnancy			23
						IFN-α	0%					
						Heparin	29%					
						None	53%					
2006	Observation study	8	10	*JAK2* V617F	63%	ASA	90%			509 (354–676) at conception	285 (172–467) at delivery	32
						IFN-α	100%					
						Heparin	60%					
2021	Retrospective	23	34	*JAK2* V617F	61%	ASA	59%			814 (615–5,000) at diagnosis	414 (116–1,442) during pregnancy	33
				CALR	26%	IFN-α	100%					
				MPL	4%	Heparin	62%					

*Excluding the patients treated with IFNα during pregnancy.

**Including the patients treated with IFNα during pregnancy.

ASA: acetylsalicylic acid, IFN: interferon, Plt: platelet.

individual correlation despite the use of statistical adjustments. Third, all pregnancies were classified as low risk or very low risk, limiting the generalizability of the findings. Finally, all patients received aspirin during pregnancy, making it difficult to completely separate the effects of pregnancy itself from those of aspirin.

The present study suggests that platelet counts decrease during pregnancy but normalize by the time of delivery in ET-complicated pregnancies. In addition, aspirin use starting in early pregnancy was associated with favorable pregnancy outcomes. These findings suggest that cytoreductive therapy with IFN-α may be avoidable in selected low-risk and very-low-risk patients, even in those with a history of miscarriage. However, these findings should be interpreted cautiously and validated in larger studies.

Author Contributions: S.H. and S.W. were the principal investigators and take primary responsibility for the paper. H.Y. designed the study; S.H. and S.W. designed and wrote the manuscript; M.S., S.Y., and K.I. contributed to patient recruitment and data extraction. All authors reviewed and approved the manuscript.

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