CASE STUDY

Essential Thrombocythemia in Pregnancy: A Case Report

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ABSTRACT

Essential thrombocythemia is a hematological problem that occurs during pregnancy. Diagnosis of essential thrombocythemia is difficult because it is a diagnosis of exclusion and there is a higher frequency of thrombocythemia due to other causes [1]–[3]. Essential thrombocythemia, which is classified as a chronic myeloproliferative neoplasm (MPN), is characterized by persistent symptoms of thrombocythemia without a clear secondary cause [4]. Essential thrombocythemia is characterized by thrombocythemia and megakaryocytic hyperplasia of bone marrow. According to World Health Organization (WHO), essential thrombocythemia can be diagnosed when thrombocyte count is more than 450,000/microliter and mutation in Janus kinase 2 (JAK2), Calreticulin (CALR) or myeloproliferative leukemia (MPL) virus oncogene, does not have a clonal or reactive cause [5], [6].

According to WHO, the annual incidence rate of essential thrombocythemia is 0.65–2.5/100,000 individuals [7]. Maze et al. show that essential thrombocythemia is the most common type of MPN during pregnancy [8]. Essential thrombocythemia patients are reported to have a higher complication rate compared to the normal population with a live birth rate of 70.9%. The most frequently encountered complication was spontaneous abortion or loss of the fetus before 20 weeks’ gestation with an incidence rate of 26.5% of all pregnancies compared with the estimated spontaneous abortion (SA) rate of 11% in the base population [9]. How et al also reported that essential

1. INTRODUCTION

Essential thrombocythemia is a hematological problem that occurs during pregnancy. Diagnosis of essential thrombocythemia is difficult because it is a diagnosis of exclusion and there is a higher frequency of thrombocythemia due to other causes [1]–[3]. Essential thrombocythemia, which is classified as a chronic myeloproliferative neoplasm (MPN), is characterized by persistent symptoms of thrombocythemia without a clear secondary cause [4]. Essential thrombocythemia is characterized by thrombocythemia and megakaryocytic hyperplasia of bone marrow. According to World Health Organization (WHO), essential thrombocythemia can be diagnosed when thrombocyte count is more than 450,000/microliter and mutation in Janus kinase 2 (JAK2), Calreticulin (CALR) or myeloproliferative leukemia (MPL) virus oncogene, does not have a clonal or reactive cause [5], [6].

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thrombocythemia in pregnancy was associated with an increased risk of obstetric complications. The study stated that as many as 48.7% of all women experienced pregnancy complications and the most common was spontaneous abortion, which occurred in 26% of all pregnancies. Material thrombosis and bleeding complications were 2.5% and 5.8%, respectively [10].

Due to the complexity of essential thrombocythemia cases, a deeper understanding of this case is needed. This is the reason that prompted the author to write this case report to describe a case of essential thrombocythemia during pregnancy.

2. CASES

A 26-year-old female patient with G1P0000 gestational weeks 30–31 came to the gynecology clinic at Bali Mandara Hospital for routine antenatal care. The patient was referred from Ubud Community Health Center because the first laboratory examination revealed thrombocythemia with a thromocyte count of 1,128,000 μL. There were no complaints of dizziness, nausea, vomiting, tingling, or fever. The patient did not have a history of systemic diseases such as hypertension, heart disease, diabetes mellitus, thyroid disease, tuberculosis, asthma, and related gynecological diseases. The patient's family had no previous similar complaints. Her mother had a history of hypertension and was not regularly monitored. Family history of other systemic diseases such as heart disease, diabetes, thyroid disease, tuberculosis, and asthma was denied. The patient's family has no history of gynecological diseases.

On physical examination, she was fatigue with comatos mentis consciousness, with blood pressure 110/70 mmHg, heart rate 85 times/minute, respiratory rate 20 times/minute, and temperature 36.5 °C. The head-to-toe examination was within normal limits. An obstetric status examination was obtained. Fundal height: 3 fingers below the xiphoid process (31 cm, with estimation fetal weight by McD formula 2945 grams) and fetal heart rate 134 times/minute.

Patients had monthly complete blood tests (Table I). The peripheral blood smear shows leukocytosis, and thrombocythemia suspected myeloproliferative disorder (MPD), essential thrombocythemia. She was tested for the JAK2V617F mutation, but no mutation was detected. Doppler ultrasound test shows the umbilical artery (RI: 0.69; PI: 0.95; S/D ratio: 2.76) and middle cerebral artery (RI: 0.74; PI: 1.48; S/D ratio 3.88) (Fig. 1). She was consulted by hematologist and was given aspirin 80 mg per day, Cal-95 1 tablet per day, and prenatal vitamins. Bone marrow biopsy and BCR-ABL were not performed.

She got caesarean delivery in gestational weeks 37–38 because of fetal transverse position and pathological cardiotocography (CTG) with reduced variability. The baby was born with an APGAR score of 5-7-8, birth weight of 3600 grams, birth length of 52 cm, and physical examination in a normal state. The patient’s thrombocytes count before delivery was 875,000 μL and 6 h after delivery was 783,000 μL. Aspirin was stopped one week before caesarean section.

3. DISCUSSION

Based on the case, the patient is a 26-year-old female with G1P0000 gestational age 30–31 weeks. Kashif et al. show that essential thrombocythemia usually appears at an average age of 50–60 years with a second peak at around 30 years of age and is more common in women [11]. Pregnancy is at low risk if all the following factors are present: no prior ET-related complications, absence of hereditary thrombophilic factors or cardiovascular risk factors, age <35 years, and platelet count <1000 G/I [7]. Pregnancy is at high risk of complications if one or more of the following factors are present or develop: previous arterial or venous thrombosis event or history of major bleeding or minor bleeding with a platelet count >1000 G/I or previous thrombohaemorrhagic complications during pregnancy or presence of hereditary thrombophilic factors or cardiovascular risk factors or severe complications in a previous pregnancy (early or late pregnancy loss, intrauterine death or stillbirth, pre-eclampsia, ante- or post-partum hemorrhage) or age >35 years or platelet count >1000 G/I [7].

This patient did not have any complaints and physical abnormalities. Kashif et al shows that more than half of cases show no symptoms and are discovered accidentally during routine blood tests. Patients in other cases may experience vasomotor (headache, visual disturbances, lightheadedness, atypical chest pain, distal paresthesia, erythromelalgia), thrombotic or hemorrhagic disorders [11].

In laboratory, examination showed that the thrombocyte level at the initial diagnosis was 1191 × 103/μL, then decreased after receiving therapy to 811 × 103/μL. This is in line with the literature that the diagnosis of essential thrombocythemia is when there is unexplained and persistent thrombocythemia (thrombocyte count >450 × 109/L). Essential thrombocythemia is a diagnosis of exclusion, which does not require the presence of reactive conditions and other clonal disorders that may be present as a cause of thrombocythemia [5]. This is supported by the World Health Organization (WHO) revised criteria for the diagnosis of essential thrombocythemia, identifying 4 major criteria and 1 minor criterion. Major criteria are (1) thrombocyte count greater than or equal to 450,000/microliter; (2) bone marrow biopsy shows proliferation, especially in the megakaryocytic lineage, with an increased number of enlarged mature megakaryocytes with hyper localized nuclei. There was no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely there was a small increase in reticulin fibers; (3) features that do not meet WHO criteria for BCRABL1 + CML, PCV, myelofibrosis, MDS, or other myeloid neoplasms; (4) +JAK2, CALR, or MPL. Minor criteria are the presence of clonal markers or no evidence of reactive thrombocythemia. The diagnosis of essential thrombocythemia requires fulfillment of all major criteria or the first 3 major criteria and minor criteria [5].

The results of peripheral blood examination reported thrombocythemia differential diagnosis MPD, essential thrombocythemia. Babukhanlou et al. show that essential thrombocythemia is a chronic myeloproliferative neoplasm characterized by an increase in the number of...
thrombocytes (thrombocythemia) in the peripheral blood and excessive megakaryopoiesis in the bone marrow [12]. Ashorobi et al. show that because of the symptoms of myeloproliferative neoplasms overlap, it is important to exclude other causes of thrombocythemia, including clonal and reactive causes, before reaching a definitive diagnosis of essential thrombocythemia [13]. To differentiate reactive thrombocythemia, acute phase reactants and an iron panel should be checked. Abnormalities in both cases have been shown to cause thrombocythemia.

The discovery of mutations in JAK2 and MPL now makes it easy to identify positive essential thrombocythemia in more than 50% of cases. Screening for JAK2 V617F treatment is an initial examination performed in all patients with suspected essential thrombocythemia, followed by MPL exon 10 treatment screening in V617F-negative cases [5]. Based on this case, the results of the JAK2V617F mutation examination showed that it was not detected. Khasif et al. reported that a 35-year-old female patient came to the outpatient department with the main complaint of pain and redness at the tips of the fingers and toes which had occurred for the previous two months and showed a negative JAK 2 examination. The diagnosis of essential thrombocythemia is made through a careful algorithmic approach that excludes secondary causes of thrombocythemia through assessment of peripheral blood smear, inflammatory markers, bone marrow histology, and iron examination [11], [14]. Bone marrow biopsy should show evidence of increased proliferation of megakaryocytic cell lines with an increased number of enlarged mature megakaryocytes [15]. However, this patient did not undergo a bone marrow biopsy. The finding is that JAK2 mutations, especially if they are associated with leukocytosis, do not have a protective role against bleeding risk [11]. They constitute a strong predictor of subsequent thrombotic events and do not have a protective role against the risk of bleeding [11].

In contrast, Iskender et al. who reported that 21 samples at the Etlik Zübeyde Hanım Mutasi Maternity Hospital reported that JAK2V617F was found positive in 52.4% of pregnant women with essential thrombocythemia [4]. The Puyade et al. reported that retrospectively from 2002 to 2015 aimed to evaluate pregnancy outcomes in women with myeloproliferative neoplasms, all samples (18 samples) had the JAK2V617F mutation [15].

Other supporting examinations in this patient were Doppler ultrasound examination with results of the umbilical artery (RI: 0.69; PI: 0.95; S/D ratio: 2.76) and middle cerebral artery (RI: 0.74; PI: 1.48; S/D ratio 3.88), showed that the condition of the umbilical artery and middle cerebral artery were within normal limits so it did not
lead to intrauterine growth restriction (IUGR). IUGR is defined as the inability of a fetus to accept its genetic growth potential in the womb, or a fetus with a body weight ≤10 percentile caused by reduced placental perfusion, chromosomal abnormalities, and environmental factors or infection [16]. When using Doppler ultrasound support, the classification of IUGR is determined based on the estimated fetal weight <10 percentile and the presence or absence of abnormalities in the umbilical artery and middle cerebral artery [16–18]. Placental microinfarction due to increased thrombocyte count, thrombocyte activation, and/or placental damage due to autoantibodies is one of the underlying pathological causes of adverse fetal effects [7]. Late obstetric complications are rare in patients with ET and include stillbirth, intrauterine growth restriction, preeclampsia, premature birth, placental abruption, and cervical incompetence [7]. How et al. reported complications of ET in the 3rd trimester of pregnancy, namely thrombosis during pregnancy, bleeding during pregnancy, gestational hypertension, preeclampsia, eclampsia, prematurity, placental abruption, intrauterine growth retardation, and stillbirth [19].

The patient was given 80 mg aspirin per day, 1 tablet of Cal-95, and 400 mcg of folic acid. Valera et al. show that in the general population, low-dose aspirin during pregnancy does not increase the risk of bleeding in the mother and has been proven safe for the fetus. Some literature shows that aspirin during pregnancy with essential thrombocythemia can reduce complications, even live births in patients receiving aspirin treatment reach 100% [7]. Kwiatkowski et al. show that the effectiveness of preventing thrombotic events from low doses of acetylsalicylic acid (ASA) in patients with essential thrombocythemia is quite good [20]. Administration of ASA during pregnancy has been reported to significantly reduce the rate of spontaneous abortion (35 vs 71.4%) [21]. How et al. also reported that multivariable analysis of aspirin use and previous history of miscarriage was associated with decreased and increased pregnancy complications, respectively [10].

Cal-95 therapy in this patient is related to management to maintain pregnancy. Calcium supplementation in pregnancy has the potential to reduce poor outcomes in pregnancy, especially in reducing the risk of developing hypertensive disorders during pregnancy which is correlated with a large risk of premature birth which is the main cause of early neonatal death and infant mortality, as well as reducing the risk of maternal death [22].

This patient also received folic acid therapy. One of the most important indications for the use of folic acid is the development of the central nervous system, namely reducing the risk of neural tube defects (NTD), such as spina bifida, in the developing fetus. Some literature states that the mechanism for NTD formation in the absence of folate is related to increased ubiquitination of genes related to neural tube closure, thereby disrupting the expression of these genes [20]. The important role of folic acid is that it can reduce homocysteine levels in NTDs. Therefore, supplementation should be started 5 to 6 months before conception [23]. Sufficient folic acid is also associated with a reduced risk of preterm birth [24].

Ashobori et al. said for pregnant patients with essential thrombocythemia, it is recommended to use low molecular weight heparin during pregnancy for 6 weeks after delivery as well as cytoreduction with pegylated interferon. In addition, in pregnant women who have very high thrombocytes (>1.5 million) where the action of interferon is slow to reduce thrombocytes, thrombocytopheresis is reported to be an option to reduce the number of thrombocytes. Hydroxyurea and anagrelide are contraindicated in pregnant patients with thrombocythemia. Hydroxyurea is potentially teratogenic. Anagrelide may cross the placenta causing possible fetal thrombocytopenia [14].

In cases of pregnancy with essential thrombocythemia, the choice of prevaginal or cesarean delivery should be made based on routine obstetric indications or worsening disease. It should be remembered that there are thrombotic changes in the postpartum period up to 6 weeks after delivery (both vaginal and cesarean). The average thrombocyte count is low in the days before delivery and increases sharply until it reaches a peak on day 11 and continues to increase up to 25 days after delivery. The time to reach peak values is between (7–15) days. This places patients at increased risk of thromboembolic events during the last few weeks of pregnancy and in the postpartum period. Thus, prophylactic doses of low molecular weight heparin (LMWH) have an important role in preventing thrombosis. Grieshammer et al. reported that a large case series and patients with ET were undergoing treatment with ASA which was discontinued approximately two weeks before expected delivery and started with LMWH in prophylactic doses. LMWH is continued until delivery, with the dose stopped immediately approximately 12 hours before expected delivery and restarted on the first day postpartum and continued for 6 weeks [25–27].

Our patient was planned for C-section surgery. Patients with essential thrombocythemia in pregnancy can give birth vaginally or cesarean, considering that thrombocythemia is not an indication for cesarean surgery. Harde et al. showed that reporting on 150 pregnant patients admitted to the maternity ward with thrombocythemia, it was found that 82 patients (54.7%) experienced normal vaginal delivery, while 68 patients (45.3%) underwent lower segment cesarean section. Lower segment caesarean section is indicated only for obstetric indications. The majority of studies mention concomitant results. Nisha et al. show that normal vaginal delivery occurred in 61.54% of patients and caesarean section was performed in 36.26% of patients [28].

4. Conclusion
Evaluation of patients with essential thrombocythemia includes a complete blood count, bone marrow biopsy, and genetic testing to evaluate gene mutations to obtain the appropriate diagnosis and therapy to prevent from its complication such as IUGR, thrombosis during pregnancy, bleeding during pregnancy, gestational hypertension, preeclampsia, eclampsia, prematurity, placental abruption, intrauterine growth retardation and stillbirth.
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CONFICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES