Case Report

Outcome of Pregnancy in the Era of Pegylated Interferon Alpha 2a in Females with Essential Thrombocythemia: An Experience from Qatar

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Keywords

Essential thrombocythemia · Myeloproliferative neoplasms · Interferon · PEG-IFN alpha-2A · Pregnancy

Abstract

Myeloproliferative neoplasms are a diversified group of diseases of the hematopoietic stem cell, such as essential thrombocythemia (ET) and polycythemia vera. They are mainly caused by mutations in the following genes: *JAK2*, *CALR*, and *MPL*. All carry an increased risk to transform into acute leukemia or chronic myelogenous leukemia along with thrombosis and hemorrhagic complications. Treatment of such disorders during pregnancy is a challenging foot-step, given the high risk of complications for both the mother and the fetus. Here, we report about two pregnant females with ET that has been treated with pegylated interferon alpha with safe and effective outcome.

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Introduction

Myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET) and polycythemia vera, are commonly diagnosed in the sixth decade, but as many as 20% of all patients are younger than 40 years [1]. MPN is caused by the clonal proliferation of myeloid

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cells, which results in elevated numbers of circulating platelets, thrombotic or hemorrhagic episodes, and occasional leukemic transformation [2]. Familial ET, or inherited thrombocythemia or thrombocytosis, is a rare disorder, which is autosomal dominant, usually presenting as sporadic ET. But studies have shown that it is likely caused by a genetic predisposition to acquire somatic mutations, rather than to direct inheritance of germline mutations. Around 90% of all cases have a somatically acquired driver mutation in the genes *JAK2*, *CALR*, or *MPL*. This is causing an upregulation of the JAK-STAT target genes, demonstrating the central importance of this pathway in the pathogenesis of ET [3].

The incidence of the disease is controlled by multiple factors, such as race, sex, and age. There is a female preponderance with an approximate female-to-male ratio of 2:1 [4]. Around half of the patients with ET are detected incidentally upon doing blood investigations for other reasons. Patients with ET show a higher incidence of thrombosis and hemorrhage; thrombosis as in, e.g., cerebrovascular accident, myocardial infarction, superficial thrombophlebitis, deep vein thrombosis, or pulmonary embolism, mainly due to qualitative and quantitative platelet alterations [5]. Treatment is usually aimed to prevent hemorrhage or thrombosis occurrence and their complications.

The treatment of ET during pregnancy is a challenging decision, as it holds the risk of abortion, thrombotic complications, and other risks. Today, there is limited data on the use of pegylated interferon alpha (PEG-IFN α), with regard to treatment and outcome on the basis of disease control and safety.

Cases Presentations

Case 1

A 34-year-old American female was diagnosed with ET according to the 2008 WHO criteria and started on PEG-IFN α 50 μ g for 2 weeks; then, the dose was escalated to 135 μ g subcutaneous once weekly. The patient and her husband were offered conventional interferon as a safe alternative, but they insisted on continuing on PEG-IFN α . The patient was referred to the high-risk pregnancy unit of the maternity hospital for a close follow-up. Eventually, she gave birth to a healthy baby girl.

Case 2

A 31-year-old Egyptian female was diagnosed with ET according to the 2008 WHO criteria and started on PEG-IFN α 50 μ g for 2 weeks; then, the dose was escalated to 135 μ g subcutaneous once weekly. This patient became pregnant while on PEG-IFN α . The patient and her husband were offered conventional interferon as a safe alternative, but they insist on continuing on PEG-IFN α . The patient was referred to the high-risk pregnancy unit of the maternity hospital for a close follow-up. Eventually, she gave birth to a healthy baby boy.

Discussion

Pregnancy is not contraindicated in patients with ET, as a normal pregnancy with normal fetal outcome is possible in patients with ET, even without therapy. However, ET in pregnant women may lead to multiple problems for the mother and/or the fetus [6]. Therefore, it is advisable to discuss possible complications associated with the current treatment options and reach a decision with the parents-to-be preferably before conception. In high-risk women with ET who are either pregnant or planning to become pregnant, therapy with a platelet-

lowering agent is essential to prevent recurrent thrombosis. Current treatment options include aspirin, IFN α , and thrombapheresis.

Aspirin works by inhibiting the cyclooxygenase activity of the platelets causing a reduction in platelet release and aggregation, which in return decreases the chances of thromboembolic complications. An advantage of aspirin therapy is its associated reduction of preeclampsia in patients at high risk for this complication. On the other hand, aspirin has also been well associated with complications during pregnancy, especially intracranial hemorrhage during delivery [6]. Thrombapheresis is a safe therapy, especially in acute situations such as massive thrombosis or hemorrhage. It can be applied during pregnancy without any risk for the fetus; however, disadvantages of this therapy are that apheresis is expensive, time-consuming, and has to be repeated frequently [6].

Several studies have shown the effectiveness of controlling platelet counts and inducing molecular responses in ET [7–14]; in addition, IFN α is not considered leukemogenic nor teratogenic. Several successful pregnancies have been reported in ET patients treated with IFN α [15–22]; however, due to its significant side effects and inconvenient frequency of administration, its use is limited to high-risk pregnant women or to patients where treatment with hydroxyurea failed.

PEG-IFN α is a pegylated form of IFN α that is naturally occurring as a biologic response modifier. It has anti-angiogenic, antiproliferative, pro-apoptotic, immunomodulatory, and differentiating properties [12]. PEG-IFN α has a longer half-life and a reduced clearance compared to IFN α and can therefore be given once weekly. Its efficacy has been investigated in several phase 2 trials which showed efficacy in controlling platelet counts in patients with ET [23–25]. However, only sparse data have been published on the safety of its use in pregnant women. A recent observational study [26], on 10 pregnancies in women with ET treated with PEG-IFN α , suggested efficacy and safety of PEG-IFN α in pregnant women with ET. In this study, the median dose of PEG-IFN α was 270 μ g/month (range 90–1,080 μ g/month), while in our reported cases, we used a fixed dose of 135 μ g/week (540 μ g/month). Moreover, in Beauverd et al.'s study [26], aspirin and/or low-molecular-weight heparin was used in all cases in addition to PEG-IFN α .

Here, we presented 2 cases of pregnant women with ET who opted to take PEG-IFN α during their pregnancy. Both women had normal deliveries of healthy babies with normal birth weight and cognitive functions. The metabolic screenings and thyroid function tests returned normal for the two babies.

Conclusion

PEG-IFN α might be a promising upcoming treatment for ET during pregnancy, given our report of two cases and their encouraging outcome. However, the efficacy and safety of PEG-IFN α for MPN, and mainly for ET treatment, have been investigated only in one recent small observational study. We would like to highlight the importance of further studies of such possible treatment for the management of MPN during pregnancy.

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Statement of Ethics

This case report was approved by the Hamad Corporation Medical Research Center.

Disclosure Statement

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Author Contributions

Mohammad Abu-Tineh and Nancy Kassem: Writing of the Manuscript. Mohammad Abdul-Jaber Abdulla, Omar Mohammad Ismail, Mahmood B. Aldapt, Rola Ghasoub: Clinical Management. Mohamed A. Yassin: Writing and Editing.

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