

Review

Polycythemia Vera in Pregnancy: A Descriptive Review of the Literature

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Abstract

Objectives: Polycythemia vera (PV) is a rare myeloproliferative neoplasm that is associated with a high risk of thrombosis due to an increase in red blood cell mass and hyperviscosity. In the setting of pregnancy, patients with PV appear to be at even higher risk for a variety of pregnancy-related thrombotic and other adverse outcomes. While a diagnosis of PV is relatively uncommon in younger reproductive age women, as mean maternal age at first birth increases, incidence of pregnancies complicated due to PV may also increase in the future. **Mechanism:** A review of the literature was conducted using the PubMed database and relevant search keywords (MeSH terms) “polycythemia” AND “pregnancy”. **Findings in Brief:** PV must be differentiated from other primary, secondary, and relative causes of polycythemia. A bone marrow biopsy is typically used to confirm the diagnosis. Most, but not all patients with PV, are identified to have a somatic mutation in the *JAK2* gene. In pregnancy, the mainstay interventions are serial phlebotomies to maintain the hematocrit in an appropriate range and daily low dose aspirin therapy. Low molecular weight heparin is added for pregnant patients thought to be at additional risk for thrombosis. For resistant cases, the use of interferon alpha has been advocated for cytoreductive therapy. **Conclusions:** Based on very limited data, these interventions have been reported to improve pregnancy outcomes. Although hydroxyurea is considered a first-line treatment for PV, it is contraindicated in pregnancy due to concerns for teratogenicity. There are a number of newer agents that have been utilized to treat PV and other myeloproliferative neoplasms in nonpregnant individuals. None of these agents have been adequately studied in pregnancy to allow support for their use except perhaps under extraordinary circumstances and with appropriate informed consent.

Keywords: pregnancy; polycythemia vera; recommended interventions; pregnancy outcomes

1. Introduction

Polycythemia is defined as an abnormally elevated hemoglobin concentration (>16.5 g/dL in men or >16.0 g/dL in women) or hematocrit level (>49 percent in men or >48 percent in women) in the peripheral blood [1]. This elevation can occur in several different ways, and each pathophysiology defines a different type of polycythemia [2]. Relative polycythemia refers to simple hemoconcentration, where hemoglobin and/or hematocrit are elevated due to a decrease in the plasma volume alone. Common causes of relative polycythemia include volume contraction from diuretics, vomiting, diarrhea, and smoking. In relative polycythemia, there is no increase in red blood cell (RBC) mass. In contrast, absolute polycythemia does involve an increase in RBC mass, which itself can be due to multiple factors. Absolute polycythemia is subsequently categorized into primary and secondary polycythemia.

Primary absolute polycythemia is typically referred to as polycythemia vera (PV) [3]. It is one of the most common types of Philadelphia chromosome-negative chronic myeloproliferative neoplasms (MPNs), where myeloid cells undergo clonal proliferation, with different levels of maturity and hematopoietic efficiency. One distinguishing characteristic of PV from other MPNs is elevated red blood

cell mass. Platelets and granulocytes also may proliferate to varying degrees. PV is most often associated with an acquired somatic *JAK2* gene mutation, although there are suspected cases of PV that are *JAK2* mutation negative.

The normal physiology of erythropoiesis involves red blood cells developing from multipotent hematopoietic stem and progenitor cells in the bone marrow. Erythropoietin (EPO) is the main driver of RBC proliferation and differentiation. Low EPO levels are highly specific for PV, and levels above normal are unusual and suggest secondary erythrocytosis, with a specificity of 98 percent [4]. Although the exact pathophysiologic mechanism for the clinical presentation of PV still needs delineation, the mutation in the *JAK2* gene appears to cause unregulated cell division with constitutive activation of the janus kinase- signal transducer and activator of transcription (JAK-STAT) pathway [5]. Interestingly, some erythroid progenitor cells in PV are able to proliferate in vitro in the absence of erythropoietin. A late complication of untreated PV is myelofibrosis as bone marrow is replaced by collagen and fibroblasts. Progression of PV to advanced states is relatively slow, and therefore the majority of attention in a younger population is focused on the thrombotic complications of the disease due to hyperviscosity in the vascular system.



In contrast to primary polycythemia, secondary absolute polycythemia refers to an increase in RBC mass due to elevated serum EPO from another underlying condition, which can be associated with high altitude, hypoxia/cardiopulmonary, and renal and autonomous EPO-producing neoplastic processes [2]. Of note, the most common causes of secondary polycythemia include sleep apnea, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD). Paraneoplastic sources of absolute polycythemia include EPO-secreting tumors such as pheochromocytoma, renal cell carcinoma, hepatocellular carcinoma, hemangioblastoma, and leiomyoma. Athletic performance-enhancing agents and cobalt toxicity are other less common causes of secondary absolute polycythemia.

Clinical manifestations of PV are not always initially seen in patients who are later diagnosed with this condition. Most patients are diagnosed based on incidental findings of elevated hemoglobin and hematocrit when a complete blood count is obtained for another reason. However, some patients do present with disease-related symptoms or complications of PV. At or prior to diagnosis, the most common presentations include hypertension, palpable spleen, pruritus, vasomotor symptoms, and arterial or venous thrombosis. Transient visual or neurologic disturbances can also occur due to small foci of thrombosis and hemorrhage in the central nervous system. Other nonspecific symptoms include peripheral tingling, burning, itching, bruising, and petechiae. Once other more common pathologies are ruled out, a bone marrow biopsy usually confirms the diagnosis of PV [1].

2. Literature Review

A review of the literature was conducted using the PubMed database and relevant search keywords (MeSH terms) “polycythemia” AND “pregnancy”. This initial search yielded 210 items of which a large number were related to neonatal polycythemia, in particular, twin anemia polycythemia sequence. Several other primary studies were focused purely on analysis of essential thrombocythemia in pregnancy. These articles that did not discuss PV were excluded from review. Few studies reported on pregnancy with only polycythemia vera. Many additional articles discuss the role of MPNs in general during pregnancy, including PV, essential thrombocythemia, and idiopathic myelofibrosis.

The diagnosis of PV is relatively rare in younger women since only 15% of PV patients are less than 40 years of age at the time of diagnosis [6]. Pregnancy itself does not appear to alter the long term prognosis of MPNs like PV. Conversely, fertility might be reduced, and an adverse outcome of pregnancy due to prothrombotic characteristics of PV may further complicate the already hypercoagulable state found during pregnancy [7]. Hypothetically the known physiologic relative reduction in red cell mass due to intravascular volume expansion in pregnancy may actually

benefit the patient with PV. This hypothesis has not been addressed in the current literature. It is interesting to speculate that because the mean maternal age at first birth has been increasing over the past decade, we may begin to see an increase in the incidence of pregnancies complicated by PV in the future [8]. The goal of this article is to provide a discussion of the current literature on polycythemia in pregnancy, given the rarity of this condition in pregnancy, and the anticipated lack of general knowledge by most practitioners.

3. Risks to Mother and Fetus during Pregnancy

One of the larger primary studies looked at the outcomes and management of 25 pregnancies in 15 women with PV [9]. The study found that these patients have an increased rate of fetal loss, especially related to the presence of specific *JAK2* mutations, in particular *JAK2V617F*. Of interest, no relationship between pregnancy outcome and age or hematological parameters at diagnosis, different mutational status, and allele burden was found. However, additional early pregnancy losses may have been unrecognized and unreported due to the nature of this study. In addition to miscarriage, pregnant patients with PV appear to be at higher risk for a variety of other pregnancy-related complications, including gestational hypertension, preeclampsia, uteroplacental insufficiency, placental abruption, fetal growth restriction, premature birth, and intrauterine fetal demise [9]. A national prospective study of maternal and fetal outcomes of pregnant women with a diagnosis of MPN followed 58 women, of which 81% of the subjects had essential thrombocythemia and only 9% had PV [10]. Nevertheless, findings from this large, UK prospective study suggests women with MPN, including those with PV, may have successful pregnancies with better outcomes than what is anticipated from the literature. Arterial or venous thrombosis and hemorrhage are other more commonly reported complications [11]. Histologic examination of the placenta from patients with PV has shown microscopic vascular thrombosis [12]. Despite the paucity of data, the increased risk for these adverse outcomes appears to be attenuated by the use of sequential phlebotomy and anti-thrombotic therapy in some patients [13].

4. Management Recommendation in Pregnancy and Postpartum

Several organizations have published guidelines on the recommended management of PV during pregnancy, including the British Society for Haematology (BSH), European LeukemiaNet (ELN), National Comprehensive Cancer Network (NCCN), and Japanese Society of Hematology (JSH) [14–17]. Many of these recommendations have been extrapolated from data on other MPNs or have been empirically derived based on expert opinion. Due to the concern for thrombosis in patients with PV, the main interventional

strategies focus on prevention of thrombotic complications. Their guidelines direct that in otherwise low-risk pregnancies, it is recommended to keep the hematocrit within a gestational-appropriate range via serial phlebotomies, and to use low-dose aspirin throughout pregnancy and the postpartum period [18,19]. When phlebotomies are performed, the patient should be maintained in left-lateral positioning, and later in pregnancy with fetal heart rate and contraction monitoring. For other medical conditions in pregnancy, when significant blood volumes are removed, transient uteroplacental insufficiency can be iatrogenically induced during this procedure with reflex fetal heart rate disturbances.

In pregnancies determined to be at higher risk for thrombosis, the recommendation is to initiate more intensive therapy by adding a prophylactic dose of low molecular weight heparin (LMWH) [15]. Therapeutic LMWH therapy may be appropriate during the entire period of pregnancy and postpartum if other additive thrombotic concerns are identified. The use of interferon alpha (IFN- α) as a second-line agent to attempt cytoreductive therapy should also be a consideration in patients resistant to the above initial interventions. A systematic review of IFN- α in pregnancy suggests it is a safe intervention when clinically indicated [20].

A meta-analysis on the number of live births and maternal complications in pregnant patients with PV found that evidence of the benefit from aspirin or interferon treatment was of moderate quality [21]. Another study followed 18 pregnancies in 8 women with PV before and after implementing these management guidelines [22]. They found that pregnancy in PV without careful attention to hematocrit level is associated with poor fetal outcome. They concluded that aggressive intervention with tight hematocrit control, aspirin, and LMWH is associated with significantly better outcomes for mother and infant. Except in cases when aspirin is contraindicated, such as with aspirin-exacerbated respiratory disease, gastric ulcer, or active bleeding, aspirin is recommended. In addition, it may be reasonable to consider screening for inherited thrombophilias in patients with PV who are pregnant or aiming to conceive due to the higher overall risk of thrombosis [18,23].

As mentioned above, cytoreductive therapy is sometimes recommended for higher-risk PV patients. In non-pregnant subjects, hydroxyurea is the preferred initial cytoreductive treatment for PV, as it has a proven efficacy, low cost, and ease of administration [13]. Despite being the standard first-line treatment recommended in multiple guidelines, animal studies have shown potential teratogenic effects on the fetus. It is therefore recommended to stop hydroxyurea at least 3 months before becoming pregnant. IFN- α is the treatment of choice in younger patients and pregnant patients due to its assumed safety in pregnancy and potential to achieve cytogenetic remission [23]. It has also been shown that IFN- α treatment significantly improved

the live birth rate compared to patients who were managed only with observation [21].

Several alternative cytoreductive treatments for PV have also been studied, although not specifically in pregnant patients. Traditional agents like busulfan have been used for PV refractory to hydroxyurea with 75% of patients achieving a complete or partial hematological response in one study [13]. Importantly, busulfan may be more appropriate for an elderly population, due to the risk of leukemic transformation. The Janus kinase (JAK) inhibitors like ruxolitinib may be used as second-line agents for PV refractory to hydroxyurea. Several other agents are being evaluated as alternative treatment options and include histone-deacetylase (HDAC) inhibitors, lysine-specific demethylase (LSD1) inhibitors, and murine double minute 2 (MDM2) inhibitors. Givinostat is an HDAC inhibitor that has demonstrated a good safety and efficacy profile in patients with PV. Bomedemstat and idasanutlin, which are an LSD1 inhibitor and MDM2, respectively, are being evaluated in patients with MPNs refractory to previous cytoreductive therapies. NCCN guidelines state that interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b can be considered for higher risk pregnant patients requiring cytoreductive therapy [10]. Ropeginterferon specifically is a mono-pegylated IFN α -2b with reduced dosing frequency and improved tolerability compared to other pegylated IFNs. It has been approved as first-line therapy for treatment of PV in patients of all ages [24]. Importantly however, these alternative therapies have not been adequately studied in pregnant women.

Author Contributions

NX reviewed the literature and wrote the original draft of the manuscript. BG also reviewed the literature, provided editorial changes to the manuscript, and supervised all other aspects of the submission process. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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