Primary myelofibrosis and pregnancy outcomes after low molecular-weight heparin administration
A case report and literature review

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Abstract
Rationale: Primary myelofibrosis is encountered with the myeloproliferative diseases and is the least prevalent among women of childbearing age. The prognosis is guided by pancytopenia, leukemic transformation and thrombosis which are the dominant complications.

Patient concerns: Data regarding protocol management during pregnancy in the context of myelofibrosis are insufficient. Fewer than ten cases have been described until now and half of this cases have resulted in fetal death due to placental infarction during the second and third trimesters.

Diagnoses: We present the case of a 34-year-old pregnant woman diagnosed with Jak 2- negative primary myelofibrosis. Personal history did not include miscarriage or stillbirth.

Interventions: The patient was previously treated with anagrelide hydrochloride, which was interrupted at 6 weeks of gestation when the pregnancy was confirmed. It was replaced with Interferon-a 3 MU/day. Because of severe thrombocytosis, administration of aspirin 150 mg/day was recommended.

Outcomes: The pregnancy was uneventful. The patient was hospitalized at 33 weeks of gestation because of moderate vaginal bleeding and high risk of preterm birth. After a specialized hematological investigation, the treatment with aspirin was replaced with low-molecular-weight heparin 0.6 ml per day. This combined treatment assisted in the natural tendency to lower platelet counts during pregnancy and resulted in stabilization of the hematological status. At 38 weeks of gestation the patient delivered a healthy baby boy via cesarean. He weight 2850 grams and his Apgar score was 9. Anticoagulant and interferon treatments were continued post-partum under hematologist surveillance.

Lessons: This case was rare and complex. Because it was related to pregnancy it required continuos collaboration and supervision between obstetrician and hematologist.

Abbreviation: PM = primary myelofibrosis.

Keywords: low-molecular-weight heparin, pregnancy, primary myelofibrosis

1. Introduction

Primary myelofibrosis (PM) essential thrombocythemia and polycythemia vera are the 3 classic disorders associated with Philadelphia-negative myeloproliferative neoplasms. Myelofibrosis is the least prevalent in women of childbearing age. The common features of these hematological diseases are increased hematopoiesis and overproduction of mature differentiated blood cells. Myeloproliferative disorders occur rarely in younger patients, their peak incidence occurs during the 6th and 7th decade of life. The main characteristics of myeloproliferative disorders are predisposition to thrombosis, hemorrhage, progression to myelofibrosis, and acute myeloid leukemia. These possible associated conditions are influenced by the prothrombotic potential of pregnancy which causes alterations in hemostatic factors and prothrombotic proteins and influences the physical mechanism of venous blood flow. Thrombosis is one of the leading cause of maternal morbidity according to recent confidential investigations regarding maternal mortality. Of all myeloproliferative disorders, myelofibrosis presents the worst prognosis, with thrombosis, pancytopenia, and leukemic transformation being dominant clinical complications.
The normal course of a pregnancy is dictated by the development and maintenance of a normal uterine blood flow and implicitly an appropriate placental development. Pregnancy is a hypercoagulable condition. In combination with a myeloproliferative disease, a profound prothrombotic status is created along with the afferent risks of placental thrombosis, fetal growth restriction or fetal demise, and maternal thrombotic events. An early marker of placental dysfunction is represented by abnormal placental invasion of the maternal spiral arteries. A later manifestation of placental dysfunction may be represented by thrombotic occlusion of the placental circulation. These warning markers are necessary in the context of complications that may be caused by placental dysfunction such as placental abruption, intrauterine growth restriction, and preeclampsia. In myeloproliferative diseases cases, the prothrombotic state is due to a combination of blood rheology, possible leukocyte adhesion, platelet activation, thrombocytosis, and platelet-leukocyte aggregates.[8] The prognosis of pregnancy is worsened if a previous thrombotic or hemorrhagic event, unexplained recurrent loss during the first trimester, intrauterine growth restriction, intrauterine death, stillbirth, placental abruption, severe preeclampsia, or significant antepartum or postpartum hemorrhage is present in the patient’s medical history.

Myelofibrosis is associated with poor pregnancy outcomes. Pregnancies associated with myelofibrosis have high maternal and fetal risks and represent a challenge for obstetricians. Significant data regarding the course, treatment, management, and outcome of these cases are limited by the sparse published information, only a few cases have been reported worldwide.[7] The reported incidence of idiopathic myelofibrosis among fertile women is 0.02–0.06/100,000[9] but the expected course is the increasing of the incidence due to the increasing age of pregnancy. Harrison[3] summarized 4 cases of pregnancy associated with idiopathic myelofibrosis. Of those 4, 2 were administered no treatment, 1 was administered only supportive treatment, and the other 1 was administered interferon during the entire pregnancy period. Pregnancies without any medication administered resulted in placental infarction and stillbirth at 30 and 27 weeks of gestation, respectively.[7,9] The other 2 cases resulted in live premature deliveries at 36 and 34 weeks of gestation respectively after elective induction because of placental insufficiency.[7,9]

For nonpregnant patients, the management of myeloproliferative diseases has great variations. Expeitant management, administration of low-dose aspirin, and cytoreductive therapy are the most frequently used approaches. Administration of low-molecular-weight heparin alone or in combination with low-dose aspirin is reserved for targeted cases that will inappropriately evolve with normal treatment. Due to the lack of prospective studies there are no evidence-based recommendations regarding management of these condition, when a pregnancy is present. In 2011, Barbu et al[39] published a series of recommendations and critical concepts for patients with myeloproliferative diseases and specific risk factors. For pregnant women with myelofibrosis the recommended management includes low-dose aspirin and prophylactic low-molecular-weight heparin after delivery and continued for 6 weeks. Interferon-a should be administered if the platelets count remains higher than 1500 × 10^9/L or in case of major bleeding, when aspirin should be interrupted. Cytoreductive therapy is preferably avoided during pregnancy due to its potential teratogenicity.

2. Case report

We present the case of a 34-year-old pregnant woman, gravida 1 para 1 who was diagnosed with Janus kinase 2 (Jak-2) negative PM and had no history of thrombotic events. Personal history did not include miscarriage or stillbirth. At 6 weeks of gestation the patient presented to her hematologist for reevaluation and began follow-up with an obstetrician at the Department of Obstetrics and Gynecology at the University Emergency Hospital in Bucharest, Romania. At that time, the patient was undergoing treatment with anagrelide 1 mg/day, drug that is prohibited during pregnancy due to its possible teratogenic effect. The written informed consent form signed by the patient at admission included the permission to present the case and images if necessary.

The general clinical examination was appropriate. The only symptom present was bleeding while brushing teeth. Complete blood count revealed the following: platelet count of 855 × 10^9/L, hemoglobin 9.2 g, hematocrit 29.2%, and a white blood cell count of 13.45 × 10^9/μL. One week after anagrelide interruption, peripheral blood smear analysis showed the following: hematocrit of 33.8, reticulocytes 6, red blood cells 3.690.000/mm with basophil punctuation and normal erythrocytes indices, white blood cells 13.550/mm, and platelets 1.192.000/mm. Thrombophilia test and coagulogram results were within normal limits. Abdominal ultrasound detected a slightly enlarged spleen, with dimensions within the upper normal limit. After explaining all the risks and possibilities during the course of her pregnancy she chose to continue the pregnancy. Accordingly, treatment with interferon-a was prescribed and the anagrelide treatment was discontinued. After a detailed clinical examination and laboratory tests she received the following recommendations: hepatic-protective diet, low sodium intake, and normal hydration; increased infection protection; test to determine whether there was a mutation of the calreticulin gene; repeated abdominal ultrasound scans (spleen and hepatic parameters) during pregnancy; interferon-a 3 MU/day; vitamin B6 250 mg/day; folic acid 1 mg/day; aspirin 75 mg/day; and vitamin C 1 g/day.

Obstetric ultrasound performed at 8 weeks and 2 days of gestation revealed a singular intrauterine gestational sac with morphology suitable for the gestational age of the embryo. It measured 18 mm and included a normal yolk sac. Cardiac activity was present with a heartbeat of 171 beats/minute. In addition, a left ovarian serous cyst with anechogenic content was present with a heartbeat of 171 beats/minute. Due to the increasing platelet count there was a mutation of the calreticulin gene; repeated abdominal ultrasound scans (spleen and hepatic parameters) during pregnancy; interferon-a 3 MU/day; vitamin B6 250 mg/day; folic acid 1 mg/day; aspirin 75 mg/day; and vitamin C 1 g/day.

Obstetric ultrasound performed at 8 weeks and 2 days of gestation revealed a singular intrauterine gestational sac with morphology suitable for the gestational age of the embryo. It measured 18 mm and included a normal yolk sac. Cardiac activity was present with a heartbeat of 171 beats/minute. In addition, a left ovarian serous cyst with anechogenic content measuring approximately 9 cm was found. Between 6 and 10 weeks of gestation, platelet counts increased from 855 × 10^9/L to 1316 × 10^9/μL and were monitored weekly. The rest of the hematological parameters were maintained within the limits of the initial values. Due to the increasing platelet count, the aspirin dose was changed to 150 mg/day. Screening during the first trimester (until 11 weeks and 5 days of gestation) was normal and revealed no suspicion of structural anomalies and no ultrasound markers of fetal aneuploidies. Fetal echography repeated at 17 weeks of gestation showed a male fetus with a normal development and no pathological characteristics.

During the following weeks of pregnancy, the hemoglobin value continued to decrease. Therefore, intravenous iron supplementation was recommended and initiated. Platelet counts remained high, at approximately 1 million, during almost the entire pregnancy. Ultrasound examination was performed monthly between 23 weeks of gestation and 31 weeks of gestation and revealed normal morphologic development, normal placentaion, and normal amniotic fluid index, with no signs of fetal anomalies or placental insufficiency. At 33 weeks of gestation the patient had a mild episode of metrorrhagia and was hospitalized. Obstetric clinical examination and transvaginal ultrasound indicated shortened uterine
cervix; therefore, acute tocolysis treatment was initiated. Aspirin administration was replaced by low-molecular weight heparin 6000 U/L and antifactor Xa assay 6 mL/day. Thereafter, the course of pregnancy was favorable, without painful uterine contractions or metrorrhagia. However, after 34 weeks of gestation ultrasound showed a slight intrauterine growth restriction of 1 week, which was maintained until 38 weeks of gestation without worsening. Subsequent to the changed therapy, the platelet count decreased and reached values of $600 \times 10^3$ /μL.

At 38 weeks of gestation labor began and a healthy male fetus, with a weight of 2850 g, and an Apgar score of 9 and height of 51 cm was delivered via caesarean section. Postoperative recovery was quick and uneventful. The patient continued treatment with low-molecular-weight heparin 6000 U/L and antifactor Xa assay 6 mL/day for 6 weeks and interferon-a 3 MU/day, as recommended by the hematologist. After the administration of low-molecular-weight heparin was completed, platelet levels increased and eventually exceeded 1 million.

3. Discussion
PM is a clonal hematological diseases. \cite{10} The main characteristics of chronic idiopathic myelofibrosis are chronic myeloproliferative, atypical megakaryocytic hyperplasia, increased bone marrow vascularity, and bone marrow fibrosis. These features result in impaired hematopoiesis, severe anemia, marked splenomegaly, and extramedullary hematopoiesis with constitutional symptoms (in the late stages of the disease). There are several hypotheses regarding the pathogenesis of this condition such as chromosomal abnormalities, abnormal megakaryocyte growth, abnormalities of the JAK/STAT pathway and myeloproliferative leukemia gene mutations, excessive cytokines, and overexpression of thrombopoietin.\cite{11,12} Regarding the pregnancy occurring with the existing PM, there is insufficient information about the management and prognosis of these cases. The reported cases\cite{13} have indicated that these pregnancies result in high fetal mortality rates; however, some pregnancies successfully progressed to term. The risk of thrombosis in these pregnancies is increased and is similar to the risk in patients with thrombophilia or antiphospholipid syndrome.\cite{14} It has been reported that the presence of the JAK2 gene mutation is an independent predictor of pregnancy complications, including thrombotic events or the risk of spontaneous abortion.\cite{15}

The management of our case included the combination of interferon-a and low-dose aspirin during the entire pregnancy period, until the episode of metrorrhagia occurred. This was effective and there were no adverse effects on the fetus. Due to this approach, the pregnancy had a favorable outcome and no major complications. It resulted in the birth of a healthy newborn, with a normal weight by caesarean section. In our country, there is an important increase in the incidence of caesarean section.\cite{16} The fetal safety of interferon-a was studied in 2012 by Yazdani Brojeni et al.,\cite{17} the conclusion included that interferon-a does not significantly increase the risk of major malformation, spontaneous abortion, fetal demise, or preterm delivery compared to the general population rates. It also suggested the fact that interferon-a may be a protective factor for pregnancy loss in cases of essential thrombocythemia.

We feel that we used the correct approach and administered efficient treatment in our case of pregnancy with PM. The hematologist’s decision to discontinue aspirin and change treatment to low-molecular-weight heparin was maintained an adequate protection from thrombotic risk and reduced the risk of hemorrhage. The particular aspect of the evolution of this case is the decrease in platelet counts at the time of replacement of low-dose aspirin with low-molecular-weight heparin was maintained during the prenatal period and postpartum. The patient continued to receive hematologic supervision after the pregnancy. The only curative treatment possible for primary myelofibrosis is allogeneic hematopoietic cell transplantation, which is recommended when the other palliative treatment options, focused on symptoms management become insufficient.

This case was rare: less than 10 such cases have been described. Because of the complexity of this pregnancy, continuous collaboration between the obstetrician and hematologist was required.

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