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Pregnancy and myeloproliferative neoplasms : A retrospective monocentric cohort

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Abstract

Background: The most frequent myeloproliferative neoplasms are essential thrombocythemia and chronic myelogenous leukemia, which usually manifests with thrombocytosis. Only essential thrombocythemia is associated with morbidity during pregnancy (recurrent miscarriages, intrauterine fetal death, small for gestational age and preeclampsia). The aim of this paper is to describe outcomes of pregnancy in women with myeloproliferative neoplasms seen at a single academic institution.

Methods: Data were collected retrospectively from 2002 to 2015. Descriptive analyses were performed.

Results: Eighteen pregnancies in 13 patients and 17 births were identified. One patient had recurrent miscarriages. There were two intrauterine fetal deaths, three small for gestational age linked to vascular placenta pathology and one preeclampsia. All of these mothers harbored JAK2V617F mutation. Two out of three patients with small for gestational age developed a venous thrombosis in the two years following delivery.

Conclusion: Thrombocytosis associated with myeloproliferative neoplasms should be considered as a risk factor for maternal and fetal complications.

Keywords

Haematology, high-risk pregnancy, neoplasm, cancer

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Introduction

While pregnancy is a physiological condition, it may lead to specific complications for the woman and/or the fetus. Some chronic maternal diseases including myeloproliferative neoplasms (MPN) can increase this risk, especially vascular placental pathology (VPP). Essential thrombocythemia (ET), chronic myelogenous leukemia (CML), polycythemia vera (PV) and myelofibrosis (MF) are the most frequent MPNs. Around 10% of patients suffering from CML and 20% from ET are less than 40 years old,[1] whereas in cases of PV or MF, patients are usually over 50 years old.[2]

CML is defined by the presence of myeloid translocation cells (9;22) leading to formation of a fusion gene *BCR-ABL1*.[3] The disease develops ineluctably: the chronic phase (three to five years) combines splenomegaly and abnormalities in white blood count (WBC): hyperleukocytosis and neutrophilia, basophilia, eosinophilia and myelemia associated with thrombocytosis. It is followed by the accelerated phase (one or two years) with cytopenia, and finally the blastic phase, which represents a transformation into acute leukemia with a poor survival rate. The prognosis for these different phases has been revolutionized by tyrosine kinase inhibitors (TKI) (imatinib, dasatinib, nilotinib), but data about their effects in pregnancy including teratogenicity are lacking.[4,5]

ET is defined by chronic thrombocytosis ($>450 \times 10^6$/L). Hyperleukocytosis is rare.[6] Mutation JAK2V617F is positive in 50% of the cases, while 35% have mutations in gene CALRX and 10% in MPLW515L or MPLW515K.[7] The few patients without mutations are called ''triple negative.'' The complications of ET are thrombosis (arterial or venous), bleeding when thrombocytosis is above $1\ 500 \times 10^6$/L because of consumption of Von Willebrand factor, and transformation into acute myeloblastic leukemia or MF (<5% of the patients).[2]

During pregnancy, ET has been associated with increased risk of early miscarriages,[8] intrauterine fetal death (IUFD),[9] small for gestational age (SGA),[8] preeclampsia (PE) or eclampsia[10] and arterial or venous thrombosis. Therefore, giving a MPN diagnosis during pregnancy (or before, if possible) is very important in determining maternal and fetal outcomes. The aim of our study was to describe the pregnancies of patients in our institution suffering from MPN.

Methods

Data

Data were extracted from hematological and obstetrical files from 2002 to the present. Pregnancy was included only if MPN was diagnosed before or during pregnancy. Pre-pregnancy parameters collected were: gestational term at delivery; body mass index (BMI); height; personal, obstetrical and family past history; hypertension; diabetes mellitus; dyslipidemia; arterial or venous thrombosis. For MPN, type of MPN, mutation, date of the first symptom or first biological abnormalities, and diagnosis date were collected. Additional information according to type of MPN was collected: for ET, bone marrow biopsy, International Prognostic Score of thrombosis for Essential Thrombocythemia (IPSET) score,[11] disease status (presence or absence of complete hematological response, with or without treatment) and for CML, disease status (major molecular response or molecular response under or not under treatment). For pregnancy, date of the beginning of pregnancy, gestational diabetes, gestational hypertension, PE, eclampsia, IUFD, SGA, use of aspirin or low molecular weight

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heparin (LMWH), natural or artificial induction of delivery and birth weight were registered. Prematurity was defined as birth before 37 weeks of gestation (WG).[12] SGA was calculated according to Gardosi curves with BIOCIG software and was defined as weight below the 3rd percentile.[13]

Statistical analyses

For descriptive analyses of quantitative variables, mean and variance or median and ranges were used. For qualitative variables, percentages were used.

Results

Patients

Eighteen pregnancies in 13 patients were identified (Table 1). Five patients had two pregnancies (one patient had a second twin pregnancy). Five patients already had offspring before the onset of MPN, without any evidence of the disease. The median age at the beginning of pregnancy was 27.4 years (range 21.1–39.3). Mean BMI was $22.6 \pm 3.2\,kg/m^2$ (between 25 and 30 for pregnancy numbers 4, 14, 15, 16 and 18). Four women were smokers (>10 cigarettes per day) and five pregnancies were exposed to tobacco (pregnancy numbers 1, 2, 7, 8 and 9). Hypertension was diagnosed before pregnancy in three patients (five pregnancies). No woman had had dyslipidemia before pregnancy, and no gestational diabetes occurred. Mean platelet count in undiagnosed patients was $624 \pm 98 \times 10^6$/L with range $466–903 \times 10^6$/L.

Pregnancy outcomes

One patient had nine miscarriages and one IUFD at 25 WG with growth restriction and her platelet counts were always greater than 450×10^6/L, leading to diagnosis of JAK2V617F positive ET. Another patient had one unexplained IUFD at 24 WG with growth restriction and ET with JAK2V617F mutation. All of these fetal losses remained unexplained. No placenta pathology was available for any case. One patient had two miscarriages followed by a normal pregnancy while taking aspirin, and three patients had one miscarriage each. Only one woman was treated with therapeutic doses of LMWH due to past history of thrombosis, and nine women received aspirin during pregnancy (160 mg/day for 8 and 75 mg/day for 1). Pregnancy number 4 was complicated with PE and there were three SGA cases. Post partum, prophylaxis for deep venous thrombosis (DVT) with LMWH was prescribed in only three cases. Aspirin was prescribed in every case of ET when diagnosis was given, whether the patient was pregnant or not. When ET was diagnosed during pregnancy, aspirin was begun as soon as the diagnosis was given.

There were three cases with SGA and one woman experienced PE. Nine women had induction of labor (four for premature rupture of membranes, two for post-term, two for convenience, one for IUFD). Excluding the two cases of IUFD, no extreme prematurity or severe prematurity occurred. Three live births were premature (33.6, 34.0 and 36.1 WG). The mean term of birth was $36.9\ WG \pm 5.0$; 17 live births took place.

MPN

Diagnosed MPNs in our cohort were 10 ET and 3 CML. No case of PV or MF was recorded in our study.

ET

Patient characteristics. ET was diagnosed in 10 patients of whom seven had a bone marrow biopsy (Table 2). At diagnosis, median age was 26 (range 19–35). Mutation JAK2V617 was found in six patients. Three patients had no mutation (JAK2V617F, CAL-RX or MPL).

Table 1. Pregnancy outcome of women with myeloproliferative neoplasm.

N° pregnancy	N° patient	HT	Max platelet count (10^6/L)	PE	LMWH	Asp	<37WG	Delivery	BW (kg)	SGA
1	1	Yes	654	No	No	No	IUFD (25)	Vaginal	0.75	No
2	1	Yes	351	No	No	Yes	No	Vaginal	2.52	Yes
3	2	No	283	No	No	Yes	No	Vaginal	3.20	No
4	2	No	358	Yes	No	Yes	Yes	Vaginal	1.92/1.98	Yes
5	3	No	728	No	No	Yes	No	Vaginal	3.86	No
6	4	No	669	No	No	Yes	No	Vaginal	3.34	No
7	5	Yes	512	No	No	No	Yes	Vaginal	1.70	Yes
8	6	Yes	722	No	No	No	No	Vaginal	2.68	No
9	6	Yes	693	No	No	Yes	No	Vaginal	2.70	No
10	7	No	767	No	No	Yes	No	Vaginal	3.50	No
11	7	No	683	No	No	Yes	No	Vaginal	3.68	No
12	8	No	963	No	No	No	IUFD(24)	Vaginal	Unknown	No
13	8	No	162	No	Yes	Yes	No	Vaginal	3.09	No
14	9	No	405	No	No	Yes	No	Caeseran section	3.68	No
15	10	No	503	No	No	Yes	No	Vaginal	3.34	No
16	11	No	263	No	No	No	Yes	Vaginal	2.00	No
17	12	No	623	No	No	No	No	Vaginal	3.17	No
18	13	No	784	No	No	No	No	Vaginal	3.65	No

HT: hypertension diagnosed before pregnancy; Max: maximum of; PE : pre-Eclampsia; LMWH : low-molecular weight heparin; Asp : aspirin; WG : week of gestation; BW: birth weight in kilogram (kg) (pregnancy 4 was twin pregnancy); SGA : small for gestational age; IUFD (24) means: in utero fetal death happened at 24 WG .

Table 2. Hematological characteristic of MPN.

N° patient	MPN	Mutation	Diagnosis /pregnancy[a]	Thrombosis score (IPSET)	Hematological treatment during pregnancy	CHR or MMR
1	ET	JAK2V617F	Missed during pregnancy n°1 Given before pregnancy n°2	HIGH	Interferon during pregnancy n°2	Yes (n°2)
2	ET	JAK2V617F	During	LOW	Interferon during all pregancies	No
3	ET	Triple neg	During	LOW	None	No
4	ET	Triple neg	During	LOW	None	No
5	ET	Triple neg	Missed	LOW	None	No
6	ET	JAK2V617F	Missed	LOW	None	No
7	ET	JAK2V617F	During	LOW	None	No
8	ET	JAK2V617F	Missed during pregnancy n°12 Before for pregnancy n°13	LOW	Interferon during pregnancy n°13	Yes
9	ET	JAK2V617F	Before	LOW	Interferon	No
10	ET	Non JAK2V617F	During	LOW	None	No
11	CML	BCR-ABL1	Before	NA	Interferon	No
12	CML	BCR-ABL1	During	NA	None	No
13	CML	BCR-ABL1	During	NA	None	Yes

[a]Missed: The diagnosis was missed during pregnancy.
During: MPN was diagnosed during pregnancy; Before: MPN had already been diagnosed; MPN : myeloproliferative neoplasm; ET: essential thrombocytosis; CML: chronic myelogenous leukemia; IPSET: international prognostic score of thrombosis (11);CHR: in case of ET, complete hematological remission; MMR in case of CML: major molecular response. Triple neg : « triple negative » i.e. no mutation found. NonJAK2V617F: means patient was tested only for JAK2V61F and not for CAL-RX and MPL, NA: Not applicable.

One patient had no JAK2V617F mutation but the other mutations had not been tested. Only one patient had a high IPSET score.

Explorations during pregnancy. Five patients had been diagnosed during pregnancy. Mutation JAK2V617F was performed for all patients and was positive twice. If negative, CAL-RX and MPL mutations were performed except in one patient (who never returned to hematological consultation after delivery). The other three patients had no mutations. Bone marrow biopsy was performed later after delivery. The diagnosis was missed in four others with chronic thrombocytosis ($>450 \times 10^6$/L).

Therapy. After diagnosis, all patients received aspirin, and three were treated with interferon (due to IUFD or past history of DVT). Two were in complete remission during the pregnancy.

Pregnancy outcome. For patients diagnosed before or during the pregnancy (10 pregnancies), all had live births with one SGA, one PE with premature birth (34.0 WG) and one premature birth (36.1 WG). For undiagnosed patients, the outcome for the five pregnancies was worse: two IUFD (24 and 25 WG) and two SGA. No placental pathology was available.

After pregnancy. Within the two years following the pregnancy, two out of three patients with IUFD (patients 6 and 8) developed thrombosis: DVT and cerebral venous thrombosis. The associated thrombophilic factors were tobacco exposure, estrogen contraceptive and MPN. There was no other documented thrombophilia.

CML

Patient characteristics. Three patients were diagnosed with CML. They were 28.5, 32.7 and 37.3 years old. Two of them were diagnosed during pregnancy.

Exploration during pregnancy. Mutation *BCR_ABL1* in the blood was positive with bone marrow karyotype with translocation (9;22) for two of these patients.

Therapy. Therapy was delayed for approximately nine weeks after delivery due to concerns about the neonatal effects of treatment and breastfeeding. Another patient whose disease was diagnosed before pregnancy had been treated with interferon in order to interrupt TKI, but did not attain major molecular response.

After pregnancy. Four months after birth, one patient's disease had transformed into acute lymphoblastic leukemia.

Discussion

In our cohort, classical complications of MPN during pregnancy occurred: recurrent miscarriages; PE; IUFD and SGA. SGA had multiple potential causes: MPN, smoking and chronic hypertension. There were only three cases of mild prematurity. VPP was predictive of thrombosis complication after pregnancy in patients previously undiagnosed but with ET.[14] The two patients with IUFD were treated during and after another pregnancy in order to achieve complete hematological response. They had normal pregnancies under treatment.

ET and pregnancy outcome

Previous studies have identified that ET can lead to maternal and fetal morbidity. For mothers, the main problems remain venous thrombosis (DVT or pulmonary embolism), arterial events (stroke, myocardial infarction), miscarriages (20 to 40% of patients)[9] or VPP. VPP is associated with SGA (4 to 10%), prematurity (6 to 15%), PE (3 to 10%) and IUFD (3 to 7%).[7,8,15,16]

Our results contrast with these data. Recurrent miscarriages occurred in only one patient, whereas most MPN diagnoses were

given during pregnancy or missed. Prematurity was not as frequent as described in the literature. PE was diagnosed in one patient (6% of the ET patients) with favorable outcome. IUFD was more frequent in percentage (13% of ET patients) than in the literature, but it was always found prior to the MPN diagnosis. However, the small number of patients in our cohort renders interpretation difficult.

During ET, platelets are activated, leading to a high level of platelet aggregation. As a result, venous or arterial, micro or macrothrombosis can occur in the placenta.[17] Mutation JAK2V617F may be associated with a higher rate of pregnancy complications and a higher risk of second and third trimester miscarriage (9.4% of JAK2 V617F pregnancies had second and third-trimester miscarriage versus none in MPL/CALR/triple negative pregnancies ($p = 0.027$)).[18] Outside of pregnancy, this mutation is known to increase thrombosis rate.[19] The risk of thrombosis is independent of the platelet count.[14] For these types of patients, coordination between the obstetrician, the hematologist and the obstetric medicine specialist is necessary.[7] Postpartum, VPP is predictive for the mother having a vascular event in the years following pregnancy.[19] Hematologists may consequently consider this event as a reason to start treatment in order to achieve complete hematological response. The goal of treatment is to reduce the risk of thrombosis.

CML and pregnancy

The main problem with CML during pregnancy is the unsuitability of tyrosine kinase inhibitors.[20] The disease itself does not appear to increase thrombosis rate or other pregnancy complications when leukocyte count is below 100×10^6/L and platelet count below 500×10^6/ L.[21,22] Otherwise at delivery, hemorrhagic complications can occur.[23] Furthermore, TKIs have shown teratogenicity in animals and humans.[4] In humans there are more spontaneous abortions than in controls and unusual congenital malformations. These include craniosynostosis, hypoplastic lungs, duplex kidney, absent kidney, exomphalos, hemivertebrae and scoliosis.[23] Most of these malformations may be linked with platelet-derived growth factor receptor-alpha pathway, a tyrosine kinase blocked by TKI. This pathway is involved in neurological, vascular and bone development in utero.[24] Therefore, pregnancy must be scheduled during a planned suspension of TKI, or alternative treatments such as interferon must be initiated.[4,25] Only when diagnosis is given near term, when clinical examination is normal, and when the white blood count (WBC) is typical of the chronic phase, can TKI initiation be postponed until after birth or following short-term breastfeeding.[26]

Thrombocytosis and pregnancy

Generally speaking, thrombocytosis cannot be due to pregnancy itself as pregnancy causes a physiological fall in the platelet count. The most common cause of an elevated platelet count in pregnancy is iron deficiency.[23] In every case of iron deficiency or inflammation if the platelet count may be elevated, it must be monitored to ensure that it normalises after correction of these conditions. If there is neither iron deficiency nor inflammation and platelet count is still $>450 \times 10^6$/L on more than one occasion, further investigation should be performed to assess for MPN.

Conclusion

Our cohort showed all the different complications reported in MPN during pregnancy. Four patients were not diagnosed even though thrombocytosis was significant.

Thrombocytosis is rare and the most likely causes are secondary to iron deficiency or inflammation. Even a mildly raised platelet count must not be neglected, since it may constitute the first sign of a serious condition including MPN, which can impact on pregnancy, fetal and/or maternal outcome.

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Ethical approval

All patients were informed of the study, no opposition was noted. (According to French law, retrospective cohort studies do not require writing but oral non opposition is encouraged.)

Institution Review Board: N/A as according to French law, it cannot give opinion on non-interventionnal retrospective study.

Guarantor

PM

Contributorship

All the authors designed the work, MP collected the data and performed statistical analysis. All the authors interpreted the data, wrote the manuscript and approved it.

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