Leukemia Research 81 (2019) 25–26

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Letter to the Editor

Management and outcome of 11 pregnancies in women with polycythemia vera

Polycythemia vera (PV) is a clonal hematopoietic disease typical of advanced age, with only 15% of cases diagnosed before age of 40 years: in addition, PV shows a male preponderance [1]. Therefore, compared to the similar setting of essential thrombocythemia (ET), pregnancy in PV is a very rare event and few data are available about pregnancy in young women with PV [2–4].

The management of pregnant patients with PV could be problematic especially due to risk of maternal hemorrhage, thrombosis and pregnancy loss [1]. The identification of predictive factors of thrombotic complications represent the major challenge for pregnancy in PV patients. In pregnancy and postpartum, several factors converge to increase thrombotic risk, including altered coagulation factors, mechanical obstruction by the enlarged uterus and pregnancy-related endothelial changes [5]. As suggested by Abdul Sultan et al, in a large population-based cohort of pregnancies, patient's characteristics and life style prior to pregnancy (maternal age, race, genetic thrombophilia, obesity - body mass index (BMI) > 30 kg/m2 - smoking), pre-pregnancy comorbidities (cardiovascular disease, diabetes, hypertension), and pregnancy complications (preeclampsia, gestational diabetes, infections) could be evaluated in the assessment of thrombotic profile, because they seem to be associated with a higher venous thrombotic risk in the third trimester of pregnancy and in the first 12 weeks after delivery [6].

In a recent systematic review of literature [4] on pregnancies in myeloproliferative chronic neoplasms (MPN), a total of 783 cases of pregnancy in ET and less than 150 in PV were reported. The live birth rate (LBR) was approximately 68.5% in ET and 63% in PV. Spontaneous abortion during the first trimester was the most frequent fetal complication occurring in about 20% of PV pregnancies. Major maternal complications were similar in ET and PV setting (3–4%).

However, apart from case reports or small series of maximum 5 patients [3,4], there are two largest series published so far [2,7]. In the first one, including 18 pregnancies in 8 women with PV, Robinson et al. [2] reported a positive pregnancy outcome in about 2/3, and maternal complication in about 1/4 of cases (Table 1).

Recently, Bertozzi et al. [7] have reported 24 pregnancies in 15 females with PV. Consistently with the previous series [2], the authors observed a LBR of 62.5%, while maternal complications seemed less frequent (16.7% vs 22.2%) (Table 1). In addition, they found no relation between pregnancy outcome and age or hematological parameters at diagnosis, mutational status, JAK2V617 F allele burden, age at conception and presence of at least one risk factor for abortion.

As in the general population of PV patients, prophylaxis with low dose aspirin (ASA) seems to reduce complications also during pregnancy [8], but nowadays an international agreement for the management of PV during pregnancy is not available [1,4].

In a Mayo Clinic single-center study [9], ASA in the first trimester was identified as possibly associated with a favorable pregnancy outcome in ET. The UK group suggested for pregnant women with MPN the use of ASA (unless contraindicated) and a minimum 6 weeks of low-molecular weight heparin (LMWH) post-partum. Moreover, for patients stratified in high-risk pregnancy category, the addition of LMWH and cytoreduction with interferon-alpha should be considered. Furthermore, women with PV may be offered venesection in addition, if the hematocrit (Ht) is above the appropriate range [4,9].

In the present report, we retrospectively analyzed outcome and complications in a series of 11 pregnancies in 7 females with PV. These patients were diagnosed and managed between 2000 and 2017 in 3 Italian Centers. PV diagnosis was performed or revised according to WHO 2016 criteria. Different therapeutic approaches have been assessed prior and during each pregnancy.

Median age at diagnosis and at conception were 24.3 (range 21.8–31.1) and 30.1 years (range 23.7–33.8), respectively. According to molecular status, all patients presented JAK2V617 F mutation. Four patients (57.1%) had two pregnancies. All patients received phlebotomies as required, with a median Ht level at the time of conception of 45.2% (range 41.4–46.8). Median values of WBC and PLT at conception were 9.9×10^9/l (range 6.7–18.3) and 510×10^9/l (range250 − 917), respectively. Only one patient presented a history of thrombosis (2 episodes of TIA) before the first pregnancy. Three (42.8%) females presented cardiovascular risk factors at the time of conception, while a genetic thrombophilic predisposition was documented in 3 patients (42.8%). Body mass index (BMI) > 30 kg/m2 was present only in one pregnancy (9%). No significant pre-pregnancy comorbilities were reported in our females.

Pregnancy features of our cohort are shown in Table 1. Among the 11 pregnancies, 8 (72.7%) ended with a full-term delivery, while 2 (18.2%) were complicated by a fetal loss in the first trimester and by an intrauterine growth retardation with preterm delivery. It is worth of note that the fetal loss was reported in the patient with prior arterial thrombosis and concomitant signs of myeloproliferation (mild leukocytosis, Ht level > 45% and PLT level > 900×10^9/l), while the intrauterine growth retardation was reported in a patient with Ht level > 45%, despite the typical hemodiluition of pregnancy. The remaining pregnancy was characterized by maternal complications, consisting of an extra-tubal pregnancy with consequent laparoscopic surgical approach and fetal death. The LBR was 81.8%. We didn't find any correlation between life style, BMI > 30 kg/m2 or other cardiovascular risk factors of females and thrombotic complications during pregnancy and in postpartum.

Anti-thrombotic treatment was administered in all but one pregnancy, consisting of low-dose ASA already started since PV diagnosis and continued during pregnancy in 6 females (54.5%), or a combination of ASA and Low Molecular Weight Heparin (LMWH) during the second and last trimester of pregnancy and postpartum in the remaining 4 pregnancies (36.4%). Two patients were also treated with interferon-alfa during their pregnancy. One patient was receiving hydroxyurea at the time of conception, which was immediately stopped.

https://doi.org/10.1016/j.leukres.2019.04.003
Received 22 February 2019
Available online 08 April 2019
0145-2126/

Table 1
Comparative features of pregnancies during PV in the 3 largest cohort of patients.

AUTHOR (year)	Robinson (2005)	Bertozzi (2018)	Present cohort (2019)
Pregnancies, n°	18	24	11
Median age at pregnancy, years (range)	31.5 (23 – 38)	34.1 (24.1 – 39.3)	30.1 (23.7-33.8)
ASA treatment, n° (%)	11 (61.1)	19 (79.1)	10 (90.9)
ASA alone	7 (38.9)	16 (66.6)	6 (54.5)
ASA + LMWH	4 (22.2)	3 (12.5)	4 (36.4)
IFN treatment, n° (%)	3 (16.6)	1 (4.1)	2 (18.2)
Full term delivery, n° (%)	8 (44.4)	10 (41.7)	8 (72.7)
Live birth rate (LBR), %	11 (61.1)	15 (62.5)	9 (81.8)
Fetal loss/stillbirth, n° (%)	7 (38.9)	9 (37.5)	2 (18.2)
Maternal complications, n° (%)	4 (22.2)	4 (16.7)	1 (9.1)

In conclusion, our data indicate that PV females may develop pregnancy complications in about 1/4 of cases (27.3%), but the risk of fetal loss (18.2%) is lower than recently reported in similar series. The vast majority of our patients received ASA +/- LMWH during pregnancy and post-partum and a tight control of Ht was performed before and after the conception. In our opinion this approach could justify the higher LBR in our series (81.8%), suggesting an important role of a combined anti-thrombotic treatment with an efficient Ht control in reducing incidence of fetal complications. Also maternal thromboembolic events seem less frequent in our patients with this therapeutic modality of intervention.

The history of prior thrombosis and the signs of myeloproliferation at conception and at delivery seem to be associated to development of fetal complications. Considering the current guidelines for the management of PV, in particular the more aggressive control of Ht with a target < 45%, it is possible that the extended application of this approach also in PV pregnancies could further improve the rate of fetal complications. Larger collaborative multicenter studies, in order to better clarify the optimal management of pregnancy in PV, are warranted.

References

[1] C. Harrison, Pregnancy and its management in the Philadelphia negative myeloproliferative diseases, Br. J. Haematol. 129 (3) (2005) 293–306.
[2] S. Robinson, S. Bewley, B.J. Hunt, D.H. Radia, C.N. Harrison, The management and outcome of 18 pregnancies in women with polycythemia vera, Haematologica. 90 (11) (2005) 1477–1483.
[3] S. Alimam, S. Bewley, L.C. Chappell, M. Knight, P. Seed, G. Gray, C. Harrison, S. Robinson, Pregnancy outcomes in myeloproliferative neoplasms: UK prospective cohort study, Br. J. Haematol. 175 (1) (2016) 31–36.
[4] M. Griesshammer, P. Sadjadian, K. Wille, Contemporary management of patients with BCR-ABL1-negative myeloproliferative neoplasms during pregnancy, Expert RevHematol. 1 (9) (2018) 697–706.
[5] H.S. Gammil, Postpartum venous thromboembolic risk: one size may not fill all, Blood 124 (18) (2014) 2764–2766.
[6] A.A. Sultan, M.J. Grainge, J. West, K.M. Fleming, C. Nelson-Piercy, L.J. Tata, Impact of risk factors on the timing of first postpartum venous thromboembolism: a population-based cohort from England, Blood 124 (18) (2014) 2872–2880.
[7] I. Bertozzi, E. Rumi, C. Cavalloni, M. Cazzola, F. Fabris, M.L. Randi, Pregnancy outcome and management of 25 pregnancies in women with polycythemiavera, Am. J. Hematol. 93 (9) (2018) E234–E235.
[8] Anonymous, CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-Dose Aspirin Study in pregnancy) Collaborative Group, Lancet 343 (8898) (1994) 619–629.
[9] N. Gangat, A.P. Wolanskyj, S. Schwager, A. Tefferi, Predictors of pregnancy outcome in essential thrombocythemia: a single institution study of 63 pregnancies, Eur. J. Haematol. 82 (5) (2009) 350–353.

E.M. Elli*, E. Diral, C. Gambacorti-Passerini
Hematology Division and Bone Marrow Unit, Ospedale San Gerardo, Monza, Italy
E-mail address: elena.elli@libero.it (E.M. Elli).

R. Calori
Oncology Department, Ospedale Civile, Vimercate, Italy

I. Carmosino, M. Breccia, R. Latagliata
Dipartimento di Biotecnologie Cellulari ed Ematologia, Università Sapienza, Rome, Italy

A. Di Veroli
Hematology Division, Ospedale Belcolle, Viterbo, Italy

* Corresponding author.