Pregnancy oucotcome and management of 25 pregnancies in women with polycythemia vera

TITLE: PREGNANCY OUCOTCOME AND MANAGEMENT OF 25 PREGNANCIES IN WOMEN WITH POLYCYTHEMIA VERA

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Running Title: Pregnancy outcome and management in PV

Keywords: Polycythemia Vera, Pregnancy, JAK2 mutation

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.25210

To the Editor:

Myeloproliferative neoplasms (MPNs), typical diseases of median-advanced age, can rarely occur in young women, posing a challenge for their management during pregnancy[1]. Only 15% of Polycythemia Vera (PV) cases are diagnosed before age of 40, therefore few data are available about pregnancy in young women with PV[2,3]. The largest series published so far, includes 18 pregnancies in 8 women with PV and described a positive pregnancy outcome in about 2/3, and maternal complication in about 1/4 of cases[2]. The remaining literature consists of case reports or small series of maximum 5 patients[3].

Essential Thrombocythemia (ET) is the most common MPN in women of childbearing age. Therefore, the majority of data about pregnancies in MPN concern ET and report a live birth rates of 50-70% and a spontaneous abortion rates of 25-50%, mostly during the first-trimester[4-6]. The risk of late fetal loss is related to the presence of *JAK2*V617F[7]. Considering that virtually all patients with PV carry *JAK2* mutation we surmise a similar picture also in PV.

Our retrospective study includes 25 pregnancies in 15 females with PV who were diagnosed and followed between 1984 and 2018 at the First Medical Clinic of Department of Medicine, University of Padova and the Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia. PV diagnosis was performed or revised in agreement with WHO 2016 criteria. All but one of our 15 patients had available *JAK2* mutational status: 12 (85.7%) carried V617F mutation (median allele burden 39%, range 10.5-68.7) and 2 carried Exon 12 mutation. The study was approved by the local ethics committees. A complete medical history was obtained for each patient. Pregnancy outcome has been classified as full term or preterm delivery, 1st trimester abortion or advanced fetal loss (2nd and 3rd trimester abortions or stillbirths). Intrauterine growth retardation (IUGR) and maternal complications (i.e. thrombosis, hemorrhage, preeclampsia, gestational hypertension or diabetes, abruptio placentae and intrahepatic cholestasis) were also assessed. The Fisher's exact test was used to compare categorical variables. Comparison between continuous variables was performed by the Mann Whitney *U*-test.

The clinical and laboratory data of our patients are summarized in Table 1. Within our 15 PV patients, 7 (28%) had one, 6 had two and 2 had three pregnancies. One pregnancy, ended by voluntary abortion, was excluded from the analysis of pregnancy outcome. Among the 24 evaluated pregnancies, 10 (41.7%) ended with a full term and 5 (20.8%) with preterm delivery, while 9 (37.5%) were complicated by fetal loss (5 in the fist-trimester, 2 in the second and 2 in the third), 4 (16.7%) by maternal complications, and 1 (5%) by IUGR. Three out of our 15 patients developed multiple abortion during follow-up.

On the best of our knowledge, this is the largest series of pregnancies described in PV. Consistently with the paper of Robinson et al[2], we observed a live birth rate of 62.5%, while maternal complications seem less frequent in our cohort (16.7% vs 22.2%). We found no relationship between pregnancy outcome and age or hematological parameters at diagnosis, different mutational status, *JAK2*V617F allele burden, age at

conception and presence of at least one risk factor for abortion. It is worth noting that both patients with Exon 12 mutation experienced one pregnancy without complications.

Miscarriages affect about one third of our PV patients (37.5%), quite similar to our previous observation in ET (30%)[7]. While second and third trimester abortions do not seem to affect women with *CALR*, *MPL* positive and triple negative ET, we observed that PV, as *JAK2* positive ET, displays a high rate of advanced fetal loss (16.7% in PV and 9.3% in *JAK2* positive ET)[7]. This finding support our previous report that identified the presence of *JAK2*V617F mutation as a risk factor for late fetal loss[7].

Key challenges in the management of MPN during pregnancy include risk of maternal hemorrhage, thrombosis and pregnancy loss[5]. The ECLAP study[8] established the use of low-dose aspirin in PV, as well as the CLASP study[9] substantiated the safety of aspirin in pregnancy, but nowadays there isn't an international agreement for the management of MPN during pregnancy[1]. A Mayo Clinic single-center study, identified aspirin therapy in the first trimester as being possibly associated with a favorable pregnancy outcome in ET[10]. Proposed guidance from UK group suggests that pregnant women with MPN are offered aspirin (unless contraindicated) and a minimum 6 weeks of low molecular weight heparin (LMWH) post-partum, moreover, if stratified in high-risk pregnancy category, the addition of LMWH and cytoreductive therapy with interferon-alpha should be considered. Furthermore, women with PV may be offered venesection in addition if the hematocrit is above the gestation appropriate range[1].

Among our cohort, 11 patients (73.3%) received antithrombotic drugs: 9 low-dose aspirin during 16 pregnancies, 2 low-dose aspirin and LMWH during 3 pregnancies. One pregnancy has been administered with interferon-alpha. Iron deficiency due to venesection may represent a critical point, for both the mother and the fetus, but the natural fall of the hematocrit during pregnancy could reduce or obviate the need for phlebotomies. All our patients received phlebotomies as required, but it is worth noting that only one pregnancy has been managed after 2012 in agreement with hematocrit threshold established in CYTO-PV study. Due to the low number of cases, we can't evaluate if there was a statistically significant impact of treatment on pregnancy outcome, but within the 19 pregnancies administered with antithrombotic drugs (single or combined therapy) and the 5 untreated pregnancies, 2 for each group (respectively 10.5% and 40%) ended with late fetal loss. This observation suggests a role of antithrombotic treatment in reducing incidence of advanced miscarriages.

In conclusion, our data confirm that pregnant women with PV have an increased risk of fetal loss. The high rate of advanced miscarriage, related to the presence of *JAK2*V617F mutation, seems to be reduced by anti-thrombotic therapy. The correct use of venesection has to be established in this setting of patients. Due to the rarity of this condition, collaborative studies are required to better clarify the best management of pregnancy in PV.

Authorship Contributions

IB, ER and MLR conceived this study, collected and analyzed data, and wrote the manuscript; CC collected clinical data; MC and FF gave major intellectual contribute.

Disclosure of Conflicts of Interest

No conflict of interest to declare. No funding sources to disclose.

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Table 1. Main demographic, clinical and laboratory findings of study patients.

No. of patients	15
Median age at diagnosis, years (range)	33.2 (9.1 – 39.1)
Median follow-up, years (range)	17 (2.9 – 33)
Median WBC at diagnosis, x 10^9/L (range)	10 (5.9 – 21)
Median Hb at diagnosis, g/L (range)	164 (153 – 200)
Median Ht at diagnosis, % (range)	49.6 (46 – 50)
Median plts count at diagnosis, x 10^9/L (range)	656 (484 – 985)
Median age at conception, years (range)	34.1 (24.1 – 39.3)
Patients with at least 1 abortion risk factor[#], n (%)	6 (40)
Patients with at least 1 miscarriage, n (%)	7 (46.7)

[#]age, smoking, diabetes, hypertension, thyropathy