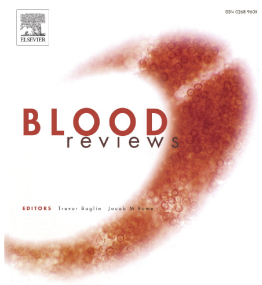

Philadelphia chromosome-negative myeloproliferative neoplasms in younger adults: A critical discussion of unmet medical needs, with a focus on pregnancy

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Philadelphia chromosome-negative Myeloproliferative Neoplasms in younger adults: a critical discussion of unmet medical needs, with a focus on pregnancy.

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Abstract

Myeloproliferative neoplasms (MPN) are traditionally regarded as a disease of older adults, though a not negligible fraction of cases occurs at a younger age, including women of childbearing potential.

MPN in younger patients, indeed, offer several challenges for the clinical hematologist, that goes from difficulties in reaching a timely and accurate diagnosis to a peculiar thrombotic risk, with a relatively high incidence of thromboses in unusual sites (as the splanchnic veins or the cerebral ones). Moreover, the issue of pregnancy is recently gaining more attention as maternal age is rising and molecular screening are widely implemented, leading to a better recognition of these cases, both before and during pregnancy.

In the present work we aim at discussing four clinical topic that we identified as areas of uncertainty or true unmet medical needs in the management of younger patients with MPN, with a particular focus on the topic of pregnancy. For each of these topics, we critically reviewed the available evidence that support treatment decisions, though acknowledging that recommendations in this field are mostly based on expert opinion or derived from guidelines of other clinical conditions that share with MPN a high vascular risk, as antiphospholipid syndrome.

Taking into consideration both the lack of evidence-based data and the clinical heterogeneity of MPN, we support an individualized strategy of counseling and management for both young patients and for expectant mother with MPN.

Introduction

The term Philadelphia chromosome-negative Myeloproliferative Neoplasms (MPN) traditionally encompasses three different disorders named polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) which, despite their different clinical course, share a common pathophysiology, i.e. a deregulated JAK/STAT signaling due to a somatic, driver event in one of three genes: *JAK2*, *MPL* or *CALR*.[1] MPN are typically diagnosed in the sixth or seventh decade of life. However, it has been estimated that at least 15% of PV cases and 20% of ET cases are diagnosed before the fourth decade.[2-4] Moreover, a more widespread access to mutational analysis and use of molecular screening for detection of driver mutations have recently allowed a prompt and timely identification of these disorders, even with milder alterations of blood counts or at a younger age[2, 5-8]. Even though MPN in younger patients is usually associated with an attenuated clinical phenotype and an indolent disease course,[9-21] in a fraction of affected patients the underlying prothrombotic state promotes severe clinical manifestations as splanchnic vein thromboses (SVT) or cerebral vein thromboses (CVT), that could occur even as the first sign of the underlying hematological disease. Based on these observations, thromboses occurring in younger patients and/or in unusual sites should rise the suspicion of an underlying disease with prothrombotic potential, as MPN, supporting the inclusion of molecular screening in the diagnostic algorithm of such events.[22, 23]

These notions are particularly relevant in women of childbearing age, in which a diagnosis of MPN opens the way to a number of therapeutic challenges for the clinical hematologist.

Indeed, the improvement of our diagnostic ability coupled with a progressive delay in mean maternal age[24] actually led to a rise of women with MPN who wish to become pregnant or who receive a diagnosis of MPN during their pregnancy[21, 25]. The vast majority of our current knowledge in this field comes from literature data regarding ET patients, with less information available for PV and PMF.[26-28]

It is important to note that even pregnancies occurring in healthy women have a definite risk of complications such as spontaneous abortion, stillbirth, or premature delivery, that is at least in part due to an increased risk of thrombosis, that is roughly six times higher as compared to healthy non pregnant women.[29]

In healthy pregnancies there is, indeed, an overall rate of spontaneous abortion (defined as those events occurring up to the 20th week) of about 11%, accounting for 80% of all fetal losses, while stillbirth (defined as an intrauterine death occurring after the 20th week or birth of an infant showing no signs of life) occurs in 0.43% of cases.[30, 31] The rate of premature delivery (birth between the 24th and the 37th week of pregnancy or birth weight <2.5 kg) is estimated to be about 9%.[32] Based on these premises, we may anticipate a full-term normal delivery rate of about 80% and a miscarriage rate of about 10%-15%.

As regards maternal complications, venous thromboembolism (VTE) is estimated to occur in 1 to 2 of 1,000 pregnancies, with increased risk according to maternal age, mode of delivery, and comorbid conditions,[33-35] while severe postpartum bleeding rates are steadily increasing over the years (from 8 cases per 10,000 deliveries in the early nineties to 40 per 10,000 deliveries in 2014, in the United States).[36]

An underlying MPN adds a layer of complexity to this clinical scenario due to an intrinsic risk of both thrombotic and hemorrhagic events. Indeed, several complications, including maternal thromboses and major bleedings, intra-uterine growth retardation (IUGR) due to placental disfunction, and spontaneous abortion, have been reported with higher frequencies in pregnant women with MPN as compared to healthy expectant mothers[6, 26, 37, 38]. In detail, the rate of

spontaneous miscarriage in the first trimester is two to three times higher than that of otherwise healthy pregnancies, while major thromboses and major bleeding events occur in 1.8% and 2.4% of cases, respectively.[6] Preeclampsia is the most commonly reported adverse event, with a pooled incidence of 3.1% (95% CI, 1.7%-4.5%),[26] which is somehow comparable to its incidence in the general population (1.4-4%).[39, 40] However, treatment received by pregnant women with MPN should be considered as a possible contributor to the actual, observed rates of complications (see table 1 for selected studies on pregnancy outcome in women with MPN).
Despite the clinical relevance of this topic, there are no randomized studies aimed at answering the most relevant questions about the optimal management of MPN patients during pregnancy, and actual recommendations are largely based on expert consensus and on observations derived from heterogenous, retrospective studies, that often included small cohorts of patients. Here, we critically review the most updated and relevant evidence in order to provide further information to the clinical hematologist who have to deal with this compelling and challenging area of maternal-fetal healthcare.

#1 MPN in young patients: diagnostic challenges and prothrombotic state

Adolescents and young adult patients aged less than 40 years (AYA) with MPN represent a distinct subpopulation, diagnosed with increasing frequency in the last two decades.[41, 42] Though previously underrecognized, being estimated to account for only 2-8% of MPN cases, recent studies showed that 20% of MPN cases, primarily ET and PV, do actually occur in AYA.[11, 12, 43-45]
Though systematic reports on young MPN patients are still limited, these cases seem to be a unique disease subset, with a relative enrichment for ET diagnoses, characterized by an attenuated clinical phenotype, a more indolent disease course and superior survival as compared to their older counterpart.[9-19, 21] As regards driver gene mutations, younger patients are enriched for *JAK2*-mutated cases with low allele burden or *CALR*-mutated ones.[21]
However, notwithstanding their milder clinical picture, MPN amplifies thrombotic risk even in AYA, where unusual site thromboses, including CVT[46, 47] and SVT,[48] may occur in a not negligible fraction of patients.

MPN are among the most frequent causes of SVT in young females with no additional intra-abdominal risk factor; in women of childbearing age, MPN account for nearly 25% of all cases of noncirrhotic portal vein thromboses.[49, 50] In such cases, the underlying MPN may be challenging to diagnose, since blood counts and bone marrow picture may be minimally altered, so that the criteria for one of the three classical MPN subtypes are not met.[51-53] A significant fraction of those cases do not develop a full-blown MPN clinical phenotype, even with a quite long follow up, while in other cases peripheral blood cytosis do gradually occur over time. So, SVT could sometimes be an early clinical manifestation of a developing hematological neoplasm,[54, 55] that could have already altered the splanchnic venous system leading to a local, prothrombotic state. The latter is modulated by factors associated with sex, with a significantly higher incidence in women,[56] and is likely due to the pleiotropic consequences of the *JAK2*V617F mutation on vascular homeostasis.[57]
This hypothesis is supported by the early age at the time of index event, as compared with usual venous thromboembolic events,[48] and by the lower *JAK2*V617F allele burden of such cases.[48, 58]
Indeed, *JAK2*V617F mutation is highly associated with MPN-SVT, being present in the vast majority of cases,[48, 59-63] including those not meeting the criteria for a definite MPN subtype[64, 65] and those who shows an isolated mutation.[55] As a consequence, it is currently included in the diagnostic

algorithm of SVT. Conversely, the other two MPN driver gene events are far more rare[63, 66-69] and, as such, not routinely screened in the absence of a clear, myeloproliferative phenotype.[68, 70]
Women who had experienced an SVT in their childbearing age may wish to get pregnant, and actually there are few case reports of pregnancy in such a complex prothrombotic setting.[49, 50, 71, 72]

CVT are another peculiar feature of the prothrombotic state associated with MPN and with the *JAK2*V617F mutation, though to a lesser extent.[22, 73, 74] Overall, gender plays a major role in such rare cerebrovascular disease, so that pregnancy, puerperium and use of hormonal contraceptives are well recognized common risk factors,[75] together with concomitant thrombophilia.
Moreover, patients with MPN who experienced a CVT showed a higher risk of recurrent thrombosis, that was almost double as compared to those who had other, typical, venous thromboses,[47] despite appropriate management with cytoreduction and anticoagulation.
In this regard, it should be acknowledged that cytoreduction is effective in reducing risk of recurrences of arterial events, though its role is unsettled in those patients with a history of venous thromboembolism.[76, 77] These observations are particularly relevant if we focus on patients of childbearing age, in whom long-term anticoagulation and cytoreductive treatment are challenging for their teratogenic potential, risk of reduced fertility, and other unfavorable pregnancy outcomes.[78-80]
Taken together, our current knowledge supports the notion that MPN in AYA are somehow more indolent and enriched in low-risk cases as compared to their older counterparts; however, clinical presentation may be subtle and, at least in a fraction of patients, the underlying vascular risk may cause severe and unusual thromboses, with consequences on quality of life and fertility issues.

#2 Pathogenesis of poor pregnancy outcome in MPN

Placental insufficiency occurs as a consequence of several processes, leading to a progressive deterioration in placental function, such that oxygen and nutrient supply to the fetus are significantly decreased. Uteroplacental thrombosis, placental infarcts and fibrin deposits are all histopathological signs of poor placental function, together with those morphological changes due to abnormal placentation, with deficient remodelling of the uterine spiral arteries during early phases of pregnancy.[81]
Of note, even if placental infarcts can be a normal finding, occurring in nearly a quarter of healthy pregnancies, increased extension of placental infarcts has been associated with fetal development abnormalities and growth restriction.[81-83] Moreover, IUGR is known to occur in other acquired and inherited causes of thrombophilia,[84-87] which are well-known cause of vascular occlusion with subsequent reduced perfusion of peripheral tissues.
In women with ET, significant placental thrombosis was documented in early reports on pregnancies,[88-90] and confirmed in recent works,[91, 92] and resulted in recurrent miscarriages, late fetal loss, preterm delivery, and IUGR.
Multiple factors are likely to contribute to the pathogenesis of thrombosis in MPN, including different driver gene mutations, degree of full blood count changes (thrombocytosis, leucocytosis, raised haematocrit), activation of circulating cells (platelets and leukocytes), formation of platelet-leukocyte aggregates, circulating pro-thrombotic and endothelial factors, and their interactions.[93, 94] The exact role of each of these features has not been directly addressed in pregnancy, where treatment recommendations are mostly based on expert opinion,[6, 27, 80] data derived from retrospective cohorts and clinical experience with other prothrombotic disorders with obstetric complications, as antiphospholipid syndrome.[95] Several lines of evidence support the role of the

*JAK2*V617F mutation in influencing pregnancy complications[96-98]as it happens for all other vascular complication in MPN,[99] though literature data are sometimes discordant on this issue.[100, 101] Traditional risk factors, as previous thromboses, are clinically significant even in pregnancy; indeed, maternal vascular risk is estimated to be higher in those women who experienced a vascular event (both venous or arterial thrombosis, or bleeding attributed to MPN), independent of whether they occurred in a previous pregnancy or not.[101] However, risk stratification of pregnancies is more complex and include information derived from patients' prior obstetric history as signs of poor utero-placental function, that are considered to raise the risk of subsequent events for both mother and fetus. These events, adapted from the revised classification of antiphospholipid syndrome (APS),[102] are, in detail: ≥ 3 first-trimester or ≥ 1 second or third-trimester losses, birth weight < 5th percentile for gestational age, pre-eclampsia, intrauterine death or stillbirth, or other recognised signs of placental insufficiency as abnormal or non-reassuring fetal surveillance tests, abnormal uterine artery Doppler ultrasound (suggestive of fetal hypoxaemia), oligohydramnios, post-natal birth weight less than the 10th percentile for gestational age.

This choice is based on the notion that prior pregnancy complication is a powerful predictor of recurrence, in particular in the presence of an underlying prothrombotic state, as APS or MPN. So, even though the precise mechanisms of pregnancy complication in MPN have not been clarified, such risk stratification allows a cautious inclusion in the high-risk category of those women who experienced recurrent miscarriages or pregnancy complications prior to the diagnosis of MPN.

In the absence of experimental data, it is tempting to speculate that the prothrombotic state associated with MPN may negatively influence placental function throughout pregnancy; indeed, it may negatively affect uterine spiral arteries remodelling that takes place in the early phase of pregnancy, thus contributing to the increased rate of miscarriages in the first trimester. At the same time, it may contribute to placental hypoperfusion through microcirculatory thrombosis, during the second and third-trimester of gestation, thus contributing to the risk of IUGR, late fetal loss and eclampsia. Indeed, frequent and accurate monitoring during pregnancy is mandatory for women with MPN, so that therapy may be escalated if signs of placental dysfunction *in vivo* should emerge through uterine artery dopplers or through serial growth scans.[27]

#3 role of cytoreduction for severe thrombocytosis in pregnant MPN women

As previously mentioned, pregnancies in patients with MPN, and in particular in those with ET, are associated with a higher risk of both first trimester miscarriages and vascular complications, as compared to pregnancies in healthy women.[96, 97, 100, 103] Thus, a careful and risk-oriented management is needed to make pregnancies safer, including appropriate use of cytoreduction with interferon, which is the only available option.[6, 27, 104] In fact, several reports support teratogenicity of hydroxycarbamide in both humans [105] and animals,[106-109] together with a negative influence on fertility,[110] so that it is recommended to discontinue this drug at least few months before trying to conceive. The same recommendation applies to anagrelide, which may cross the placental barrier and cause fetal thrombocytopenia.[111, 112]

Ruxolitinib, a non-selective JAK1/JAK2 inhibitor widely used for both myelofibrosis[113] and hydroxycarbamide resistant/intolerant PV,[114] is contraindicated in pregnancy and lactation, as well.[115, 116] There are no reports on its use in pregnant women to inform drug-associated risks, but animal studies showed adverse developmental outcomes as reduced birth weight. Moreover, ruxolitinib and/or its metabolites were found in the milk of lactating rats, with a theoretical risk of

inducing secondary hematological toxicity, and recent data suggest that it may influence early central nervous system development, crossing a still immature blood-brain barrier.[117]

Conversely, there are no data supporting teratogenicity of interferon, which is widely accepted as the only available agent to be used in pregnant women, both in its original[6, 27, 104] and pegylated formulation (PEG-IFN).[72] Its efficacy in the setting of pregnancy is supported by consistent literature data[6, 118-120] and is confirmed by a recent meta-analysis that showed a higher live birth rate in women treated with this drug (odds ratio for live birth: 8.05; 95% CI, 2.25-28.80).[26] So, thanks to its improved tolerability and more convenient schedule of administration, PEG-IFN is gaining wider use in those countries where it is commercially available.

However, it should be acknowledged that interferon is not licensed for use in pregnancy and lactation, and that there are no long-term data on growth and development of children with prenatal exposure to the drug. Overall, use of interferon has to be carefully considered, balancing the expected benefits and potential risks to the fetus on a case by case basis.[121]

According to current recommendations,[6, 27, 104, 122] cytoreductive therapy during pregnancy should be offered to those patients with a pre-existing high-risk MPN (i.e. patients with a history of previous vascular event) and to those women regarded to be at higher risk of pregnancy complications due to their previous obstetric history (e.g. those with at least one of the following pregnancy complications: IUGR, intrauterine death or stillbirth, pre-eclampsia, placental abruption and recurrent unexplained loss within the first trimester). Accordingly, a recent review published by Robinson et al. support the use of cytoreductive therapy if the woman has an indication for cytoreduction pre-dating pregnancy or in case of thrombocytosis exceeding 1.500x109/L..[27]

In detail, among the indications to start a cytoreductive therapy, the criteria of platelet count ≥1.500x10^9/L in an otherwise low risk patient is the most controversial, even outside the setting of pregnancy.

In this regard, there is significant heterogeneity in the preferred treatment approach even among MPN-dedicated physicians: in an international survey of 90 physicians, only 74% considered a platelet count ≥1.500x10^9/L as a threshold for starting cytoreduction, while 11% would have waited for an even higher threshold (platelet count ≥2.000x10^9/L) and 15% did not recommend cytoreduction in a low risk setting, regardless of platelet count.[123] In the same survey, there was no consensus even on the optimal target of platelet count, for those receiving cytoreduction.[123]

This issue is not trivial since approximately 22% of ET patients show a platelet count exceeding 1000x10^9/L, a condition commonly referred as extreme thrombocytosis (ExT).[21, 25] Many clinicians opt for cytoreduction in such clinical scenario due to concern of increased vascular risk, even though recent research does not support this association.

Indeed, in a cohort of 99 low-risk ET patients with ExT, a similar rate of thrombotic events was shown in patients receiving cytoreduction as compared to those who did not.[124] These observations have been confirmed by the same group in a recently published report on 183 patients with low-risk ET and ExT.[125] With a median follow-up of more than 15 years, rates of thrombosis and thrombosis-free survival (TFS) were comparable among patients with ExT and those with platelet count less than 1.000x10^9/L (n= 250).. An analysis of the ExT group revealed both a significant lower rate of thrombosis and higher TFS in patients who received aspirin (p = 0.03) but not in those who were on cytoreduction. Taken together, results of this well-annotated cohort do not confirm a clear association between ExT and vascular risk, and also raise doubts on the protective role of cytoreduction in patients with ExT and otherwise low-risk ET.[125]

The same controversy applies to pregnant women with ExT and otherwise low-risk ET, in particular since platelet counts do generally decrease during pregnancy in all women, with or without MPN, beginning in the first trimester;[126] thus it may be anticipated that a fraction of MPN patients would no longer meet the criteria of ExT after the first weeks or months of pregnancy, depending on

their baseline. Moreover, though better tolerated than before thanks to the pegylated formulation, interferon has a number of undesired consequences, including a possible negative influence on fertility.[121]

To the best of our knowledge, in most of the available studies that support the use of cytoreduction during pregnancy, only a minority of women were reported to have ExT as the sole indication to start cytoreductive therapy,[119, 120, 127] and their specific outcome was not assessed as a subgroup analysis.

In a recent retrospective, multicenter study,[91] a total of 27 pregnancies in 14 women with MPN (9 ET and 5 PV) were reported; most of the cases were classified as high risk (18/27, 67%). Overall, cytoreductive therapy was used in 6/14 patients and 11/27 pregnancies. A sustained platelet counts higher than $1000x10^9$/L was reported in only two pregnancies: one developed preeclampsia and the other one was complicated by disseminated intra-vascular coagulation and abruptio placenta leading to stillbirth. However, none of them received cytoreduction.

In a case series report, Beauverd et al.[72] described a total of 10 high-risk pregnancies in 8 women with ET, all treated with PEG-IFN. A sustained platelet count above $1500x10^9$/L was reported in 4 women and 6 pregnancies as the sole indication to cytoreduction. Treatment with PEG-IFN was reported to be effective in reducing platelet count and, notably, no major maternal vascular complications occurred, including thromboses or bleeding, throughout pregnancy and puerperium. Six out of 8 women had prior pregnancies (n=9) that were managed without PEG-IFN; with the limitations of such a comparison, a significantly higher rate of live births and fewer miscarriages were observed with PEG-IFN as compared to those previous pregnancies.

Schrickel et al.[118] reported outcomes of 34 high-risk pregnancies in 23 women with ET. In 8/23 patients, cytoreduction was used because of a sustained platelet count above $1500x10^9$/L. Of them, six out of eight (75%) resulted in live births and no maternal complications, while the others two (25%) pregnancies ended in miscarriages.

Based on these observations, while safety of cytoreduction with interferon has been consistently confirmed, no meaningful comparison among subgroups and no firm conclusion can be drawn on its efficacy in those women with ExT. So, their management requires special consideration and individualized counseling, since recommendations rely mainly on assumptions from non-pregnant patients that are not clearly evidence-based.

#4 role of primary prophylaxis with aspirin in otherwise low risk pregnancies, in *CALR*-mutated women

Risk of vascular event in MPN has been consistently associated with patients' genotype, with higher figures reported for the *JAK2*-mutated population, in both ET[128, 129] and PMF.[130, 131] However, influence of the different driver mutations has not been fully clarified in the setting of pregnancy, where data are, indeed, not consistent. Before 2013, when *CALR* mutations have been identified,[132, 133] retrospective cohorts of pregnant MPN patients assessed and compared outcomes of *JAK2*-mutated and wild type patients as a whole. Passamonti et al. [96] reported on a mostly low risk cohort and found a significant association between the *JAK2* mutation and poor pregnancy outcome, with aspirin being an effective therapeutic intervention in reducing rates of pregnancy complications in *JAK2*-mutated women. Of note, rates of complications (including fetal and maternal events) among 32 women who were wild type for the *JAK2* mutation were significantly lower without aspirin (23%, vs 52% with aspirin).[96] The work of Melillo et al.,[97] that reported on a large Italian cohort, supported the same association, except for the protective role of aspirin, that was not confirmed. On the other hand, Randi et al.[101] did not observe any meaningful link between the *JAK2*V617F mutation and pregnancy outcome. The same conclusion

was drawn by Gangat et al.,[100] though molecular information were available only for a small proportion of patients (20 out of 63). After 2013, a single study,[98] that included full information regarding patients' genotype, reported an association between the *JAK2*V617F mutation and late pregnancy loss, thus suggesting that *CALR* mutations may be associated with less eventful pregnancies. In detail, this study described thirty pregnancies in nineteen *CALR*-mutated women; there were nineteen full-term and four preterm delivery, seven abortion during the 1st trimester, with no cases of 2nd and 3rd trimester loss. There was a numerically lower rate of maternal complication, including a single case of IUGR. However, pregnancy risk was not reported, so an imbalance in the distribution of high-risk cases among the groups may not be excluded. Moreover, this study confirmed comparable rates of first trimester losses among different genotypes, pointing to a careful and timely approach to a pregnant patient.

Three additional studies included a small number of pregnancies in *CALR*-mutated women,[91, 118, 134] from which few conclusions may be drawn: among high-risk patients, treatment with interferon seems to be equally effective, regardless of genotype;[118] spontaneous abortion is an issue even in *CALR*-mutated women (Lapoirie et al.[91] reported on a woman with a history of two first trimester loss and a normal pregnancy, who experienced a further gestation with aspirin prophylaxis that, however, ended in an early loss); Ext at delivery is a concern, due to the risk of peripartum bleeding (How et al.[134] reported on two patients with Ext at delivery, that had bleeding complications, though information on genotype or acquired von Willebrand Syndrome (AvWS) were not reported).

At present, treatment algorithms for pregnancies should not be changed according to genotype, so that aspirin is recommended in every MPN pregnant patient with no clear contraindication.[135] However, it should be recognized that this recommendation is mostly based on an expert consensus, given the lack of adequately powered observational studies. Aspirin use has been associated with a higher risk of bleeding in ET non-pregnant patients, with no clear benefit in terms of reduced vascular risk.[136, 137] So, observation can be considered a reasonable option for asymptomatic patients with classical low risk *CALR*-mutated ET outside the setting of pregnancy, especially if they do not have concomitant cardiovascular risk factors, since their risk of thrombosis is expected to be very low.[135] (
Based on these premises, optimal management of an otherwise low risk *CALR*-mutated woman who wishes to become pregnant is still to be settled.

#5 should pregnant patients be screened for AvWS?

A clinical concern regarding aspirin use in MPN is the possible co-existence of AvWS, a rare, acquired bleeding condition that can be associated with several diseases, including lymphoproliferative disorders and MPN.[138] In the latter, AvWS is thought to be due to an accelerated turnover of von Willebrand factor (vWF) high-molecular weight multimers, caused by an increased adsorption on the surface of platelets, and by an increased and atypical proteolysis.[139] Even though current guidelines recommend to test for VWF activity in MPN patients with ExT,[122] it should be acknowledged that there is no clear evidence that vWF parameters are associated with a definite platelet count.[140-145] Moreover, from a clinical perspective, bleeding risk in MPN is actually modulated by several factors, with aspirin use and previous haemorrhagic events acting as significant predictors of recurrence.[144, 146] Indeed, literature data on the association between Ext and risk of bleeding are not consistent,[124, 147, 148] so that optimal

management of these cases remains unsettled, both in terms of antiplatelets agents and need for cytoreduction.

Among patients of child-bearing potential, testing for AvWS may be particularly useful, regardless of platelet count or genotype. There is evidence, indeed, that AvWS is more frequent than previously thought (affecting nearly half of the patients, according to some reports),[149] seems to be associated with the *JAK2*V617F mutation but may be an issue even in *CALR*-mutated patients, since they display higher platelet counts as compared to patients with other genotypes.[149]
As regards pregnancy, in a report of 24 pregnancies in 18 ET patients, AvWS was evident at initial testing in most cases (83%), even if platelet count was less than $1.000x10^9$/L (median value $701x10^9$/L).[150] Notably, aspirin was held in those cases that met the criteria for severe AvWS (vWF activity below 30%) and repeated testing during the third trimester showed resolution of the vWF abnormalities in all women, thus supporting the strategy of sequential monitoring to better guide treatment decisions.
So, AvWS might be an issue during the first trimester, in low risk patients that are candidates to low-dose aspirin: in such cases, AvWS may go undetected, in particular if platelet count does not meet the criteria for Ext.
At present, there is no consensus on testing for AvWS during pregnancy. Though the available evidence is limited to a single, monocentric cohort,[150] a management approach based on sequential monitoring is intriguing and may deserve prospective validation and testing. Based on the physiological changes associated with pregnancy, it is expected that those few cases with severe reduction of vWF activity should spontaneously resolve by the end of the first trimester. However, we acknowledge that temporary holding aspirin is a challenging decision in such a delicate clinical context, since risk of early miscarriage is highly significant (three-fold higher than that of healthy pregnancies, as previously mentioned).

#6 which is the best prophylactic strategy during puerperium in patients with MPN?

While platelets count gradually decreases during pregnancy, clinicians dealing with pregnant women with MPN need to be aware that platelet count may rapidly rise after delivery, with eventual severe thrombocytosis.[151] This rebound may increase the risk of vascular complications during puerperium, which is *per se* a period of significant thrombotic risk, both in clinical conditions associated with enhanced vascular risk, as inherited or acquired thrombophilia, and in healthy women. Indeed, risk of a venous thromboembolic event is nearly two-fold higher in the first and second trimester, nine-fold higher in the third trimester, and eighty-fold higher in the first 2 to 6 postpartum weeks, as compared to nonpregnant women.[152]
From a therapeutic standpoint, a pharmacological prophylaxis is supported by literature estimates of risk. In detail, according to a recent meta-analysis, that included 756 ET pregnancies, antepartum VTE risk is estimated at 2.5%, which is below the threshold of 3% for a clear benefit of low-molecular weight heparin (LMWH) prophylaxis in otherwise low-risk patients. On the other hand, VTE risk in the first weeks postpartum is as high as 4.4%, thus justifying antithrombotic prophylaxis.[38]
Of note, postpartum thrombotic events include a not negligible percentage of unusual site thromboses.[91, 153]
MPN patients have a peculiar vascular risk, that include both thrombotic and haemorrhagic events, that may be augmented by pharmacological intervention. Indeed, there are reports of women with MPN that experienced bleeding complications peripartum, while having severe thrombocytosis.[134]

Guidelines recommends the use of both aspirin and prophylactic dose of LMWH (the latter for the first six weeks after delivery),[154] though in clinical practice aspirin is often held in such setting. Combined therapy with aspirin and LMWH is the recommended treatment approach for pregnant patients with obstetric antiphospholipid syndrome (prophylactic doses of heparin) and for those with thrombotic antiphospholipid syndrome (therapeutic doses of heparin, throughout pregnancy and puerperium):[95, 155] in both conditions there is a definite and clinically significant prothrombotic state, that can justify the increased risk of bleeding of a combined antiplatelets and anticoagulant strategy.
However, this notion cannot be directly translated into the MPN scenario, in which vascular risk is complex and includes both thromboses and major bleeding, especially in the first weeks post-partum.

Conclusion and future directions

MPN are increasingly recognized and diagnosed in AYA, and several clinical challenges are, thus, emerging. Fertility and pregnancy are important issues in this age group, as well as quality of life and possible concerns about long-term use of cytoreduction.
At present, guidelines do not include separate treatment recommendations for younger patients, and their management is, indeed, quite heterogenous in routine clinical practice.
In fact, even though some authors recommended to reserve cytoreduction only to those younger patients who experienced a major vascular event,[12] extreme thrombocytosis remains a frequent reason to start treatment in a *real-life* setting.[11]
In the present work we critically reviewed four unsettled topics or unmet needs in the management of MPN in AYA, focusing on pregnancy and its therapeutic management.
Some of them, as the role of interferon for low-risk women with extreme thrombocytosis and of aspirin in *CALR*-mutated patients, need to be tested in adequately powered studies: indeed, available evidence is not sufficient to inform clinical practice and support individualized decisions.
The issue of AvWS in MPN is not limited to expectant women, is probably underestimated and reflects the double-edged face of these disorders, that are prone to thromboses as well as to bleeding events. Since testing for AvWS is not routinely performed, this topic is unlikely to be settled through retrospective analysis. Pending further prospective evidence, we believe that testing should be encouraged: it will not change, at present, our treatment strategy, but such information may improve patient's counselling and education.
Moreover, as regards the last topic, we recommend caution in combining aspirin and LMWH during puerperium, keeping in mind that such strategy is used for severely prothrombotic conditions with no clear bleeding tendency, as obstetric or thrombotic antiphospholipid syndrome.

Practice points

- MPN in AYA frequently occur with an attenuated clinical phenotype and indolent course, though having a definite vascular risk that can translate in unusual site thromboses and pregnancy complications.
- Long-term cytoreduction and anticoagulation may be an issue in younger patients.
- Poor pregnancy outcome in MPN is likely multifactorial, with placental thrombosis and poor placental function having a significant role. In this regard, efficacy of cytoreduction for ExT cannot be adequately assessed from literature data, even outside the setting of pregnancy.

- Treatment algorithm for pregnant women with MPN should not be changed according to genotype: aspirin is recommended in every patient with no clear contraindication.
- AvWS in MPN is not limited to expectant women and its occurrence is likely underestimated. From a clinical point of view, AvWS can be an issue in the first weeks of pregnancy and during puerperium, when a marked rebound of platelet count may occur.

Research agenda

- Larger, collaborative studies are needed to appropriately inform clinical practice in AYA with MPN.
- Influence of patients' genotype on the risk of poor pregnancy outcome and maternal complications needs to be addressed in adequately powered, multicentre, observational studies.
- Prospective studies, including longitudinal testing of VWF parameters, should be encouraged even outside the setting of pregnancy.

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Table 1. selected studies on pregnancy in women with MPN: cohorts of at least 10 patients, with full information on fetal and maternal outcomes.

Reference	Year	Number of pregnancies	Outcomes
Data merged from: Griesshammer et al.[156] Beressi et al.[157] Pagliaro et al.[158]	1995-1996	121 (all in ET)	- 55% live births, 35% spontaneous abortion; - intrauterine death, premature delivery and IUGR 4-7%.
Bangerter et al.[90]	2000	17 (all in ET)	- 65% live births, 6 (35%) spontaneous abortions; - maternal complications in 6 pregnancies (35%), including 3 major bleedings in 2 patients with AvWS.
Cincotta et al.[159]	2000	30 (all in ET)	-57% live births, 5 spontaneous abortions (17%), 7 stillbirths (23%), and one ectopic pregnancy (3%); - 5 pregnancies were complicated by placental abruption.
Candoni et al.[160]	2002	17 (all in ET)	- 41% live births, 59% spontaneous abortions (8 out of 10 occurred in the 1st trimester); - no significant maternal complications were reported except for three, mild vaginal bleedings.
Niittyvuopio et al.[161]	2004	40 (all in ET)	- 62% live births, 38% spontaneous abortions in the 1st trimester, 2 late abortions (weeks 22 and 28); - 3 cases of pre-eclampsia.
Passamonti et al.[96]	2007	163 (all in ET)	- 64% live births, 31 abortions: 27 (87%) in the 1st trimester and 4 (13%) in the 2nd; - 9% maternal complications, mostly preeclampsia and hypertension. A single case of deep venous thrombosis during puerperium; - 40% fetal complications including abortion, stillbirth and IUGR.
Gangat et al.[100]	2009	63 (all in ET)	- 60% live births, 20 (35%) 1st trimester spontaneous abortions; - [56 first pregnancies] 61% live births, 12 out of 14 pregnancy losses during the 1st trimester; - [17 second pregnancies] 71% live births; - maternal complications (11%): pre-eclampsia (n = 1), hematoma after Cesarean-section (n = 2) and post-partum hemorrhage (n = 1).
Melillo et al.[97]	2009	112 (all in ET)	- 75.4% live births (2 cases of IUGR, 12 pre-term delivery), 21.3% spontaneous abortions, 3.3% stillbirths; - 8.2% maternal complications (5 deep vein thrombosis, 3 pre-eclampsia, 1 post-partum vaginal bleeding and 1 abruptio placentae.
Giona et al.[13]	2012	15 (all in ET)	- 60% live births, 13% spontaneous abortions.
Randi et al.[101]	2013	237 (all in ET)	- 71% live births, 29% fetal loss: 1st trimester abortion 60 (87%), 2nd/3rd trimester abortion 8 (11.5%), stillbirth 1 (1.5%); - 16 (7%) maternal complications 16: 9 cases of pre-eclampsia and 7 cases of hypertension.
Rumi et al.[98]	2015	155 (all in ET)	- 69.7% live births, 30% fetal loss (37 in the 1st trimester, 6 in the 2nd and 3 in the 3rd), 8.6% IUGR; - 18 (11.8%) maternal complications.
Alimam et al.[5]*	2016	58 (47 in ET, 5 in PV, 5 in MF, 1 MPN-U)	- 96.6% live births, miscarriage incidence 1.7/100, perinatal mortality rate 17/1000; - 22% (12/54) of neonates were below the 10th percentile for growth; - maternal complications; 9% pre-eclampsia, 9% post-partum bleeding and 3.5% post-partum haematoma; - no maternal thrombosis.
Beauverd et al.[72]	2016	10 (all in ET, on	- 90% live births, 10% miscarriage rate;

		PEG-IFN)	- no maternal events including puerperium.
Lapoirie et al. [91]	2018	27 (19 ET, 8 PV) 67% high-risk	- 70% live births, early spontaneous abortions (22%), IUGR (15%), and premature delivery (15%); - maternal thrombosis 15%: one disseminated intravascular coagulation and one portal vein thrombosis during the pregnancy, one portal vein thrombosis during the early post-partum period, and one myocardial infarction) and major bleeding that required blood transfusion (11%: one digestive and two post-partum hemorrhages).
Birgegård et al.[112]	2018	54 (all in ET)	- 75.9% live births, with no IUGR; - 3/40 patients had 6 spontaneous abortions (all but one during the first trimester).
Schrickel et al.[127]	2020	34 (all in ET, high-risk)	- 73.5% live births, 26.5% spontaneous abortions; - 1 major bleeding and no maternal thromboses.
How et al.[134]	2020	121 (all in ET)	- 69% live births, 26% spontaneous abortions, 2 ectopic pregnancies and 1 stillbirth; - pre-term delivery and IUGR occurred in 7.4% and 2.5%; - 2.5% maternal thrombosis, 5.8 % major bleeding (including 5 bleeding post Caesarian section, 1 3rd trimester bleeding due to placenta previa, and 1 vaginal bleeding after a therapeutic abortion.
Edahiro et al.[119]	2020	10 (all in ET)	- 100% live births; - no maternal thrombosis or bleeding.

*prospective study.

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