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Topics of Interest in Women With Myeloproliferative Neoplasms

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ABSTRACT

Overview: Sex and gender have emerged as central modifiers of disease biology, phenotype, and clinical outcomes in myeloproliferative neoplasms (MPNs). This review will uniquely highlight issues affecting women with MPN and articulate their relevant determinants.

Epidemiology and Diagnosis: A higher overall prevalence of MPN has been established in women. The incidence of essential thrombocythemia (ET) predominates, while, conversely, polycythemia vera (PV) and myelofibrosis (MF) are seen in lower frequencies as compared to men. Diagnostic criteria are dictated by sex-driven physiological variances in hemoglobin and hematocrit levels in PV, mandating separate diagnostic thresholds, respectively: > 16.0 g/dL and > 48% in women vs. > 16.5 and > 49% in men.

Genetic Framework and Phenotype: Women with MPN harbor fewer acquired somatic mutations and a lower frequency of high-risk mutations than their male counterparts; lower *JAK2V617F* driver variant allele frequency and attenuated allele burden kinetics have also been reported. Women with MPN are younger at diagnosis than men and, contingent on subtype, display more indolent disease features. Importantly, validated symptom burden assessments consistently disclose higher scores in women vs. men.

Thrombosis and Outcomes: Women with MPN have a unique thrombotic diathesis with respect to men, more frequently involving the splanchnic venous system in those ultimately diagnosed with PV. Outcomes data depict female sex as a variable associated with more favorable clinical trajectories, including lower rates of MF/leukemic transformation and secondary cancers, as well as improved overall survival rates vis-à-vis men.

Life-Cycle Windows, Pregnancy, and Postpartum: Potential challenges at each significant life stage will be addressed: puberty, preconception and fertility, and perimenopause; these include issues surrounding oral contraceptives and hormone use. Prospective studies suggest overall favorable maternal and fetal outcomes with pregnancy in women with MPN. Full details on risks and reported outcomes will be discussed, as well as a risk-adapted approach to management informed by obstetric and thrombosis history. Recommendations include aspirin 81 mg daily in all patients and cytoreduction with interferon-α in those with antecedent thrombosis, as well as in low-risk cases with higher-risk features (e.g., poorly controlled hematocrit and recurrent fetal loss). Antepartum anticoagulation with low molecular weight heparin (LMWH) is recommended in cases with previous venous thromboembolism.

Conclusions and Future Directions: This review highlights female sex and gender as critical drivers of MPN incidence, presentation, and natural history. It further outlines the impact and management of MPN as related to unique female reproductive phases. A sex-informed lens will be required in order to recalibrate current prognostic tools, a requisite to refining patient

counselling and clinical decision-making in line with precision medicine. Moreover, while several mechanisms underpinning sex-defined discrepancies have been defined, these mandate further prospective study. Finally, sex and gender-based differences must be weighted in clinical trials with systematized procedures to correct participation imbalances in favor of sex and gender equity.

1 | Introduction

Sex has been identified as a key regulator of susceptibility to cancer, response to therapy, disease outcomes, and associated mortality [1]. The mechanisms underpinning sex-biased disparities include distinct genetic profiles [2], hormone patterns [3], immune responses [4], and drug metabolism [5]. More recently, sex-dependent differences were delineated in hematopoietic stem cell aging processes, accounting for skewed myeloid differentiation and rates of leukemia development between women and men [6]. In the cadre of myeloproliferative neoplasms (MPNs), the role of sex in mediating phenotype and outcomes is incompletely understood. Correspondingly, issues specific to women with MPN have historically been underappreciated. This review will address topics uniquely corresponding to women with MPN, beginning with an overview of epidemiological, phenotypic, and outcomes-based specificities, then capturing a life-cycle perspective relating to puberty, preconception and fertility, pregnancy and postpartum, and the perimenopause period (Figure 1). More widely encompassing themes of thrombosis, secondary neoplasms, and sexual health in women with MPN will also be considered.

2 | Clinical Distinctions in Women With MPN

2.1 | Epidemiology

Distribution of MPN is unbalanced between sexes. A seminal study from the Swedish Cancer and Blood Cancer Registers found a higher overall prevalence of MPN in women, with incidences of essential thrombocythemia (ET) higher in women compared to men, and conversely, PV and myelofibrosis (MF) predominating in men [7]. These findings have been corroborated by a number of additional studies [8–10].

2.2 | Diagnostic Approach

Androgens drive hemoglobin (Hb) levels such that, as of puberty, Hb measures are on average 12% lower in females [11, 12]. While erythropoietin levels are comparable across sexes [13], additional contributory mechanisms putatively include sex-disparate rheological effects, blood flow velocity, and viscosity changes, as well as hormone-based modulation of vasodilation [14, 15]. These sex-based physiological variances in Hb and hematocrit (Hct) values mandate disparate de facto diagnostic criteria thresholds for polycythemia vera (PV) in women; Hb > 16.0 g/dL or Hct > 48% (vs. > 16.5 or > 49% in men) [16, 17]. A noteworthy caveat is disease diagnosis in the context of splanchnic vein thrombosis (SVT), enriched in women with MPN [18]. Associated portal hypertension and plasma volume expansion may lead to underestimation of Hct levels, obscuring classical features of MPN (~15% of Budd–Chiari/portal vein thrombosis cases) [19, 20]. In such instances, standard hematologic parameters may not be reliable. While red cell mass (RCM) evaluation would prove useful in accurately classifying underlying MPN in cases of *JAK2V617F*-mutated SVT verging on Hb/Hct criteria, this is now discontinued in most centers; however, importantly, bone marrow morphology has been reported as a surrogate of increased RCM, reliably identifying cases of both overt and early or masked PV [21]. In cases not meeting the criteria for PV or ET, diagnosis of MPN-unclassifiable (MPN-U) should be considered. Some such cases may also represent clonal hematopoiesis of indeterminate potential (CHIP), although *JAK2V617F* mutations have not been shown to be enriched in females in this condition [22].

As regards MF, an international panel from the expert International Working Group – European LeukemiaNet recently endorsed sex-adjusted Hb thresholds defining anemia, revising cutoffs for clinical trial inclusion and response adjudication from < 10 g/dL in all to < 11 and < 10 g/dL in men and women, respectively [23]. This accounts for the previously overlooked differences in Hb levels across sexes and their relative contributionto prognostic determination.

2.3 | Genetic Framework

While *JAK2, CALR*, and *MPL* drivers are reciprocally distributed among sexes in MPN, a higher proportion of triple-negative cases has been identified in women [9]. Moreover, women have lower *JAK2V617F* variant allele frequency (VAF) in CD34+ cells, fewer homozygous *JAK2* mutant colonies [24], fewer acquired somatic mutations, and lower frequency of high-risk mutations compared to men [9, 25, 26]; hypothesized to reflect a lower frequency of mitotic recombination events in the former. Interestingly, a selective *JAK2* expression in platelets has been observed in women with ET [27]. *JAK2V617F* VAF kinetics have also been shown to differ between sexes, with slower allele burden increases in women vs. men with MPN [25]. This may potentially be considered when evaluating responses to drugs such as interferon and JAK inhibitors. Gene expression profiling assays in 19 patients with PV revealed fewer differentially expressed genes in women with respect to men; however, the former exhibited more than a threefold increase in activated molecular pathways [28]. These distinct metabolic mechanisms may account, in part, for the sex influence on pathogenesis and phenotype in PV.

The frequency of cytogenetic abnormalities appears uniform between sexes based on a series of 815 patients with PV, ET, and primary MF [9]. A study restricted to secondary MF cases from the MYSEC project disclosed commensurate driver mutation frequencies and cytogenetic profiles in women and men [29]. Of note, the rate of complex (not monosomal)

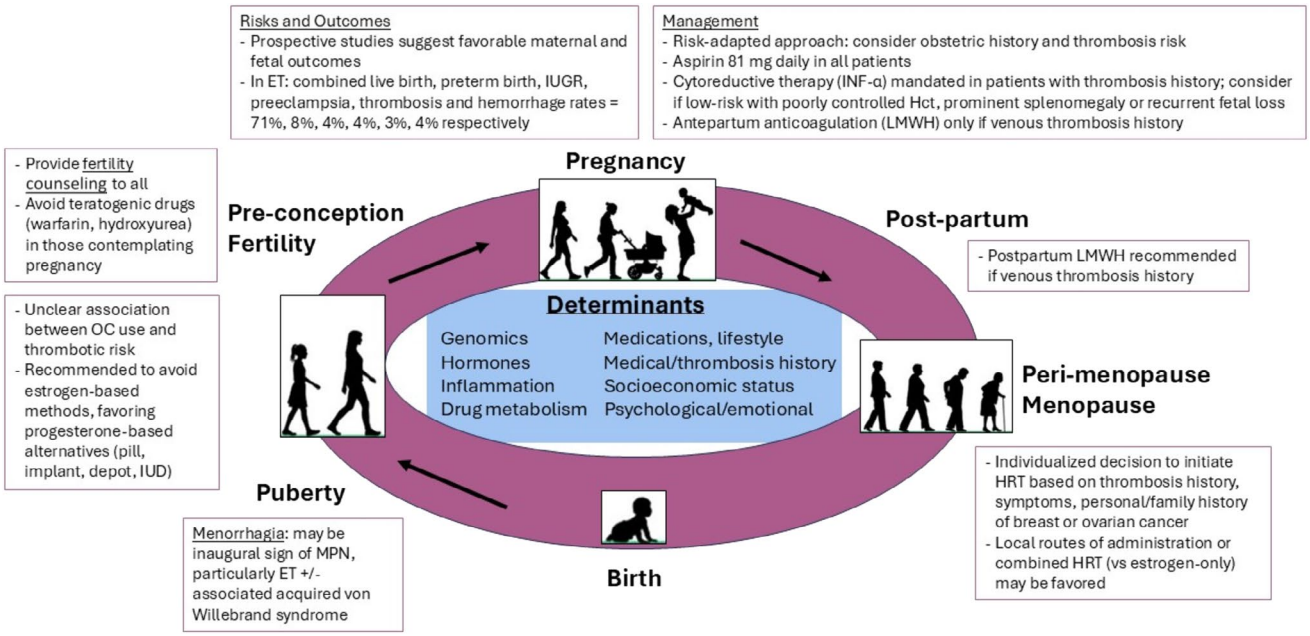

FIGURE 1 | Schematic representation of life-cycle phases, specific risks, and influencing factors in women with MPN. Hct, hematocrit; HRT, hormone replacement therapy; INF-α, interferon-alpha; IPSET-thrombosis, International Prognostic Score for thrombosis in ET; IUD, intrauterine device; IUGR, intrauterine growth retardation; LMWH, low molecular weight heparin; OC, oral contraceptive.

karyotype was lower in females vs. males ($p = 0.03$) in this population.

2.4 | Phenotype and Symptom Burden

Women are younger at MPN diagnosis than their male counterparts [9, 10]. Their disease presentation is also distinct. In PV, the ECLAP trial counting 1638 patients found the phenotype to be more indolent in women compared to men, documenting lower Hcts, higher platelet counts, and less frequent splenomegaly in the former [30]. Women also had lower rates of myocardial infarction and peripheral arterial disease at baseline. In ET, splenomegaly is also less frequently recorded in women [26]. The phenotype is similarly attenuated in women with secondary MF; Barraco et al. demonstrated higher platelet counts, less frequent palpable splenomegaly, and lower % circulating blasts in female subsets [29].

Sex is a strong modulator of symptom burden in MPN [10, 31]. A prospective analysis of the validated symptom assessment tool, the MPN symptom assessment form (MPN-SAF; MPN-10 TSS), in 2006 MPN patients revealed that despite a lack of statistical differences in disease-specific risk scores, therapies, or antecedent complications, females registered higher total scores and more frequent and severe individual sub-item scores [10]. These findings have been reiterated in more contemporary series [32, 33]. The signature symptom spectrum in women is dominated by abdominal pain and microvascular manifestations (headache, dizziness, etc). Interestingly, when quality of life was appraised, no sex-driven differences were found. This may be related to disparities in the perception of symptoms and the disposition to express them, social behavioral and hormonal factors, as well as potential limitations in the sensitivity of testing tools [31].

2.5 | Thrombotic Risk

Women with MPN have a unique thrombotic diathesis with respect to men. A retrospective analysis of 270 *JAK2*-mutated MPN patients by Stein and colleagues revealed a history of vascular complications was at least as common in women (27%) as it was in men (18%) ($p = 0.09$) [34]. Traditional cardiovascular risk factors were accounted for in this study, with the prevalence of hypertension and diabetes mellitus being similar between sexes; and a history of dyslipidemia and smoking being less frequent, in fact, in women. In both sexes, vascular events occurred most frequently within the first decade of disease. Types of thrombotic events differed between sexes, more commonly implicating the splanchnic venous system in women ultimately diagnosed with PV, consistent with previous literature [35–37]. Whether this is ascribable to cooperating risk factors such as hereditary thrombophilias, use of oral contraceptives (OCs), and/or pregnancy—more frequently encountered in younger and female subjects—remains a subject of contention as the documentation of these factors was not systematically performed. Work by Colaizzo et al. appraising 180 patients with SVT, and accounting for circumstantial vascular risk factors, found that *JAK2V617F* mutations were identified more frequently in women [35]. Moreover, the *JAK2* 46/1 haplotype was found to be associated with the occurrence of somatic *JAK2V617F* mutations in women but not men. This led to the speculation that the higher prevalence of *JAK2* mutations in women with SVT may be driven by sex-specific factors, such as interaction with the 46/1 haplotype, potentially representing a gender-related "susceptibility allele" for SVT.

The prevalence of *JAK2V617F* mutations in women having experienced venous thromboembolism (VTE), cerebral vein thrombosis (CVT), or portal or mesenteric venous thrombosis in the setting

of OC use has also been assessed [38]. No enrichment in *JAK2* lesions was found in women with OC-related VTE or CVT; however, mutations were detected in ~22% of women with OC-related SVT; of note, none of these carried additional underlying causes of thrombophilia, suggesting that in addition to OC use, JAK2 might be a pathogenic "trigger" for SVT in young women without other established causes of thrombophilia. It was suggested that OC-related SVT may represent the inaugural sign of MPN.

In a series of 815 MPN patients by Karantanos et al., VTE but not arterial thrombosis was more common in female subjects (14.7% vs. 7.2%; $p < 0.001$) [9]. Male sex was, in fact, associated with a lower risk of VTE (odds ratio, 0.45; $p = 0.002$) independent of age, phenotype at diagnosis, and driver mutation. This recapitulates findings from the ECLAP study in PV showing a more common history of VTE in women than men (11.4% vs. 7.9%) [30]. Interestingly, despite the higher incidence of venous vascular complications in women, these do not appear to account for increased mortality in this group [34].

Congenital thrombophilia is a genetic condition with an increased predisposition to venous thrombosis. While it affects both sexes, women are particularly vulnerable to the effects of congenital thrombophilia due to various hormonal and physiological factors that influence blood coagulation. The impact of inherited thrombophilia on thrombotic risk and MPN management is a critical area of study. The presence of thrombophilic mutations (including genetic mutations such as those affecting Factor V Leiden, prothrombin, and methylenetetrahydrofolate reductase (MTHFR) polymorphisms), particularly when combined with *JAK2V617F*, plays a pivotal role in determining the thrombotic risk profile of patients with MPN. Tevet et al. [39] found that patients with the *JAK2*V617F mutation had a relative risk (RR) of thrombosis of 2.94, compared to 0.93 in wild-type patients. For those with both a *JAK2V617F* mutation and inherited thrombophilias (per mutations defined above), the RR increased to 3.56, indicating an additive effect of these two risk factors. In addition, women with MPN and inherited thrombophilia are at higher risk for adverse pregnancy outcomes, such as recurrent miscarriage, preeclampsia, and fetal loss [40]. In younger *JAK2* mutated ET patients, the thrombotic risk is further increased by the presence of inherited thrombophilia. A study of 132 patients < 60 years with ET [41], including 5% with inherited thrombophilia, found that the RR for thrombosis in those with both the JAK2 mutation and thrombophilia was 2.23 (95% CI: 1.57–3.18) and 7.66 (95% CI: 2.66–22.03) compared to mutated or wild-type patients without thrombophilia, respectively.

2.6 | Outcomes and Survival

Male sex has consistently emerged as an independent predictor of poor outcomes in MPN, correspondingly shifting favorable prognosis to women [9]. Men with MPN have been found to have higher rates of myelofibrotic (PV/ET) and leukemic transformation, secondary cancers, as well as inferior overall survival rates vis-à-vis women, regardless of age at diagnosis, disease subtype, and driver mutation status [9]. In ET, a study of 1494 patients found the male sex to be associated with worse survival independent of age, leukocyte count, and IPSET (International Prognostic Score of thrombosis in Essential Thrombocythemia) score [8]. It was questioned whether gender may even supersede thrombosis history in the risk schema for overall survival. The adverse impact of male sex also subsumed a higher risk of leukemic transformation and was especially pronounced in older patients and those with high-risk diseases. These outcomes may reflect higher rates of non-MPN-specific somatic mutations and a higher-risk genetic backdrop in men vs. women.

Anemia is a well-established risk factor for survival in MF. Until recently, however, the Hb cut point defining anemia (< 10 g/dL) had been conspicuously sex-agnostic. A seminal analysis of 1109 PMF cases by Nicolosi et al. revealed that mild anemia, defined as Hb levels between 10 g/dL and the sex-adjusted lower limit of the reference range (corresponding to the laboratory-specific value of 11.6 g/dL), was an independent predictor of reduced survival in men but not in women [42]. These findings ratified both sex-specific and dose-dependent contributions of anemia in PMF, paving the way for contemporary sex-stratified anemia thresholds in clinical risk models [43, 44].

In the MYSEC secondary MF cohort [29], slower disease progression from PV/ET to MF was confirmed in females; no significant differences were observed for leukemic transformations. Overall survival from the time of diagnosis of secondary MF was superior in females (10.1 vs. 8.1 years; $p = 0.013$); this retained significance even after adjusting for age at MF diagnosis.

With regard to transplant-related outcomes, a study from the EBMT (European Society for Blood and Marrow Transplantation) registry evaluated the outcomes of allogeneic hematopoietic stem cell transplant (allo-HSCT) in 556 MF patients aged ≥ 65 years vs. a matched population managed with conventional therapies ($n = 176$) [45]. When comparing excess mortality, male patients appeared to benefit more than females from allo-HCT, primarily due to their worse prognosis with standard/non-transplant modalities. The authors posited that these data could be used to enhance patient assessment and counseling and aid in treatment decision-making for transplant-eligible MF patients.

2.7 | Drug Efficacy and Treatment Patterns

Sex-based discrepancies in pharmacokinetics and pharmacodynamics have been well established, owing to variations in endogenous hormones, physiological variables (body weight/composition, etc.), and the expression and activity of CYP isoenzymes involved in drug biotransformation, among others [46]. Women have also been shown to experience more frequent and serious adverse drug events compared to men overall [47]. With respect to MPN specifically, there are limited data on sex-biased differences from a drug metabolism standpoint. In a subgroup analysis of the COMFORT trials (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment), women receiving ruxolitinib exhibited better survival than men [48]; it was conjectured that sex-defined differences in clearance and volume of distribution of ruxolitinib could underpin these efficacy discrepancies [49].

Treatment patterns according to sex have been inconsistent. A series of 270 *JAK2*-positive MPN patients showed no difference in

drug type/exposure between women and men [34]. Conversely, in a study of 815 MPN patients, treatment paradigms varied significantly between the sexes: more women than men received anagrelide and interferon, while more men received hydroxyurea and ruxolitinib [9]. Further, statistically more men than women underwent allo-HCT.

2.8 | Representation in Clinical Trials and Emerging Therapies

While important strides have been made to remediate sex/gender imbalances in clinical study participation, challenges still remain [47], the MPN milieu being no exception. Seminal trials in MPN have consistently demonstrated male preponderance [50–52] with notable exceptions being those conducted in ET populations [53–55]. Interestingly, symptom surveys involving MPN patients show a marked predominance of female respondents, while male participation is ~50% lower than expected based on disease prevalence [56, 57]. This tenably results in overestimation of symptom scores and underestimation of mean differences in scores between genders. Conversely, data from 291 MPN trial participants found that clinical trials exhibited less gender-based sampling bias. What is clear is that efforts are needed to bridge the gender data gap in MPN research. Prospectively, strategies must be implemented to evaluate/account for gender participation imbalances, recalibrate these imbalances, and apply weighted estimates as needed.

As novel therapeutics with the potential to modify the treatment landscape in MPN emerge, including strategies targeting iron metabolism as well as the immune system (e.g., vaccines, monoclonal antibodies), sex-driven differences in iron homeostasis [58] and responses/toxicities to immunotherapy [59], among others, will need to be factored in as differential benefits and dilemmas will undoubtedly surface. The prospect of truly individualized therapy in the context of these new modalities thus mandates high-level attention to female sex; not only as a determinant of the commensurate value of these therapies, but also as a source of potential bias that must be appreciated and addressed.

3 | Issues in Adolescent Women With MPN

3.1 | Menstrual Disorders and Contraception

Heavy menstrual bleeding may be the presenting sign of MPN, particularly ET, especially when accompanied by acquired von Willebrand syndrome (AvWS) [60, 61]. While it is recommended to obtain a formal assessment by a gynecologist, from a hematological standpoint, the management approach may include reducing the aspirin dose, administering low doses of clot-stabilizing drugs (e.g., tranexamic acid), or using a hormone-coated intrauterine device (IUD) such as Mirena. Consultations with female MPN patients of childbearing age should integrate discussions regarding forms of contraception and preconception planning.

Of paramount and recurring concern is the potential thrombotic risk associated with contraceptive use. There is currently insufficient evidence to support a clear association between estrogen-based contraception and thrombosis in MPN, with a retrospective review disclosing that estrogen-based therapy appeared safe in ET outside the setting of the combined OC pill [62]—the latter's use may be associated with an increased risk of deep vein thrombosis [62]. It may therefore be reasonable to recommend avoidance of estrogen-based contraception in favor of alternatives—progesterone-only pill, implant, depot, IUD (e.g., Mirena), or barrier methods [63, 64]. Moreover, it is vital to discuss the potential teratogenic effect of cytoreductive therapy as well as requisite contraceptive measures as needed [62, 65].

4 | Pregnancy in MPN

Young women of childbearing potential constitute ~10% of newly diagnosed MPN cases; in a Mayo Clinic study of 3023 MPN patients, 361 patients (12%) were younger than 40 years, of which 60% were women; the most common MPN subtype was ET in 61%, followed by PV in 22% and PMF in 17% [66, 67]. In the aforementioned study, life expectancy in patients ≤40 years of age was minimally compromised, with median survival estimates of 35, 37, and 20 years for PV, ET, and PMF, respectively [67]. In view of the favorable survival expectations for young women with MPN, the clinical focus is on quality of life, and reproductive health and pregnancy are important considerations.

4.1 | Reproductive Patterns and Fertility

According to a Swedish population-based study of 1141 women with MPN aged 15–44 years (ET 54%, PV 24%, PMF 11%, and MPN-U 12%), age-matched to 4564 controls, women with MPN were found to have a 22% lower childbirth rate compared to the control population [68]. At the time of MPN diagnosis, women with MPN had fewer children, an average of 1.29 compared to 1.43 children in the control population. Interestingly, childbirth rates were found to be lower in women with MPN aged 15–25 years compared to their age-matched counterparts (HR: 0.64) [68]. However, among patients with MPNs, the childbirth rate was not reduced in ET (HR: 1.02), while it was significantly lower in PV (HR: 0.50) and PMF (HR: 0.45) [68]. The study found no significant difference in miscarriage rates before or after MPN diagnosis (12.4% and 12.5%, respectively; HR: 1.25) [68]. In general, information on the effects of commonly utilized cytoreductive therapies in MPN, including hydroxyurea and interferon-alpha (INF-α), on fertility is limited. A recent meta-analysis suggests that the use of hydroxyurea for sickle cell disease can diminish anti-Müllerian hormone levels and ovarian reserve in females [69]. By contrast, in another study that evaluated the impact of hydroxyurea on ovarian reserve in women with sickle cell disease, exposure to hydroxyurea did not appear to affect primordial follicle and growing follicle density [70].

4.2 | Pregnancy Outcomes

Historically, pregnancy in MPN has been associated with inferior outcomes, with an increased risk of fetal loss, preterm birth, stillbirth, preeclampsia, thrombosis, and bleeding complications

[71]. With the exception of two population-based studies [72, 73], the majority of information on pregnancy outcomes in MPN is derived from multicenter and single institutional series [71]. A Swedish population-based study (1973–2018) of 342 pregnancies (238 in ET, 43 in PV, 33 in PMF, and 28 in MPN-U) in 229 women with MPN that had reached gestational Week 22 (Week 28 before 2008) compared pregnancy outcomes to age, calendar year, and parity matched control pregnancies [72]. Notably, in 69 (20%) of pregnancies, the MPN diagnosis was established during pregnancy or within 60 days postpartum. Previous miscarriage (early pregnancy loss) or recurrent (≥3) miscarriage was reported in a similar proportion of MPN pregnancies (26% and 4%) and controls (20% and 2%) [72]. The childbirth rate was 12.2 per 100 000 pregnancies, suggesting an increasing trend of pregnancies in MPN likely due to a combination of earlier MPN diagnosis through peripheral blood *JAK2/CALR/MPL* mutation screening and delayed childbirth [72]. Not surprisingly, delivery through induction and Cesarean section was significantly more common in women with MPN (31% vs. 16%). Also, preterm birth (14% vs. 4%), in particular, iatrogenic preterm birth (51% vs. 14%), and consequently low birthweight (<2.5 kg) was more likely in MPN pregnancies; stillbirth was rare (0.6% vs. 0%), and neonatal mortality rates were exceedingly low (0.3% in MPN and control pregnancies) [72]. Overall, venous thrombosis was uncommon (1% vs. 0%), and no arterial thrombotic events were reported in either MPN pregnancies or controls. On the other hand, pregnancy-related bleeding was non-significantly higher in MPN pregnancies (14% vs. 9%), while the incidence of preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets), and gestational hypertension did not differ between MPN and control pregnancies [72].

In another prospective study from the United Kingdom (2010–2012), on maternal and fetal outcomes in 58 women with MPN (47 ET, 5 PV, 5 MF, and 1 MPN-U), the overall incidence of MPN pregnancies was 3.2/100 000 pregnancies; 58 were live births, one stillbirth, and one miscarriage resulting in a miscarriage rate of 1.7 per 100 pregnancies and a perinatal mortality rate of 17 per 1000 live and stillbirths [73]. 85% of women delivered at term, and 45% of deliveries were through induction of labor and Cesarean section. In regard to fetal outcomes, 22% and 15% of neonates were below the 10th percentile for growth and had low birth weight (<2.5 kg), respectively, with 13% requiring neonatal intensive care admission; however, there were no neonatal deaths [73]. Maternal complications included preeclampsia in 9%, postpartum hemorrhage in 9%, and postpartum hematoma in 3.5%; notably, there were no thrombotic events or maternal deaths [73]. Antepartum management consisted of aspirin in 88%; 38% and 3% were prescribed prophylactic and therapeutic low molecular weight heparin (LMWH), respectively, and 14% received INF-α [73]. Overall, the above prospective studies suggested favorable maternal and fetal outcomes in women with MPN.

Of all MPNs, pregnancy is most likely in the setting of ET and has been well-studied through several large retrospective analyses conducted over the past two decades. In Table 1, we have highlighted and synthesized results from 598 pregnancies in 338 women with ET, with combined live birth, preterm birth, intrauterine growth retardation (IUGR), preeclampsia, thrombosis, and hemorrhage rates of 71%, 8%, 4%, 4%, 3%, and 4%, respectively. Treatments during pregnancy included aspirin (65%), antepartum/postpartum LMWH (14/18%), and INF-α (10%) [74–78]. Prior fetal loss was found to be the most consistent predictor of fetal loss in ET, whereas data on the impact of driver mutations on fetal loss and pregnancy-related complications have been conflicting [76, 79, 80]. With respect to management, the benefit of aspirin in the prevention of fetal loss has been confirmed in several studies, while the additional value of LMWH and INF-α remains to be determined [74, 75, 81]. In a Mayo Clinic study involving 200 pregnancies and 100 women with ET, with a live-birth rate of 72% (24% fetal loss in the first trimester), antepartum management included no specific therapy in 52 (26%) pregnancies, aspirin alone in 112 (56%), and aspirin combined with cytoreductive drugs and systemic anticoagulation in 23 (12%) [74]. In the particular study, predictors of first-trimester pregnancy loss included prior fetal loss (43% vs. 18%), diabetes mellitus (67% vs. 23%), and absence of aspirin therapy (45% vs. 14%). Importantly, aspirin use was beneficial in preventing first-trimester pregnancy loss in both *JAK2* (18% vs. 50%) and *CALR* (8% vs. 43%) mutated cases, whereas systemic anticoagulation did not appear to impact fetal or maternal outcomes. The study also found an association between *CALR* mutation and maternal hemorrhage (13% vs. 4%) and diabetes mellitus and preeclampsia (33% vs. 5%) [74].

Unlike the case in ET, pregnancy in PV is fairly uncommon. A recent report from the European LeukemiaNet described 129 pregnancies in 69 women with PV; 23 and 106 deliveries were before/at and after PV diagnosis, respectively [82]. The live birth rate was 68%; full-term birth was 50% and preterm birth was 18%, with 21% of deliveries via Cesarean section. The miscarriage rate was 32%, with 25% spontaneous abortions and 7% stillbirths. The following treatments were utilized in 87 of 129 (67%) pregnancies: aspirin with LMWH ($n=38$, 30%), aspirin alone ($n=24$, 19%), LMWH alone ($n=11$, 9%), and INF-α ($n=14$, 11%; INF-α alone $n=2$), and the live birth rate was significantly higher in pregnancies receiving vs. not receiving PV-directed therapy (78% vs. 48%) [82]. In particular, aspirin in combination with LMWH or INF-α was associated with a significantly lower risk of fetal loss [82]. Maternal complications were reported in 29 (23%) of pregnancies, which included bleeding ($n=20$), preeclampsia ($n=5$) and thrombosis ($n=4$), and complication rates were similar with or without PV-directed therapy (24% vs. 20%) [82]. In a separate Italian study on 25 pregnancies in 15 women with PV, live births occurred in 15 (60%) with preterm birth in 5 (20%); majority of fetal loss was in the first trimester in 8 (24%) of pregnancies, with two losses (8%) each in the second and third trimester. Nineteen patients received aspirin ±LMWH, while five pregnancies were untreated; two from each group (11% and 40%), respectively, ended with late fetal loss [83]. Similarly, in a study from the United Kingdom on 18 pregnancies in 8 women with PV, 11 pregnancies were managed with aggressive phlebotomy + aspirin + LMWH for 6 weeks postpartum (3 also received INF-α and 3 LMWH antepartum), and 7 were untreated [84]. In the latter group, there was only 1 (14%) live birth; while in the treatment group, there were 10 (91%) live births, suggesting Hct control, aspirin ± LMWH were associated with significantly better outcomes [84]. In a Mayo Clinic study that included five pregnancies in four women with PV, all received treatment with aspirin ± LMWH and had successful outcomes [80]. Table 2 provides collated results from

TABLE 1 | Pregnancy outcomes in women with essential thrombocythemia.

	Mayo Clinic study [74]	Italian study [77]	Italian study [78]	Partners Boston study [75]	Combined results
Women/pregnancy, *n*	100/200	94/155	92/122	52/121	338/598
Genetics, *n/n evaluable* (%)					
JAK2 mutated	44/86 (51)	59/94 (63)	16/37 (43)	29/52 (56)	148/269 (53)
CALR mutated	21/76 (28)	19/94 (20)	—	6/52 (12)	46/222 (21)
MPL mutated	0/76 (0)	2/94 (2)	—	0/52 (0)	2/222 (1)
Triple negative	4/76 (5)	14/94 (15)	—	4/52 (8)	22/222 (9)
Treatment, *n/n evaluable* (%)					
Aspirin	135/200 (68)	—	93/122 (76)	62/107 (51)	290/429 (65)
LMWH (antepartum)	19/200 (10)	—	19/93 (20)	10/84 (12)	48/377 (14)
LMWH (postpartum)	29/200 (15)	—	—	17/84 (20)	46/284 (18)
Interferon	17/200 (9)	—	20/122 (16)	2/121 (2)	39/443 (10)
No treatment	52/200 (26)	—	—	—	52/200 (26)
Live birth, *n* (%)	144 (72)	106 (68)	92 (75)	84 (69)	426/598 (71)
Fetal complications, *n* (%)					
Fetal loss	56 (28)	46 (30)	30 (25)	39 (32)	171/598 (29)
First-trimester loss	51 (26)	37 (24)	19 (16)	—	107/477 (22)
Spontaneous	48 (24)	37 (24)	19 (16)	32 (26)	136/598 (23)
Elective	3 (2)	—	—	4 (3)	7/321 (3)
Second-trimester loss	3 (2)	6 (4)	7 (6)	—	16/477 (6)
Third-trimester loss	0 (0)	3 (2)	—	—	3/355 (2)
Stillbirth	2 (1)	3 (2)	4 (3)	1 (0.8)	10/598 (2)
Preterm birth	6 (3)	20 (13)	12 (10)	9 (7)	47/598 (8)
IUGR	5 (3)	13 (8)	2 (2)	3 (3)	25/598 (4)
Maternal complications, *n* (%)	26 (13)	18 (12)	10 (8)	15 (12)	69/598 (11)
Thrombosis	2 (1)	—	5 (4)	3 (3)	10/343 (3)
Major bleeding	13 (7)	—	1 (1)	7 (6)	21/343 (4)
Pre-eclampsia	11 (6)	—	3 (3)	4 (3)	18/343 (4)
Placental abruption	1 (0.5)	—	1 (1)	0 (0)	2/343 (0.5)
Gestational hypertension	—	—	—	1 (1)	1/121 (1)

Abbreviations: IUGR, intrauterine growth retardation; LMWH, low molecular weight heparin.

the above-discussed 177 pregnancies in 97 women with PV, with combined live birth, preterm birth, stillbirth, IUGR, pre-eclampsia, thrombosis, and bleeding rates of 67%, 41%,7%, 9%, 5%, 3%, and 13%, respectively [80, 82–84].

In patients with PMF, the exceedingly rare occurrence of pregnancy is reflected in the scanty published literature. The largest multicenter (Mayo-Florence) series on 24 pregnancies in 16 women (pre-fibrotic PMF 16, PMF 5, and post-ET MF 3) reported live births in 17 (71%), first-trimester fetal loss in 5 (21%), and preterm birth in 2 (8%) [85]. Treatments included aspirin in 14 (58%), INF-α in 2 (8%), and LMWH in 1 (4%); aspirin was protective for fetal loss (fetal loss in 14% vs. 50% in the absence of aspirin) [85]. Additional predictors of fetal loss included prior fetal loss (60% vs. 21%), pre-fibrotic MF (44% vs. 0%), presence of *JAK2* mutation (57% vs. 19%), and thrombosis history (80% vs. 16%) [85]. Notably, in a prospective study from the United Kingdom, all five pregnancies in the context of PMF resulted in live births [73].

4.3 | Management Recommendations

Fertility counseling should be provided to all young women with an established MPN diagnosis; however, it should be noted that not

TABLE 2 | Pregnancy outcomes in women with polycythemia vera.

	European LeukemiaNet study [82]	Italian study [83]	UK study [84]	Mayo Clinic study [80]	Combined results
Women/pregnancy, *n*	69/129	15/25	8/18	4/5	97/177
Treatment, *n/n evaluable* (%)					
Aspirin alone	24/129 (19)	16/25 (64)	—	2/5 (40)	42/159 (26)
Aspirin + LMWH	38/129 (30)	3/25 (12)	11/18 (61)	3/5 (60)	55/177 (30)
LMWH (antepartum)	11/129 (9)	—	—	—	11/129 (9)
LMWH (postpartum)	—	—	11/18 (61)	—	11/18 (61)
Interferon	14/129 (11)	1/25 (4)	3/18 (17)	0 (0)	18/177 (10)
No treatment	42/129 (32)	5/25 (20)	7/18 (39)	0 (0)	54/177 (31)
Live birth, *n* (%)	88 (68)	15 (60)	11 (61)	5 (100)	119/177 (67)
Fetal complications, *n* (%)					
Fetal loss	41 (32)	10 (40)	7 (39)	0 (0)	58/177 (33)
First-trimester loss	32 (25)	6 (24)	4 (25)	0 (0)	42/177 (24)
Spontaneous	32 (25)	5 (20)	4 (25)	0 (0)	41/177 (23)
Elective	3 (2)	1 (4)	0 (0)	0 (0)	4/177 (2)
Second-trimester loss	0 (0)	2 (8)	0 (0)	0 (0)	2/177 (1)
Third-trimester loss	0 (0)	2 (8)	0 (0)	0 (0)	2/177 (1)
Stillbirth	9 (7)	0 (0)	3 (17)	0 (0)	12/177 (7)
Preterm birth	64 (50)	5 (20)	3 (17)	1 (20)	72/177 (41)
Neonatal death	0 (0)	0 (0)	1 (6)	0 (0)	1/177 (0.5)
IUGR	—	1 (5)	3 (17)	—	4/43 (9)
Maternal complications, *n* (%)	29 (23)	4 (17)	4 (22)	1 (20)	37/177 (21)
Thrombosis	4 (3)	—	1 (6)	1 (20)	5/152 (3)
Bleeding (major + minor)	20 (16)	—	0 (0)	0 (0)	20/152 (13)
Pre-eclampsia	5 (4)	—	3 (17)	0 (0)	8/152 (5)

Abbreviations: IUGR, intrauterine growth retardation; LMWH, low molecular weight heparin.

infrequently in ~20%–30% of cases, MPN is diagnosed during pregnancy. In general, in women with ET, the risk of fetal loss and pregnancy complications is not substantially different from the general population [68]. An obstetric history of recurrent first trimester or late miscarriages, gestational diabetes, hypertension, preeclampsia, placental insufficiency/abruption, IUGR, stillbirth, or preterm birth warrants increased vigilance in collaboration with high-risk obstetrics. Accordingly, a risk-adapted management approach is advised, taking into consideration obstetric history and thrombosis risk; the latter is extrapolated from the revised International Prognostic Score for thrombosis in ET (IPSET-thrombosis) [86]; very low-risk (absence of thrombosis and *JAK2* mutation), low-risk (presence of *JAK2* mutation), and high-risk (arterial or venous thrombosis history). In regard to assisted reproductive technology, the risk of venous thrombosis is doubled with in vitro fertilization (IVF), compared with the background pregnant population stemming from a 5- to 10-fold increased risk during the first trimester in IVF pregnancies, which is in turn related to a substantially higher risk after ovarian hyperstimulation syndrome [87]. Given the lack of evidence in MPN pregnancies, the use of prophylactic LMWH outside the setting of ovarian hyperstimulation requires thoughtful consideration.

In young women with MPN contemplating a future pregnancy, warfarin and hydroxyurea should be avoided due to their teratogenic potential. Also, the safety of direct oral anticoagulants for use in pregnancy has not been established [88]. Aspirin 81 mg daily is recommended for all pregnancies, with aspirin twice daily considered in *JAK2* mutated cases or in the presence of cardiovascular risk factors. Laboratory and controlled clinical trial data support the use of twice-daily aspirin in patients perceived to have a higher risk for thrombosis that is not considered high enough to require cytoreductive therapy, for example, JAK2-mutated low-risk patients, especially in the presence of cardiovascular risk factors [89, 90]. Nonetheless, the optimal dose of aspirin therapy in MPN pregnancies requires further

study. In patients with extreme thrombocytosis, with a platelet count over 1 million/μL, AvWS should be ruled out before instituting aspirin therapy. In general, there is no optimal platelet count target during pregnancy; moreover, the platelet count is expected to decline in each trimester, with the nadir expected in the third trimester [74]. In PV, in addition to aspirin, periodic phlebotomy should be continued in order to strictly maintain Hct < 45%. Cytoreductive therapy in the form of INF-α is mandated in all high-risk patients with a prior thrombosis history and should also be considered in low-risk patients with poorly controlled Hct levels, prominent splenomegaly, or recurrent fetal loss [71]. The use of antepartum systemic anticoagulation with LMWH is advised only in patients with a venous thrombosis history, and treatment should be interrupted 24 h before delivery via Cesarean section or use of neuraxial analgesia [71]. Similarly, postpartum LMWH is recommended only in the presence of a venous thrombosis history [71].

Taken together, there is a paucity of data on reproductive patterns and fertility in women with MPN, and pre-conceptual counseling and optimal management are primarily guided by retrospective observations and personal experience [71, 91]. Given the marked heterogeneity in management practices, collaborative efforts are sorely needed to generate prospective data and develop evidence-based management strategies for pregnancies in women with MPN.

5 | Menopause and Hormone Replacement in MPN

Hormone replacement therapy (HRT) may effectively relieve symptoms of menopause (hot flashes, night sweats, etc.) caused by declining ovarian reserve; these can be distressing to patients and greatly affect quality of life. HRT typically combines estrogen and progesterone to mimic ovarian hormones and is approved by the Federal Drug Administration (FDA) [92]. Systemic HRT can be administered via oral, vaginal, or transdermal route, each with a distinct risk/benefit profile. While early randomized controlled data relayed an increased risk of ischemic stroke among menopausal patients using HRT, contemporary studies suggest this risk is principally in older women (> 60 years) initiating HRT 10 years+ following the onset of menopause [93]. With respect to venous thrombosis, the seminal Women's Health Initiative (WHI) trial documented a twofold increased incidence with HRT; the highest risk was within the first year of use and with higher doses [94]. More recent studies have shown a lower risk of venous thromboembolic events with transdermal estrogen formulations than with oral treatments [95, 96].

While corresponding studies specifically addressing MPN cohorts are lacking, a series examining 305 women with ET showed estrogen-based HRT did not significantly impact the overall risk of arterial or venous thrombosis [62]. However, a twofold increase in cardiovascular events was recorded in HRT users vs. non-users, largely angina (11% vs. 4%) and peripheral artery thromboembolism (6% vs. 3%), respectively, while the opposite was true for stroke rate (15% vs. 24%). While these results do not support withholding HRT in ET patients who require therapy for fear of increased thrombosis risk, the decision to initiate HRT in subjects with MPN needs to be individualized based on factors that include thrombosis history, personal/family history of breast or ovarian cancer, etc. Local routes of administration or combined HRT (vs. estrogen-only) may be favored in patients with MPN; additionally, alternatives such as anti-depressants may also be explored. Risks and benefits should be discussed with both hematology and gynecologist specialists. Interestingly, the association between hormonal and reproductive history and the risk of developing a future MPN has also been investigated. Using a population-based cohort study, Leal and colleagues found ever use of hormone therapy and bilateral oophorectomy were both associated with an increased risk of ET (risk ratio [RR] = 1.63 and 1.58) but a decreased risk of PV (RR = 0.58 and 0.32, respectively) [97]. No statistically significant association was drawn between OC or reproductive factors with MPN risk overall, or by MPN subtype. There was also an increased risk of PV with a higher number of ovulatory years (RR = 1.68 for > 36.8 vs. ≤ 27.6 years; $p = 0.045$); adjusting for confounders did not alter results.

6 | Bone Health

It has been shown that bone morbidity in MPNs is often overlooked, but recent studies have highlighted its significant impact on patient quality of life. The relationship between MPNs and bone health is multifaceted. In a nationwide population-based cohort study, the risk of osteoporotic fractures in patients with MPNs was explored [98]. This study demonstrated a notable association between MPNs and an increased risk of fractures, especially among older individuals. Specifically, patients with PV and primary MF had higher rates of osteoporotic fractures compared to the general population. This increased risk was particularly evident in individuals over the age of 60, where bone fragility and the effects of disease progression combined to exacerbate fracture susceptibility.

Bone complications, such as osteoporosis, can result from a variety of mechanisms, including altered hematopoiesis, the effects of treatment regimens, and clonal hematopoiesis that often accompanies a general inflammatory state [99]. The role of inflammation is significant, as chronic inflammation often leads to osteoclast activation, promoting bone resorption. Moreover, the use of certain treatments, such as cytoreductive therapies or corticosteroids, can further accelerate bone loss. In MF, bone marrow fibrosis itself can disrupt normal bone marrow function, potentially leading to a decrease in bone density.

Recently, the SEER cancer registry [100] revealed that MPN patients had a significantly higher prevalence of osteoporosis (10% vs. 8%) and osteoporotic fractures (1% vs. 0.2%). After adjusting for baseline characteristics, MPN diagnosis (OR = 1.34), age ≥ 70 years (OR = 1.62), female sex (OR = 7.73), and a Charlson Comorbidity Index ≥ 3 (OR = 1.54) were significant predictors of osteoporosis and fractures. Notably, an increased risk of osteoporosis and fractures was observed in patients with PV, ET, and MPN-U, but no such association was found for MF.

Given the elevated risk of fractures and bone morbidity in patients with MPNs, careful monitoring of bone health is essential. Bone mineral density assessments and fracture risk evaluations should be part of routine care for these patients, particularly those with a history of fractures, advanced age, or long-standing disease. Therapeutic strategies might include the use of bisphosphonates,

denosumab, or other bone-sparing agents. Moreover, addressing modifiable risk factors such as smoking, alcohol use, and physical inactivity is crucial in mitigating bone-related complications. There are, however, no indications of the use of HRT to prevent osteoporosis in MPNs.

7 | Special Issues in Women With MPN

7.1 | Secondary Neoplasms

Extensive data from nationwide Swedish registries have explored the issue of second malignancies in patients with MPN vs. matched controls. While a significantly increased risk of all non-hematologic cancer was reported in subjects with MPN (hazard ratio: 1.6), this risk was shown to be similar among men and women [101, 102]. Corresponding data exist for secondary hematological malignancies [103]. However, cancers primarily affecting women, namely breast cancer, were not shown to be enriched in the MPN population in comparison with the general population in these analyses [101]. While rare cases of coexistence of ET and breast cancer have been reported [104, 105], the corpus of literature on this subject is overwhelmingly scarce, and further studies are required to draw definitive conclusions.

Interestingly, an analysis of 2485 evaluable PV patients enrolled in the REVEAL trial demonstrated that the most common malignancies before MPN diagnosis included breast (1.5%), prostate (1.3%), colorectal (0.8%), and melanoma (0.8%) [106]. Conversely, in this study, breast cancer was reported two times as frequently in women with PV compared to an unselected control population.

7.2 | Sexual Health

Sexuality-related complaints are prevalent in MPN and are rooted in both physiologic and psychologic determinants. Sexuality issues correlate directly with MPN symptoms, disease features, and quality of life [107]. Interestingly, in a prospective evaluation of 1971 MPN patients, sexuality scores were significantly deficient compared with age-matched, healthy controls [108]. While sexual dysfunction was more severe in older patients (>65 years), those with cytopenias/transfusion requirements, and those receiving specific therapies (immunomodulators and steroids), no differences were observed between sexes, MPN subtypes, or disease-specific risk scores [108].

The occurrence of vaginal ulcers or mucosal atrophy as a manifestation of hydroxyurea-induced skin toxicity has been reported [109, 110]. Genital ulcers and erosions induced by long-term therapy with hydroxyurea may be underrecognized in clinical practice, and this could further limit normal sexual activity and negatively affect women's sexual health. However, if identified, withdrawal of hydroxyurea leads to quick resolution of these lesions and the associated pain. An insightful 2016 editorial from Gerds advocates for a "thoughtful conversation about sexual symptom burden" as part of the routine comprehensive assessment of MPN patients [111]. It is therein proposed to systematically integrate questions regarding sexuality-related concerns at the time of consultation, routinely prompting MD-patient discussions of sexuality-related symptom burden.

8 | Conclusion

Sex remains a critical independent factor influencing MPN phenotype, symptom expression, and clinical outcomes, including survival. It is imperative to increasingly adopt a sex-informed lens to secure optimized and personalized counseling and therapeutic decision-making. In reviewing the multiple and significant sex-based discrepancies in MPN, the overarching message is that *sex matters*. Moreover, women with MPN face unique issues relating to fertility, conception, and menopause, each holding the potential to modulate disease.

Knowing the extent to which sex is a cooperative player in MPN, current risk models warrant revisiting to evaluate their sex/gender-specific performance. One could ask whether risk stratification according to sex would in fact be more appropriate [9].

Similarly, while clinical trials have made progress in attending to sex/gender-specific disparities, important gaps still remain in their inclusion and trial participation of women. In addition, systematic gender-specific analyses of drug toxicity and efficacy should be performed in order to discern discrepant pharmacologic responses that may mandate sex-specific dose adjustment and monitoring. Finally, potentially novel prospective insights into sex-differential pathobiology could inform targeted approaches for therapy.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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