Myeloproliferative Disease in Pregnancy and Other Management Issues

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The goal of this review is to assess the current treatment and outcomes of special clinical situations in patients with myeloproliferative disease (MPD) such as pregnancy, major thrombotic and bleeding complications and surgical interventions. However, only a limited literature to support optimal management strategies is available. Many of the proposed strategies are the results of common sense or derive from the extrapolation of data from other studies not specifically designed to solve these problems. Therefore, practical recommendations to guide clinical decisions in these settings still remain largely empirical.

Management of Pregnancy

Normal pregnant women are at an increased risk of thrombosis, calculated to be approximately six times higher than in non-pregnant women, and the risk is compounded if they also have myeloproliferative disease (MPD). As a consequence, women with MPD may present a high incidence not only of pregnancy-related venous thromboembolism, but also of other vascular complications of pregnancy involving occlusion of the placental circulation.[1,2] The paucity of published data, however, makes it difficult to obtain a clear view of the overall risk of these events.

Clinical epidemiology and risk factors

In the recently published Italian Guidelines for the Therapy of Essential Thrombocythemia (ET),[3] we pooled the outcomes of 461 pregnancies reported in retrospective and prospective cohort studies. Most reports dealt with single cases or small numbers, and there is some suspicion of reporting bias, since there seems to be a tendency to describe patients with complications rather than those with an uncomplicated pregnancy. Elliott and Tefferi[4] restricted their review to series comprising at least 6 patients but, interestingly, the results were no different from those in the systematically retrieved literature that formed the basis of the ET Italian guidelines.

The mean age at pregnancy was 29 years, with a mean platelet count at the beginning of pregnancy of 1000 × 10^9/L. During the second trimester, a spontaneous decline was registered to a nadir of 599 × 10^9/L. This decrease seems larger than the reduction seen in normal pregnancies, which is attributed to an increase in plasma volume. The mechanism is not known, but could involve placental or fetal production of a factor that downregulates platelet production. In the postpartum period the platelet counts rise back up to their earlier levels and rebound thrombocytosis may occur in some patients. This increases the probability of vascular complications at this time, which is a period of high thrombotic risk, as in other conditions of thrombophilia as well as in normal women.

Overall, 50-70% of ET women had successful live births; first-trimester loss occurred in about 25-40% and late pregnancy loss in 10% of cases. Abruptio placentae was reported in 3.6% of cases, higher than in the general population (1%).[3] Pre-eclampsia rates were similar to the normal population (1.7%) and intrauterine growth retardation (IUGR) was reported in 4-5%.[3]

Pregnancy in polycythemia vera (PV) is rarer than in ET. A recent study reviewed a total of 38 pregnancies in 18 PV patients[5]; 22 successful live births were reported (57%). Similar to ET, spontaneous abortion during the first trimester was reported in 22% of cases and preterm delivery in 13.8%. In idiopathic myelofibrosis (IMF), only 4 pregnancies have been described and the outcome appears to be similar to that of ET and PV.[1]

Maternal thrombosis or hemorrhage are uncommon. In the pooled analysis cited above,[3] postpartum thrombotic episodes were reported in 13 patients, occurring in 5.2% of pregnancies, and minor or major, pre- or postpartum bleeding events in other 13 cases. The maternal vascular risk may be higher in women with previous venous or arterial events or hemorrhages attributed to MPD, independent of whether they occurred in a previous pregnancy or not. Similarly, severe complications in a previous pregnancy, such as ≥ 3 first-trimester or ≥ 1 second or third-trimester losses, birth weight < 5th centile of gestation, pre-eclampsia, intrauterine death or stillbirth, are considered to raise the risk of subsequent events for the mother and the fetus. Other vascular risk factors in pregnant women are age, obesity, immobilization and other causes of genetic and acquired thrombophilia including antiphospholipid antibodies.

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Treatment

A detailed personal and family history should be taken, and a woman with MPD who plans a pregnancy should be put under the joint care of a hematologist and an obstetrician experienced in the care of patients with high-risk pregnancies in order to assess the risks and agree on the most appropriate therapy. It is recommended that the patient stop any possibly teratogenic drugs at least three months before conception. Depending on the risk of maternal vascular events and pregnancy morbidity, the various treatment options range from no therapy, aspirin alone, low-molecular-weight heparin (LMWH) to cytoreductive therapy (**Table 1**).

Aspirin. The rationale for the use of low-dose aspirin in MPD is supported by the recent results of the ECLAP trial (European Collaboration on Low-dose Aspirin in Polycythemia Vera).[6] However, the largest series of pregnant ET patients published to date failed to find any benefit of aspirin even in women with previous fetal losses.[7] In a systematic literature review up to October 2003,[3] we found that pregnancy was successful in 74% of ET patients treated with aspirin (79 out of 106), compared to only 55% of the women not receiving aspirin (80/145). The Italian Guidelines concluded that although there was no direct evidence of the efficacy of aspirin overall in pregnant ET women, the drug is recommended for these women if they have a history of microvascular symptoms or at least one previous adverse pregnancy event.[3]

According to Harrison[1] and Griesshammer,[2] in the absence of clear contraindications, all patients with ET and PV should be given aspirin (75 or 100 mg daily) throughout pregnancy and for at least 6 weeks after delivery. Low-dose aspirin is considered safe in pregnancy and should preferably be started before conception to facilitate placental and fetal development. Bleeding complications are rare but particular attention should be paid to patients with platelet count above 1,000-1,500 $\times 10^9$/L since the risk of bleeding may increase significantly.

Low-molecular-weight heparin. LMWH in pregnancy is indicated for prophylaxis and treatment of deep venous thrombosis in selected high-risk ET women, and to reduce fetal morbidity. The suggested dose of enoxaparin is 4000 units (40 mg) once daily increasing to 4000 U twice daily from 16 weeks, dropping to 4000 U daily for 6 weeks postpartum, preterm delivery and IUGR. To increase the antithrombotic efficacy in very high-risk situations LMWH was used in combination with low-dose aspirin. Randomized clinical trials in antiphospholipid syndrome patients indicated that the combination of heparin plus low-dose aspirin significantly improved the live birth rate, to 71-80%, and was superior to aspirin alone (live birth rate about 40%) (reviewed in [8]).

These results cannot be translated directly to MPD patients in whom the pathogenesis of vascular occlusion may be different, with an apparently prominent role of leukocyte activation and interaction between platelets, leukocytes and endothelium, as shown by Falanga et al.[9] Nonetheless, LMWH may be considered in addition to low-dose aspirin in high-risk ET women with a history of late fetal loss, pre-term delivery and IUGR.[1,2]

Cytoreductive therapy. This is a very controversial area. During pregnancy, hematocrit (Hct) and platelet count may undergo a natural fall and this could reduce the need of phlebotomy or cytoreductive drugs. The target Hct in PV is not yet well established. According to Robinson et al[5] the recommendation is to reduce Hct to below 0.45 by venesection, since currently no evidence to support a different level in males and females is available. Platelet-lowering therapy in pregnancy is also controversial, since the available data did not indicate a relation between platelet count and adverse pregnancy outcome. In any case, drugs should be avoided in the first trimester. According to the Italian guidelines[3] and expert judgment,[1,2] candidates for platelet-lowering drugs are women with a previous history of major thrombosis or major bleeding, or when platelet count is greater than 1000-1500 $\times 10^9$/L, or when familial thrombophilia or cardiovascular risk factors are documented. If cytoreduction has to be given, Interferon-alpha (IFN) is probably the safest option. Other cytotoxic drugs like hydroxyurea, busulfan and anagrelide should be avoided particularly during organogenesis in the first trimester.

In conclusion, evidence-based recommendations for the most appropriate treatment of pregnancy in women with ET and PV cannot be given to date, since only anedoctal data or, at best, retrospective studies have been published. Within the European LeukemiaNet a prospective observational registry of pregnancies in MPDs was established with the aim to address the numerous questions still unanswered.[2]

Table 1. How we manage pregnancy in myeloproliferative disease (MPD).

1. Risk stratification
   At least one of the following defines high-risk pregnancy:
   - previous major thrombotic or bleeding complication
   - previous severe pregnancy complications*
   - platelet count > 1500 $\times 10^9$/L
2. Therapy
   a) Low-risk pregnancy
      - Target hematocrit should be kept below 45%
      - Aspirin 100 mg/day
      - Low-molecular-weight heparin (LMWH) 4000 U/day after delivery until 6 weeks postpartum
   b) High-risk pregnancy
      As above, plus
      - If previous major thrombosis or severe pregnancy complications: LMWH throughout pregnancy (stop aspirin if bleeding complications)
      - If platelet count > 1500 $\times 10^9$/L: consider interferon (IFN)-α
      - If previous major bleeding: avoid aspirin and consider IFN-α to reduce thrombocytosis

* Severe pregnancy complications: ≥ 3 first-trimester or ≥ 1 second or third-trimester losses, birth weight < 5th centile of gestation, pre-eclampsia, intrauterine death or stillbirth.

Management of Thrombosis

Incidence and phenotype

Thrombotic events are a major cause of morbidity and mortality in PV and ET.[10] In one recent clinical trial in PV, the cumulative rate of cardiovascular complications ranged from 2.5% per patient-year in younger, asymptomatic subjects to 5.0% per patient-year in patients aged more than 65 years or with a history of thrombosis.[11] In other studies the corresponding figures for ET were 1.9% and about 3% per patient-year respectively in low- and high-risk patients.[3,12]

Large-vessel arterial events are the main cause of morbidity and mortality and include ischemic stroke, myocardial infarction and peripheral arterial occlusion. Lower extremity deep venous thrombosis and pulmonary embolism account for the majority of venous events. Both ET and PV have an unusual prevalence of intra-abdominal (hepatic, portal and mesenteric) vein thrombosis and are the most common (30-50%) identifiable cause of a thrombosis in this site. Young patients with MPD appear to be particularly vulnerable to this complication, so the search for underlying MPD should be part of the diagnostic work-up of splanchnic thromboses.[13] The recent identification of the V617F JAK2 mutation may be very helpful in diagnosing an occult MPD in these patients.[14,15]

Microcirculatory disturbances such as erythromelalgia and transient neurologic and visual symptoms are more characteristic of ET patients. Erythromelalgia presents with asymmetric erythema, congestion and burning pain in hands and/or feet that may progress to acrocyanotic ischemia and even gangrene. These manifestations are caused by recurrent occlusion of dermal vessels by platelet thrombi. Other symptoms such as recurrent headache and hearing symptoms have a more uncertain thrombotic nature. The criteria for the diagnosis of most of these disturbances are ill defined, which may explain the widely varying figures for the incidence of these phenomena reported in various studies.[3]

Mechanism and risk factors

A detailed discussion of the mechanisms underlying thrombotic complications in MPD is beyond the scope of this chapter, and the reader is referred to recent comprehensive reviews on this topic.[10,16,17] Multiple factors are likely to contribute, including increased red cell mass (in PV), platelet number perhaps, and activation of platelets and leukocytes and their interaction to form platelet-leukocyte aggregates. Recent studies have focused on the correlation between these putative pathogenic mechanisms and JAK2 mutational status and demonstrated increased platelets and leukocytes in ET patients with the V617F mutation.[18,19] In line with these new findings is the demonstration of a benefit of pan-myelosuppressive (hydroxyurea) over selective platelet-reducing therapy (anagrelide) in preventing thrombosis in ET[12] and the increased thrombotic risk of JAK2-mutated ET patients.[20,21] However, the association of JAK2 V617F mutation with thrombosis in ET was not confirmed in all studies.[22,23] In conclusion, further data are required to establish whether these and other molecular and cellular biomarkers can be considered reliable predictors of thrombosis in an individual patient.

Major risk factors for vascular complications in PV and ET are older age and previous thrombotic events.[11,24] These constitute the basis for risk-stratified myelosuppressive therapy.[25] Conventional risk factors for atherosclerosis, including hypertension, hyperlipidemia, diabetes and smoking, should be evaluated and, if present, managed aggressively in all patients.[3,26] The utility of inherited and acquired thrombophilia screening is debated. According to the British guidelines,[26] there is no current evidence to support routine thrombophilia screening in PV. However, Italian investigators recommended that ET patients with a family or personal history of thrombosis should be screened for congenital and acquired thrombophilic factors.[3]

Primary prevention

In all patients with PV, current guidelines recommend phlebotomy to keep the hematocrit within normal values.[25,26] An antithrombotic preventive strategy with low-dose aspirin is also indicated since a recent randomized clinical trial (ECLAP study) demonstrated the safety and the efficacy of this drug in PV.[6] The addition of cytoreductive drugs for primary prevention of thrombosis is suggested in older patients (> 60 years), those with poor control of the hematocrit by phlebotomy alone or with uncontrolled myeloproliferation, such as progressive leukocytosis or thrombocytosis or massive splenomegaly.[25,26]

In ET, primary prevention of thrombosis with myelosuppressive drugs is recommended in patients over 60 years of age or with platelet count in excess of 1500×10^9/L.[27] According to the Italian guidelines, patients between the ages of 40 and 60 years are also candidates for platelet-lowering treatment if their platelet count is over 1000×10^9/L and they have a cardiovascular risk factor such as smoking, arterial hypertension, hypercholesterolemia or diabetes mellitus, or familial thrombophilia.[3] Translating evidence from the ECLAP randomized trial in PV cited above,[6] low-dose aspirin can also be considered for primary prophylaxis of vascular events in ET. However, the risk:benefit ratio is less clear, because the expected incidence of thrombosis is lower than in PV and formal clinical trials assessing this therapeutic strategy have not been reported to date. Aspirin in asymptomatic patients with ET is not recommended by the Italian guidelines.[3]

Treatment of acute events and secondary thromboprophylaxis

Acute thrombotic events should be managed according to current guidelines.[28] However, thrombosis in unusual sites calls for particular comments (**Table 2**). Cerebral vein thrombosis requires anticoagulant therapy even in the presence of radiological signs of intracranial hemorrhage because these are considered secondary to the obstruction of

Table 2. Management of thrombosis in unusual sites.

Cerebral vein thrombosis[29-31]

Common presenting symptoms
- Severe headache (> 90% of cases)
- Paresis, aphasia
- Seizures, mental status disorder

Recommended diagnostic procedures
- Magnetic Resonance Imaging
- Angiography

Treatment
- Standard anticoagulant therapy*

Abdominal vein thrombosis (hepatic, portal, mesenteric)[15,32,33]

Common presenting symptoms
- Abdominal pain
- Hepatomegaly and ascites (in hepatic thrombosis)

Recommended diagnostic procedures
- CT scan
- Hepatic ultrasonography (in hepatic thrombosis)
- Angiography

Treatment
- Standard anticoagulant therapy*
- Invasive procedures if needed (in hepatic thrombosis)
- Liver transplantatiom if needed (in hepatic thrombosis)

Mesenteric artery thrombosis[38]

Common presenting symptoms
- Abdominal pain
- Nausea, vomiting, diarrhea

Recommended diagnostic procedures
- Angiography

Treatment
- Emergency treatment often needed
- Full heparinization
- Surgical procedures if needed

* Standard anticoagulant therapy: full heparinization followed by oral anticoagulation with PT INR range 2.0-3.0 (long-life ?)

the venous outflow.[29-31] Full-dose anticoagulation despite the high risk of gastrointestinal bleeding is also recommended for the acute management of portal and mesenteric vein occlusions. In a survey of the current outcome of portal vein thrombosis in 136 patients, 42 (31%) with a myeloproliferative disorder, anticoagulant therapy reduced the risk of recurrence or extension of thrombosis by two thirds without any real increase in the incidence or severity of bleeding.[32] In the Budd-Chiari syndrome, intensive medical management including anticoagulation is mandatory but more aggressive procedures, such as trans-jugular intrahepatic portosystemic shunt, angioplasty with or without stenting, surgical shunts, up to liver transplantation should be considered in the most severe cases.[33]

In ET, symptomatic patients presenting with microvascular circulation disturbances should be immediately treated with a loading dose of aspirin (300 to 500 mg per day) followed by a lower maintenance dose (100 mg per day).[34] Low-dose aspirin therapy (100 mg per day) is also recommended for patients with a recent major arterial vascular event (ischemic stroke, transient ischemic attack, peripheral arterial occlusion, myocardial infarction, unstable angina) or for whom there is clinical and laboratory evidence of coronary artery disease, provided there is no contraindication to antiplatelet therapy, such as previous clinically significant bleeding.[3]

The role of alternative antiplatelet agents, such as the ADP-receptor antagonists ticlopidine and clopidogrel, in MPD patients is still not clear.[10] These agents have an important role in the management of atherosclerotic (cerebral, cardiac and peripheral) vascular disease in the general population. However, there is little information on their use in MPD, and available data are too limited to form a basis for specific management recommendations.

For secondary prevention of VTE, warfarin is indicated with the aim of keeping PT INR in the conventional therapeutic range (2.0-3.0). Close clinical and laboratory monitoring has been recommended because of a potentially greater bleeding risk and unpredictable drug influences in MPD patients.[10] However, it is still not clear whether to give warfarin for 3-6 months, according to standard practice, or to continue with long-term prophylaxis, considering that MPD is an important persistent risk factor for thrombotic recurrences.

Table 3 summarizes our current management of thrombosis in MPD.

Management of Bleeding

Incidence and phenotype

Hemorrhage is both a less frequent and generally less severe clinical complication than thrombosis in patients with MPD. Untreated low-risk PV patients in the control arm of the ECLAP trial showed a rate of major and minor bleeding of 0.3 and 1.5 events per 100 persons per year, respectively.[6] Recent large prospective studies enrolling high-risk patients, mostly treated with hydroxyurea plus aspirin, reported rates of major bleeding of respectively 0.8 and 0.9 events per 100 persons per year in PV and ET.[11,12]

The main sites affected are skin, mucous membranes and gastrointestinal tract. Intracranial bleeding occurs rarely but can be severe and potentially fatal, requiring hospital admission. Intra-articular, retroperitoneal and deep intramuscular hematomas, like those seen in hemophilia, are distinctly unusual.[10]

Mechanism and risk factors

Hemorrhagic symptoms are more frequent in patients with platelet counts in excess of 1,000-1,500 $\times$ 10^9/L and this may be related to an acquired deficiency of von Willebrand factor (AvWS; reviewed in [10]). AvWS in MPD patients is characterized by the loss of large vWF multimers, which results in a functional defect of the protein, with increasing platelet counts. This is not restricted to MPD and has also been described in patients with reactive thrombocytosis, suggesting a primary effect of absolute platelet number as opposed to dysfunctional clonal platelets. Normalization

Table 3. How we manage thrombosis in myeloproliferative disease (MPD).

1. Risk stratification
   At least one of the following defines high-risk patients:
   - age above 60 years
   - previous major thrombotic complication
   - platelet count > 1500×10^9/L in ET
2. Therapy
   a) Primary prevention
   Low-risk patients
   - PV: Target hematocrit below 45% plus aspirin 100 mg/day
   - ET: aspirin 100 mg/day if cardiovascular risk factors

   High-risk patients
   As above, plus
   - Myelosuppressive therapy (see text)

   b) Acute events
   - Manage ongoing thrombosis according to current guidelines[30]
   - Aspirin 500 mg/day for acute microvascular symptoms in ET

   c) Secondary thromboprophylaxis
   - Aspirin 100 mg/day long-life after arterial or microvascular thrombosis
   - Warfarin, PT INR 2.0-3.0 (long-life ?) after venous thromboembolism
   - Myelosuppressive therapy (see text)

Abbreviations: ET, essential thrombocythemia; PV, polycythemia vera

of the platelet count was accompanied by restoration of a normal plasma vWF multimeric distribution and regression of the hemorrhagic tendency. However, the exact mechanism linking very high platelet count to AvWS is not known. A practical consequence of these observations is the recommendation to give prophylactic cytoreductive therapy to all ET patients whose platelet count is over 1500×10^9/L.[3] Qualitative platelet abnormalities in PV and ET have long been investigated and recently reviewed.[10,17] Unfortunately, there is a disappointing lack of clinical correlation with hemostatic complications, and these abnormalities have not been shown to have any relevant role in identifying patients at risk of bleeding.

Serious bleeding may be triggered by simultaneous antithrombotic therapy with anticoagulants or antiplatelet agents. These drugs should be avoided in patients with previous hemorrhagic events, AvWD or anatomical conditions with a high bleeding risk (e.g., gastric ulcers or esophageal varices secondary to abdominal vein thrombosis and portal hypertension). The combination of aspirin with anagrelide can increase the risk of bleeding, as shown in the PT1 clinical trial.[12] This finding may indicate a synergistic action of anagrelide with aspirin to impair platelet function. Anagrelide blocks platelet phosphodiesterase activity and some effects on platelet volume, chemistry and function have been reported.[35] Therefore, if anagrelide is used, concurrent aspirin therapy should be prescribed with caution.

Treatment

Treatment of bleeding events in MPDs should start with withdrawal of any concomitant antithrombotic therapy and correction of extreme thrombocytosis if associated with AvWS. This latter situation is usually treated with hydroxyurea but platelet pheresis may be indicated in an emergency.[10] Other potential measures include antifibrinolytic agents, such as tranexamic acid, but desmopressin or vWF-containing therapeutic products are of limited value.[10] Platelet transfusions have been rarely used, although the defective platelet function in MPDs may represent a rationale for their indication. The utility of recombinant factor VII has not been reported on in MPD patients with uncontrolled life-threatening bleeding and merits further study.[26] Occasional patients may present with a simultaneous occurrence of both bleeding and thrombosis: in such difficult cases, treatment should be based on the prevalent clinical symptoms and tailored on individual basis.

Management of Surgery

Patients with MPDs have an increased risk of morbidity and mortality when they require surgical procedures.[10] In a retrospective survey on the outcome of 179 surgical interventions in 64 patients with PV and 87 with ET, Italian investigators recorded 9 cases (5%) with postsurgery arterial thrombosis (1 myocardial infarction, 5 peripheral arterial thrombosis, 3 TIA), 9 (5%) with VTE, 15 (8%) with major hemorrhagic complications requiring transfusions and 4 (2.2%) surgery-related deaths within 3 months from the procedure (Ruggeri et al, submitted). Although it is conceivable that different types of surgical interventions may carry different risks of bleeding and thrombosis, the data in literature are too scanty to allow any stratification of patients.

A high-risk intervention is splenectomy, particularly when it is needed for the management of symptomatic splenomegaly because of portal vein thrombosis[36] or IMF. In one large series of patients with IMF,[37] perioperative fatal and nonfatal bleeding occurred in 4.5 and 14.5% of patients, respectively; fatal and nonfatal major thrombotic events were reported in an additional 1.3 and 7.2% and overall operative mortality was as high as 9%. Thrombocytopenia (platelet count < 100×10^9/L) was the only preoperative variable that was significantly correlated with postoperative thrombosis. Severe thrombocytopenia (platelet count < 50×10^9/L) and bone marrow hypocellularity or normocellularity were significantly associated with a worse perioperative survival.[37]

The optimal management of MPD during surgery is uncertain because of the lack of controlled trials. The appropriate control of erythrocytosis and thrombocytosis with phlebotomy and/or myelosuppression has been recommended.[10] Platelet count should be kept below 400×10^9/L, particularly when splenectomy is planned, because of the potential for postoperative extreme thrombocytosis. This may lead to the development or exacerbation of an

AvWD and associated hemorrhagic diathesis. Aspirin should be withheld for at least 1 week before elective surgery involving a high risk of bleeding or in which even minor bleeding could result in life-threatening complications, such as neurosurgery, or requiring heparin prophylaxis. The drug can be restarted 24 hours after stopping heparin.[3] LMWH at a prophylactic dose (4000 U s.c. starting 12 hours before surgery) is probably indicated in all patients with MPD because of the high thrombotic risk, although there are no prospective studies in this setting. Finally, these patients must be followed carefully for the paradoxical predisposition to both bleeding and thrombotic peri-operative complications.

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