Haematological malignancies in pregnancy: An overview with an emphasis on thrombotic risks

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Summary
With increase of maternal age, the incidence of haematological malignancies during pregnancy is rising and posing diagnostic and treatment challenges. Lymphoma is the fourth most common malignancy diagnosed in pregnancy; Hodgkin lymphoma is more frequent in pregnant women than non-Hodgkin lymphoma (NHL). The proportion of highly aggressive lymphomas in pregnant women is significantly higher than in non-pregnant women of reproductive age. Reproductive organ involvement is observed in almost half of pregnant women with NHL. The association of acute leukaemia and pregnancy is infrequent and it is assumed that pregnancy does not accelerate the disease course. Both cancer and pregnancy induce a procoagulant state which can lead to maternal venous thromboembolism (VTE) and placental occlusion. Pregnancy in woman with myeloproliferative neoplasms (MPN) promotes thrombotic environment, associating with an augmented risk of placental thrombosis, intrauterine growth retardation or loss and maternal thrombotic events. Haematological malignancies during pregnancy often require urgent diagnosis and management and are associated with potential adverse fetal outcomes. Most chemotherapeutic agents are teratogenic and should be avoided during the first trimester. Their use during the second and third trimesters may cause intrauterine growth restriction, premature birth and intrauterine fetal death. All chemotherapeutic drugs should be administered only after a detailed discussion with the patient and with close fetal monitoring. Chemotherapy and biological agents might also augment thrombotic risk. Guidelines for VTE prophylaxis in pregnant women with hematologic malignancies, apart from MPN, are currently unavailable, and therefore, clinical judgment should be made in each case.

Keywords
Haematological malignancy, pregnancy, hypercoagulability, venous thromboembolism, chemotherapy

Introduction
The diagnosis of cancer is established in about 0.1 % of pregnancies, making it the second most common cause of maternal death after gestation-related vascular complications. The majority of cases are associated with solid tumours, while haematological malignancies appear to be less frequent in this patient population (1, 2). Although uncommon, the incidence of cancer during pregnancy is rising with an increase in the maternal age. Haematologic malignancies during pregnancy present diagnostic evaluational and therapeutic challenges.

Thrombotic risk of pregnant women with cancer
Pregnancy-mediated hypercoagulability accounts for a four-fold increase in the risk of venous thromboembolism (VTE) during gestation, with this value rising to 20 folds immediately post-partum (3).

In a recently published retrospective population-based cohort study using the Health Care Cost and Utilization Project database from 2003 to 2011, a total of 2826 pregnant women with malignancies were identified in the cohort of about 8 million women. The VTE risk was found to be elevated in pregnant women with cervical cancer (odds ratio [OR] 8.64, 95% confidence interval [CI] 2.15–34.79), ovarian cancer (OR 10.35, 95% CI 1.44–74.19), Hodgkin lymphoma (OR 7.87, 95% CI 2.94–21.05) and myeloid leukaemia (OR 20.75, 95% CI 6.61–65.12), while no such increase was observed in women with brain cancer, thyroid cancer, melanoma or lymphoid leukaemia. These findings may suggest that thomboprophylaxis should be considered in pregnant women with haematological and gynaeological malignancies (4).

Cancer in pregnancy creates procoagulant environment which can lead to maternal VTE and placental occlusion, frequently manifested by preeclampsia, fetal growth restriction or loss, and...
placental abruption. Multiple gestation increases the risk even higher. The mechanisms of thrombogenicity could involve pregnancy-induced procoagulant activity, tumour adhesion to vascular endothelium, inflammatory cytokine and microvesicle generation (Table 1) (5).

The past decade has witnessed important advances in our understanding of the mechanisms involved in gestational vascular complications and cancer development during pregnancy.

Microvesicles (MVs), released from cell membranes upon activation or apoptosis, vary in their origin and may derive from tumour cells, monocytes, platelets, endothelial cells (ECs), and placental trophoblasts. MVs have been found to induce cell signalling that may lead to a variety of processes, including cell invasion, migration, proliferation, angiogenesis or apoptosis, which implies MV potential involvement in thrombosis, inflammation as well as vascular dysfunction in general (6), and gestational vascular complications in particular. MVs bearing tissue factor (TF), the main activator of the coagulation cascade, could play a role in both cancer- and pregnancy-associated thrombogenesis (7). Moreover, emerging evidence suggests that MVs may serve as biomarkers of disease dynamics in patients with haematological malignancies (8).

Heparanase is an endo-beta-D-glucuronidase capable to cleave heparan sulphate side chains of heparan sulphate proteoglycans on cell surfaces and extracellular matrix. It is reported to be highly expressed by the placenta and cancer cells leading to a significant increase in tissue factor (TF) levels. Heparanase, might also contribute to the procoagulant, proangiogenic state in pregnant women with cancer (9, 10).

### Haematological malignancies

Lymphoma is judged to be the fourth most common malignancy diagnosed in pregnancy, with an estimated prevalence of one in 6000 pregnancies (11, 12). Hodgkin lymphoma is more frequently observed in pregnant women than non-Hodgkin lymphoma (13, 14).

In a systematic review of published data on non-Hodgkin lymphomas in pregnancy, indolent lymphomas were found to be reported in 5%, aggressive non-Hodgkin lymphomas in 48%, and highly aggressive non-Hodgkin lymphomas in 47% of patients (15). Seventy-six percent of patients presented with stage IV disease. Reproductive organ involvement, including breast, ovary, uterus, and placenta, was reported in 49% of patients. Simultaneous involvement of several reproductive organs was observed in about a quarter of patients presenting with breast lymphoma and three quarters of those diagnosed with an ovarian disease. The six-month mortality rate was 34% for this population, and 53% of patients were alive at six months following the diagnosis of lymphoma. Overall survival was significantly lower in patients diagnosed and treated before the year 2000 compared with those treated after 2000, with six-month and 12-month overall survival rates of 42% and 36% vs 73% and 70%, respectively (95% CI 1.29–5.09, p=0.0076).

According to these findings, the proportion of highly aggressive lymphomas reported in pregnant women was significantly higher than their prevalence in non-pregnant women of reproductive age, in whom highly aggressive non-Hodgkin lymphoma accounted for less than 5% of cases (16–19).

The mechanisms responsible for the association between non-Hodgkin lymphoma and reproductive organs are not fully understood; however, the findings obtained might indicate a potential link between sex hormones and disease evolution in pregnancy-associated non-Hodgkin lymphoma. Other possible mechanisms could include involvement of MVs originating from vascular cells (ECs, trophoblasts), blood and tumour cells (7) and various activities of heparanase, which may open new therapeutic pathways (20–22).

The diagnosis of both Hodgkin and non-Hodgkin lymphoma has its own set of clinical challenges. Disease staging requires imaging studies, usually computerized tomography (CT) or positron emission tomography (PET) combined with CT; however, these tests should be avoided during pregnancy because of the risks of fetal exposure to radiation (12, 23). Chest radiography with abdominal shielding can be performed in pregnant women. Ultrasonography can also be used. Gadolinium-based contrast agents are known to cross the placental barrier, resulting in growth retardation and skeletal malformations in animals. The risk of gadolinium-based contrast agents for the fetus remains unknown and may be harmful; hence, they are not recommended at the early gestational stage and may be considered only in selected cases after the first trimester (24–26). While MRI without gadolinium may be used in pregnancy (24), its effects in the prenatal period have not been fully elucidated. Therefore MRI should be employed only when the results may influence treatment decisions (Table 2).

The association of leukaemia and pregnancy is infrequent. Its incidence is estimated at 1 in 75,000 to 100,000 pregnancies. Most leukaemias diagnosed during pregnancy, are reported to be acute:
two thirds are myeloid and one third are lymphoblastic (27). While the issue of interaction between gestation and leukaemia remains debatable, the majority of researchers assume that pregnancy does not accelerate the disease course (28–30).

Acute leukaemia is frequently diagnosed in the second and third trimesters of pregnancy (31, 32). The disease can engender leukostasis, thrombosis, and disseminated intravascular coagulation, that may be exacerbated by the pregnancy-associated hypercoagulability (33), ultimately adversely impinging on maternal and fetal outcomes.

In general, the risk of VTE in patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) is in the range of 5% (34), while coagulopathy of acute promyelocytic leukaemia (APL) is associated with thrombo-hemorrhagic manifestations (35, 36). The diagnosis of acute leukaemia requires urgent full-scale treatment, irrespective of gestational stage, since any delay or modification of therapy may aggravate the maternal prognosis (32, 37).

Myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), is a group of clonal haematological diseases (38), characterised by enhanced haematopoiesis and overproduction of mature differentiated blood cells. MPNs are associated with an increased risk for thrombotic and haemorrhagic complications. The JAK2V617F mutation, a distinctive feature of MPNs, is revealed in almost all PV patients and half of patients with ET and PMF (39).

The pathogenesis of thrombosis in MPN is complex and includes elevated haematocrit, thrombocytosis, an increased blood viscosity, abnormal platelet function and impaired adhesion of endothelial cells. A major risk factor for thrombosis is leukocytosis, accompanied with leukocyte activation (40).

Emerging data suggest JAK2V617F to play an important role in this pro-thrombotic process. JAK-2-activating mutation may bring about increased red cell adhesiveness through modification of surface adhesion molecules, facilitating thrombosis. Additionally, JAK-2 mutation may render platelet hyper-responsiveness, inducing an altered expression of CMPL signal transduction for thrombopoietin (TPO)-induced platelet priming (41). Carriers of this mutation displayed higher levels of TF and platelet-polymorphonuclear leukocyte (PMN)/platelet aggregates, than patients exhibiting a wild-type JAK-2 (42). In addition, plasma levels of soluble thrombomodulin (sTM) were increased in ET patients with JAK-2 compared to non-carriers (42), reflecting an endothelial damage observed in JAK-2 positive patients (43). It is noteworthy that in the non-pregnancy setting, an increased risk for thrombotic events has been reported in ET and PV patients with this mutation (44, 45), indicating the pathophysiological role of JAK-2 in the thrombotic tendency characteristic MPNs. The presence of JAK2 V617F mutation has been suggested to increase the risk of pregnancy loss (46). Heparanase protein forms a complex and enhances the TF activity resulting in elevated factor Xa production and ensuing activation of the coagulation system (47). JAK-2 involvement in heparanase up-regulation is suggested as erythropoietin increases, while JAK-2 inhibitors decrease the heparanase level and procoagulant activity (48).

Table 2: Lymphoma staging: safety of imaging studies during pregnancy.

<table>
<thead>
<tr>
<th>Imaging study</th>
<th>Safety</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>Yes</td>
<td>With abdominal shielding</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Computer tomography (CT)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Yes</td>
<td>Without gadolinium</td>
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It is noteworthy that about 20% of ET patients are in their reproductive age. The rise in the prevalence of MPNs during pregnancy may be attributed in part to the increasing age of pregnancy in the Western world and the growing use of sensitive diagnostic tools, particularly molecular ones, which may result in „over-diagnosis” (49). The conjunction of pregnancy with MPN promotes thrombotic environment, associating with an augmented risk of placental thrombosis, intrauterine growth retardation (IUGR) or loss, observed in almost one third of pregnancies, and maternal thrombotic events, particularly, deep-vein thrombosis (DVT) and preclampsia (PE) (50–53).

Indeed, an analysis of 461 cases of pregnancy-associated ET, conducted in three recent studies, revealed a significant elevation in fetal loss (51, 52, 54). Successful delivery was reported in 50–70% of women diagnosed with ET, while first-trimester fetal loss occurred in 25–40% and late pregnancy loss in 6–11% of cases. Placental abruption was reported in 3.6–4.5%, IUGR in 3–5% and preterm delivery in 8–12.8%. Maternal thrombosis and hemorrhage appeared to be less frequent.

PV was also found to have an adverse impact on both fetus and mother (50), with maternal morbidity and mortality approaching 50% in this group of patients. The most frequent complications included preclampsia, pulmonary emboli and severe postpartum haemorrhages.

Therapeutic approaches

Dilemmas associated with an urgent need to diagnose and manage a potentially lethal disease and concerns regarding adverse fetal outcomes may place physicians in a quandary.

Chemotherapy can inhibit the migration and proliferation of trophoblasts in first trimester human placental explants, which might partly explain the low birth weights of babies whose mothers received chemotherapy (55). Most cytotoxic drugs are 250–400 kDa and can therefore cross the placenta (56). Most chemotherapeutic agents are teratogenic, especially when administered in combination, and should be avoided during the first trimester. The use of these agents during the second and third trimesters may cause intrauterine growth restriction, premature birth and intrauterine fetal death (57). All chemotherapeutic drugs and especially the new, targeted therapies, should be administered only after a detailed discussion with the patient and her family,
and with close fetal monitoring. Chemotherapy and biological agents might also augment thrombotic risk. Asparaginase and methotrexate, therapeutic agents used for the management of acute lymphoblastic leukaemia, are associated with an increased incidence of vascular events. Low-molecular-weight heparins, which do not cross the placenta, are the drug of choice in pregnancy because of their efficiency and safety in women at risk (58). The effect of aspirin on prevention of VTE is limited, hence the drug is not recommended in women with haematological cancers. However, antiplatelet agents are useful for prevention of arterial thrombosis and are recommended in women with MPNs. The complex thrombohemorrhagic manifestations in acute promyelocytic leukaemia can be partly ameliorated by transfusion of platelet and blood products (35). Notably, the risk of intrauterine growth restriction associated with multiple pregnancy increases substantially in the presence of cancer due to increased maternal thrombogenicity and placental hypoperfusion. Moreover, management of haematological cancers often includes chemotherapeutic agents that might affect placental trophoblasts, resulting in fetal growth restriction.

Women with MPN at highest risk for pregnancy-related complications are those who experienced a prior thrombotic or haemorrhagic event and those who had MPN-related complications in prior pregnancies, e.g. unexplained recurrent first-trimester loss, intrauterine growth restriction, intrauterine death, stillbirth, placental abruption, severe preeclampsia (necessitating preterm delivery <34 weeks) or significant ante- or post-partum haemorrhage. A sustained elevation in platelet count, up to $1,500 \times 10^9/l$, also indicates a significantly higher risk for pregnancy-associated complication.

In the lack of prospective studies in pregnancy, the European LeukaemiaNet has recently published consensus-based recommendations, providing treatment-tailored approach, adopted to women specific risk factors (59). The recommended management of all MPNs pregnant women includes aspirin, venesection for those presenting with a haematocrit level higher than 45%, and prophylactic LMWH after delivery, continued for six weeks. Patients fulfilling the mentioned above criteria of being at a remarkably high risk for complication during pregnancy, need to take extra-precautions, and should be managed more vigorously. Women who experienced a major thrombotic event or a significant complication during prior pregnancy should receive LMWH, started at first trimester, in conjunction with aspirin, and continued throughout gestation (aspirin should be stopped in case of bleeding complications).

Interferon alpha should be considered in women whose platelet count remains higher than $1,500 \times 10^9/l$, and those reporting on a previous major bleeding in the presence of a relatively high platelet count, in whom aspirin should be avoided.

According to the Italian guidelines and expert judgment (52, 54), the candidates for platelet-lowering drugs are women with a previous history of major thrombosis or major bleeding, or when the platelet count is greater than 1,000 to $1,500 \times 10^9/l$, or when familial thrombophilia or cardiovascular risk factors are documented.

Guidelines for VTE prophylaxis in pregnant women with haematologic malignancies, apart from MPN, are currently unavailable, and therefore, clinical judgment should be made in each case.

**Conclusion**

Haematological malignancies in pregnancy, albeit uncommon, have a major effect on maternal and fetal health. Paucity of data hampers advance in diagnostic and therapeutic approaches in this clinical setting. Collaborative studies, prospectively exploring the biological, clinical and therapeutic aspects of pregnancy-associated malignancies are highly warranted.

**Conflicts of interest**

None declared.

**References**


