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# Chronic myeloid leukemia in pregnancy: an absolute contraindication to neuraxial anesthesia?

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**ABSTRACT**
Chronic myeloid leukemia is rare in pregnancy with an estimated incidence of 1:75 000. It is a genetic myeloproliferative disorder marked by increased and unregulated growth of myeloid cells in the bone marrow. The terminal phase of chronic myeloid leukemia may develop into a blast crisis, defined as >30% myeloblasts in the circulation. A blast crisis resembles an acute leukemia and is associated with rapid clinical deterioration and short survival. Targeted gene therapy with tyrosine kinase inhibitors is effective in treatment but when these agents are discontinued, as in pregnancy, the patient may relapse and blast cells may enter the circulation. Theoretically, a central nervous system blast crisis may be induced by inadvertent intrathecal seeding of circulating blast cells, and is associated with a high mortality rate and a median life expectancy of three months. We describe the anesthetic management of a patient with chronic myeloid leukemia and blast cells in the circulation who required cesarean delivery. After considering the potential anesthetic risks and benefits, general anesthesia was chosen. Although an iatrogenic central nervous system blast crisis is extremely rare, the high morbidity and mortality associated with such an event should be considered when formulating an anesthetic plan.


***Keywords***: Chronic myeloid leukemia; Cesarean delivery; General anesthesia

## Introduction

Chronic myeloid leukemia (CML) is rare in pregnancy with an estimated incidence of 1:75 000[1]; 10% of cases of CML occur in women of childbearing age.[2] A low incidence limits the development of robust anesthetic guidelines. Chronic myeloid leukemia is linked to the Philadelphia chromosome, a translocation between the long arms of chromosomes 9 and 22. Atypical translocations are also found in 5–8% of cases.[3] The Philadelphia chromosome produces the breakpoint cluster region, Abelson leukemia (BCR-ABL) gene, a tyrosine kinase, which leads to unregulated growth of myeloid cells in the bone marrow. The course of CML may be divided into three phases: a chronic phase, an accelerated phase, and a terminal phase. The terminal phase can develop into a blast crisis, defined as >30% myeloblasts in the circulation, which may resemble an acute leukemia and is associated with rapid clinical deterioration and short survival.

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Diagnosis of CML is made via peripheral blood smear with leukocytosis and increased immature cells of the myeloid cell line. The Philadelphia chromosome can be detected through cytogenetic analysis of bone marrow cells. Symptoms and signs of CML are non-specific and include fatigue and weight loss. A patient may develop bleeding, petechiae and fevers in the acute phase. The introduction of gene targeted therapies, tyrosine kinase inhibitors (TKIs), in 2001 has dramatically improved the prognosis of CML patients.[4,5] The only curative treatment for CML remains allogeneic stem cell transplantation, which is associated with significant morbidity and mortality.[6] The ultimate goal is to terminate myeloproliferation through targeted elimination of cells with the mutant BCR-ABL gene.

Treatment of CML during pregnancy is particularly difficult, because effective drugs, including TKIs, are teratogenic in animal models. Given the improved life expectancy with targeted drug therapies, anesthesiologists are likely to encounter more patients with CML. An anesthetic, obstetric and hematological plan for delivery should be established at the earliest opportunity.

## Case report

A 32-year-old grand multiparous G8P7 woman with dichorionic-diamniotic twins presented to our antenatal high-risk anesthetic clinic at 34 weeks of gestation, the day before a scheduled cesarean delivery. She had CML which had been diagnosed 11 weeks before becoming pregnant. She had initially started dasatinib, a TKI, which controlled CML and resulted in normal white blood cell (WBC) counts. She discovered her pregnancy at eight weeks of gestation. Dasatinib is a pregnancy category D drug. It was replaced with interferon-alpha (IFN-α), a pregnancy category C drug which is a glycoprotein with anti-proliferative properties, to reduce the risk of spontaneous abortion. Interferon-alpha, is thought to undergo minimal placental transfer due to its high molecular weight.[6,7] The change in CML medication regimen led to a steady increase in WBC count up to $121 \times 10^9$/L (Fig. 1), including 2% circulating blast cells, and thrombocytosis with a platelet count exceeding $>660 \times 10^9$/L. In view of the accelerated disease progression, a decision was made by the hematologist and obstetrician to schedule cesarean delivery at 34 weeks of gestation after which TKI therapy could be restarted.

The literature on CML in pregnancy is limited, but highlighted the theoretical risk of an inadvertent central nervous system (CNS) blast crisis. This may arise through dural puncture with introduction of blast cells, or a traumatic puncture of the epidural plexus. Regardless of the mechanism, a CNS blast crisis is associated with both poor prognosis and response to treatment. In our patient, who had a normal airway examination and elevated blast cells in the circulation, general anesthesia appeared the safest option.

In addition to the quantitative laboratory assessment of coagulation profile, a rotational thromboelastometry (ROTEM) sample was also measured to assess coagulopathy. Normal pregnancy is associated with a hypercoagulable profile: an increase in maximum clot firmness and early clot amplitude at 5 and 15 min in the ROTEM extrinsic coagulation profile (EXTEM), intrinsic coagulation profile (INTEM), and fibrinogen profile (FIBTEM) are expected during the second and third trimesters of pregnancy.[8] Our ROTEM analysis

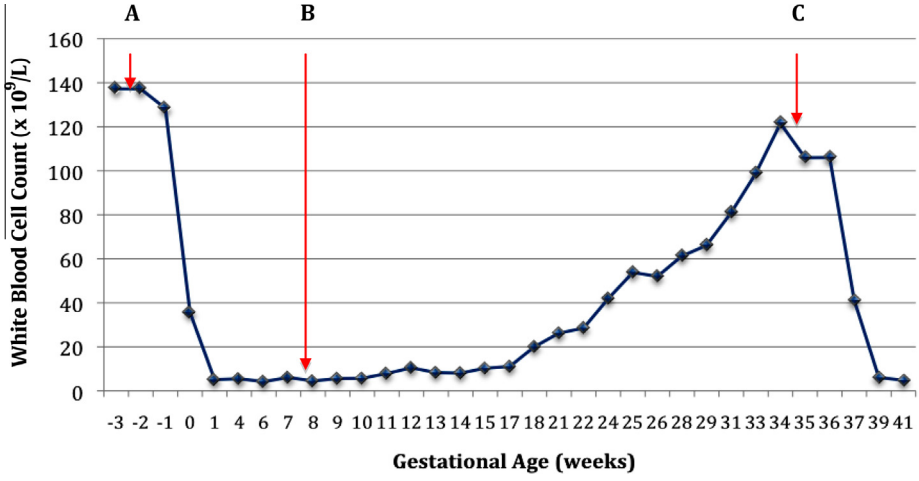


**Fig. 1** Patient's WBC count from CML diagnosis to post-delivery. *Point A* indicates patient's CML diagnosis, three weeks before conception. Dasatinib is commenced and reduces patient's WBC count. *Point B* reveals the transition from dasatinib to IFN-α during pregnancy, upon confirmation of patient's pregnancy at eight weeks of gestation, leading to a gradual increase in WBC. *Point C* demonstrates the resumption of dasatinib therapy after cesarean delivery at 34 weeks of gestation, causing a reduction in WBC to pre-pregnancy values.