

# Leukemia During Pregnancy

## Abstract

Leukemia affects approximately 1 in 10000 pregnancies. Women with leukemia have nonspecific symptoms and some of them could also be attributed to pregnancy. Antineoplastic chemotherapy uses cytotoxic agents with potential adverse effects on the fetus, especially in the first trimester causing malformations or weight gain restriction in the second and third trimester and delay in neurological development during all the pregnancy, but if the therapy is delayed until birth the prognosis for the mother is critical. During pregnancy, it is important to take into account the metabolic changes associated with pregnancy that could impact the bio distribution and drug clearance. The damage in the fetus is correlated with the time of exposition and the fetus is most vulnerable during organogenesis phase. Although chemotherapy has effects in the fetus, there are reports of cases with successful pregnancy. It is necessary to study the relation among chemotherapy, the leukemia and the fetus in long term studies where the fetus has been exposed to chemotherapy agents and is reported with normal characteristics at birth.

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## Introduction

Cancer and pregnancy, together constitutes a problem, life-saving chemotherapy for the mother is life-threatening concerns for the developing fetus. Until recently the treatment was the pregnancy interruption. Nowadays, doctors need to face this problem, taking into account the different aspects of the disease, including therapeutic alternatives and maternal and fetal risks.<sup>1</sup> Cancer rarely affects the fetus directly.

The incidence of cancer during pregnancy is uncommon; incidence is about 1 out of 1000 pregnancies. The most common diagnosed types of cancer in pregnant women are: breast and cervical cancer, melanoma, leukemia and lymphoma.<sup>2</sup> Although leukemia is the most common type of cancer worldwide, the current incidence during gestation is not well known.<sup>3</sup> It has been proposed that it affects approximately 1 in 10, 000 pregnancies. Most of these leukemias are acute and predominantly myeloid.<sup>4</sup> During pregnancy 23% of acute leukemias are diagnosed within the first trimester of pregnancy, 37% in the second trimester and 40% in the third trimester. Unfortunately, women with cancer have nonspecific symptoms such as fatigue, weakness, dyspnea, pallor, anemia, leukocytosis, thrombocytopenia which also are attributed to pregnancy.<sup>3</sup>

The diagnosis of a disease such as leukemia in pregnancy is more complicated than in non-pregnant women, since anemia and thrombocytopenia are common in pregnant women; If neutropenia is found it should be suspected and monitored. In the presence of circulating blasts, a bone marrow biopsy should be performed. The diagnostic criteria for leukemia in pregnant women are the same as for the normal population

## Interaction of leukemia in pregnancy

The treatment of leukemia during pregnancy requires a multidisciplinary team management and accompaniment, including an oncologist, obstetrician, hematologist, neonatologist and a psychologist. Chemotherapy uses cytotoxic agents with potential adverse effects on the fetus, if the therapy is delayed it affects the prognosis of the mother. The fetus is especially vulnerable when is exposed during organogenesis (weeks 2-8), and after this 0 phase the eyes, genitals, hematopoietic system and Central nervous system are vulnerable.<sup>5,6</sup>

During pregnancy occur many physiological changes in the mother such as an increased plasma volume, the presence of amniotic fluid, hepatic oxidation, and alterations in renal clearance, all of them can affect drug distribution, metabolism, and excretion.<sup>7,8</sup>

However, it should be emphasized that pregnancy alone does not have an adverse effect on the disease, although estrogen receptors have been found in leukemic cell lines.<sup>9</sup> Like a HL-60, which is an estrogen receptor localized in the plasmatic membrane of human myeloblastic leukemia cells, whose expression occurs throughout the cell cycle, progressively increasing as cells mature from G1 to S to G2/M.<sup>10</sup>

The Leukemia increases the risk of susceptibility to infections, cytopenia and autoimmune phenomena. Infectious episodes constitute a serious maternal and fetal risk, and not all antibiotics can be safely administered during pregnancy. It is very important to evaluate the presence of cytomegalovirus and herpes virus, because of the increased risk of reactivation during leukemia and the potentially catastrophic neonatal complications.<sup>11</sup>

Cytopenias may also lead to a severe event, including infection and bleeding. In the setting of marrow failure, erythrocyte and platelet transfusions should be used to maintain a hemoglobin level of ~10 g/dL and the platelet count of >50–100 × 10<sup>9</sup>/L (with close monitoring of platelet level at the delivery time).<sup>11</sup>

Pregnant patients with acute promyelocytic leukemia (APL) should be under careful surveillance, given that common manifestations of APL are pancytopenia, disseminated intravascular coagulation and hyperfibrinolysis, which represent a medical emergency.<sup>12</sup> The chemotherapy during the first trimester increases the risk of spontaneous abortion, fetal malformation, fetal death.<sup>13</sup> When the diagnosis of leukemia is made in the first trimester and elective termination of pregnancy should be considered. During second and third trimester chemotherapy rarely causes congenital malformation, but the risk for prematurity, fetal growth restriction, neonatal neutropenia and sepsis.

## Cancer treatment during pregnancy

One of the most important problems of cancer during pregnancy is the treatment, due to the effects that can have on the fetus. These effects are influenced by the time and frequency of drug exposure and their ability to cross blood-brain and placental barriers (Table

1). In addition to the impact of the treatment, the prognosis depends on the diagnosis and the gestational stage.<sup>14</sup> No pharmacokinetics studies have been done in pregnant women receiving chemotherapy. The doses that a pregnant woman receives are weight-based doses similar to non-pregnant women. During pregnancy the blood volume increases (almost 50%), renal clearance increases and consequently the drug concentration might decrease. In pregnant woman is important to take into account the hormonal changes and the metabolic changes associated with pregnancy.

It is necessary to contemplate the possible interruption of the pregnancy during the first trimester when it is indispensable to give an immediate treatment, the abortion does not affect the disease or

the treatment results of leukemia.<sup>15</sup> Since the use of chemotherapy during the first trimester is associated with congenital malformations. Chemotherapy during the second and third trimesters, it is not associated with significant physical fetal defects.

Chemotherapy inhibits the migration and proliferation of trophoblast in first trimester human placental explants, which might partially explain the lower birth weights of infants whose mothers received chemotherapy.<sup>16</sup>(Table 2). The trophoblast corresponds to the outer layer of the blastocyst and contributes to the mechanism of implantation in the endometrium and the formation of the placenta.<sup>18</sup> It is important to mention that chemotherapeutic agents interrupt vital cell functions during different phases of the cell cycle.

**Table 1** Effects of chemotherapy during pregnancy

Gestational stage	Effects
First trimester	Spontaneous abortion, Organogenesis
Second and Third trimester	Growth Restriction, Intrauterine death or Neonatal death, Prematurity and Myelosuppression

**Table 2** Shows the guidelines for the European Society for Medical Oncology Clinical Practices for managing leukemia during pregnancy according to trimester<sup>17</sup>

Types of Leukemia	First Trimester	Second Trimester	Third Trimester
Acute leukemia	Abortion	Induction therapy with doxorubicin and cytarabine	Induction of labour and subsequently, initiation of therapy
Acute promyelocytic	Abortion	Doxorubicin and All Trans-Retinoic Acid	Induction of labour and subsequently, initiation of therapy
Chronic myeloid leukemia	Interferon-alpha	Interferon-alphaorimatinib	Interferon-alphaorimatinib

Pregnancy can affect the metabolism of drugs due to the creation of a third space by the presence of the amniotic sac. Also, there are some changes in liver metabolism and renal excretion. Some articles have identified drugs that can be harmful during the pregnancy<sup>4</sup> (Table 3). During pregnancy and leukemia women should undergo to a series of studies, some procedures are safe during all the pregnancy, but some

others may have negative consequences for the mother, the fetus or both<sup>19</sup> (Table 4). Women receiving chemotherapy are at increased risk of sepsis. Changes in the immune system *per se* make women more susceptible to infection. During chemotherapy patient could present chemotherapy induced anorexia, then it is also important to observe the maternal nutritional deficiencies.

**Table 3** Different drugs, the mechanism of action and its reported consequences in pregnancy

Name	Mechanism of action	Relation with pregnancy
Imatinib	Tyrosine kinase inhibitor, blocks proliferation and induces apoptosis. <sup>20</sup>	It has been related to some foetal abnormalities and miscarriage. Teratogenic in rats. <sup>24</sup> Some authors suggest that imatinib can be safely administered during all the pregnancy, but further studies are needed to prove the safety during the first trimester. <sup>20</sup>
Nilotinib	Tyrosine kinase inhibitor, blocks proliferation and induces apoptosis. <sup>20</sup>	Studies in animal models suggests that nilotinib is related to mortality, abortion and decreased gestational weights at a dose of 300mg/kg/d Some authors consider Nilotinib is not teratogenic factor, some authors have shown successful pregnancies. <sup>20</sup>
Retinoic acid	Involved in the regulation of the transcription of target genes that control cellular proliferation, differentiation, and apoptosis. <sup>25</sup>	Teratogenic effects (craniofacial alterations, neural tube defects, cardiovascular malformations, and thymic aplasia, <sup>16</sup> ), especially during the first trimester. Miscarriages (40% of the cases). During the second and third trimester of pregnancy has a lower risk of teratogenic effects.
Hydroxyurea	Inhibit the DNA synthesis. <sup>3</sup>	In rats, has demonstrated to increase the risk of teratogenic effects. <sup>16</sup> . Some articles refer that can cause abortion, intrauterine growth retardation and congenital malformation, but does not specify in which trimester. <sup>26</sup> . It is recommended to avoid cytarabine during all the pregnancy.
Cytarabine	Antimetabolite, which means that acts as a false substrate for reactions required in DNA replication and RNA synthesis. <sup>7</sup>	During the first trimester may cause severe limb malformations. During the second and third trimester is related with transient cytopenias, intrauterine fetal death, intrauterine growth retardation and neonatal death from sepsis and gastroenteritis. <sup>16</sup>

Table Continued...

Name	Mechanism of action	Relation with pregnancy
Methotrexate	Antimetabolite, which means that acts as a false substrate for reactions required in DNA replication and RNA synthesis. <sup>7</sup>	As most of the drugs, should be avoided during the first trimester of pregnancy. If necessary, it can be used during the second and third trimester. Authors don't specify what complications for the mother or the fetus could exist. <sup>16</sup>
Rituximab	Antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and induction of apoptosis are the mechanisms of actions of rituximab. <sup>27</sup>	Lower risk of teratogenicity than other drugs, but it should be avoided during the first semester of pregnancy. Some authors unveiled that Rituximab can be safer than other drugs during the second and third trimester of pregnancy. <sup>16</sup>
Thalidomide and Lenalidomide	Immunomodulation, anti-inflammatory, inhibits the anti-apoptotic effects, anti-angiogenic effects by inhibiting interleukin-6 (IL-6) and tumor necrosis factor $\alpha$ (TNF $\alpha$ ) production, release, and signaling, enhancement of natural killer (NK) and T cell-mediated cytotoxicity. <sup>27</sup>	Teratogenic, should be avoided during all the pregnancy. <sup>16</sup>

**Table 4** Radiological studies and its effects on pregnancy

Radiological Study	Effects on Pregnancy
Core Needle or Excisional Biopsies and Bone Marrow Biopsy	Safe
Ultrasonography	Safe
Computed Tomography (CT) and Positron Emission Tomography	Carcinogen, teratogen or spontaneous abortion
Magnetic Resonance Imaging (MRI) and Gadolinium	Magnetic resonance imaging (MRI) can be safely used during the second and third trimester of pregnancy only if it is strongly indicated, given that the procedure still represents a risk for the fetus. Gadolinium of contrast: can cross the placenta and affect the fetus development, producing malformations and growth restriction. Iodinated contrast can cross the placenta and can produce thyroid function depression.

### Postpartum effects

Chemotherapy should not be given in the last weeks of pregnancy to avoid the delivery without the recovery of bone marrow. During the delivery in a patient with leukemia is necessary to take into account some complications since thrombocytopenia can make a caesarean or vaginal delivery dangerous due to excessive bleeding. Severe anemia can complicate the delivery of oxygen to the fetus. Also obstetric infections can be serious if neutropenia is present,<sup>30</sup> which is why the administration of chemotherapy should be interrupted 3 weeks before the delivery,<sup>31</sup> to allow the fetal drug excretion via placenta, reducing the risk of neonatal myelosuppression.

Planned delivery is preferable to allow timely administration of chemotherapies. If a cesarean section is necessary in neutropenic or thrombocytopenic woman. Once the baby is born, it must be considered

that breastfeeding should start 2 weeks after the administration of the last chemotherapy, due to the toxicity of the chemotherapeutic agents<sup>4</sup> because the drugs can be secreted through breast milk (although to a lesser extent). Once chemotherapy is completed, woman should wait between 6 months and 2-5 years to allow the oocytes to recover from the damage caused by the treatment, only if she wishes to return to pregnancy.<sup>32</sup>

### Stories of success

Successful chemotherapy treatments during second and third trimester are well documented and delivery of non-malformed healthy babies are reported. Particular consideration needs to be given, however, to balancing the risk of fetal prematurity and risk of fetal chemotherapy exposure later in the third trimester (Table 5).

**Table 5** Successful pregnancies in patient with different types of leukemia

Type	Age (years)	Weeks of Detection	Treatment
CML <sup>15</sup>	30	7.4	Imatinib and Nilotinib.
ALL <sup>2</sup>	22	26	Intravenous HyperCVAD(cytoxan, vincristine, adrimycin, dexamethasone).
CML <sup>23</sup>	22	0	Hydroxyurea the first 6 months (2g/day). Then Imatinib (400mg/day). After that, imatinib was suspended and IFN- $\alpha$ remained during all the pregnancy.
CML <sup>24</sup>	32	October 1996	IFN- $\alpha$ .
CML <sup>24</sup>	30	7	IFN- $\alpha$ .
CML <sup>24</sup>	23	8	IFN- $\alpha$ Hydroxyurea.
ALL (L2) <sup>25</sup>	26	22	Not possible due to low platelet count
ALL <sup>26</sup>	22	16. October 1981	Vincristine (2g/week) Prednisone (65 mg/day/3 weeks) 6-mercaptopurine
AML <sup>27</sup>	38	20	Daunorubicin (120mg/day) AraC (160mg/day) Thioguanine Ara C
AMOL <sup>27</sup>	29	25	Thioguanine Daunorubicin Mitoxantrone

Table Continued...

Type	Age (years)	Weeks of Detection	Treatment
AML <sup>28</sup>	28	20	Ara C Thioguanine Daunorubicin Mitoxantrone
AML <sup>29</sup>	34	27	Thioguanine Cytosine arabinoside Daunorubicin

CML: Chronic Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; IFN- $\alpha$ : Interferon alpha; AL: Acuteleukemia; AMOL: Acutemonocyticleukemia; AML: Acutemyeloidleukemia

### Fertility in women survivors

With the increase in post-treatment survival, effects that were previously not considered, such as infertility, are being presented. Clinically, there is amenorrhea accompanied by elevation of Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH), in addition to a decrease in serum estradiol, an atrophy of the vaginal epithelium and endometrial hypoplasia occurs (simulating menopausal symptoms).<sup>3</sup>

Young patients, have the ability to tolerate high doses of chemotherapy drugs, also they have a higher probability of menstruation returning.<sup>5</sup> Oncological treatment can also affect patient's fertility, causing infertility, this will depend on dose (high dose is likely to have more profound effects on fertility than lower doses); some drugs are extremely toxic and the effects may depend on age (women administered chemotherapy under 40 years-old have a much higher chance of regaining the normal ovarian function, however, women over 40 years-old will have an early menopause by decreased ovarian reserve.<sup>33</sup>

Conchon et al.<sup>15</sup> reported the case of a woman who became pregnant twice during her chronic myeloid leukemia treatment shows that it could be possible that nilotinib treatment does not affect significantly the fertility of a woman, but more evidence is needed to prove that nilotinib does not cause infertility.<sup>15</sup>

When there is no complete remission of the disease, pregnancy should be avoided; however, cases have been reported where both the first and the second product of pregnancies in a woman with chronic myeloid leukemia are totally healthy, even when the disease has not been eliminated.<sup>15</sup> Nowadays, the association between pregnancy and a relapse of leukemia remains uncertain.<sup>32</sup> Advising on contraception and family planning constitutes a preventive measure in order to avoid disease complication.

Brenner et al.<sup>33</sup> recommended avoidance of pregnancy for at least 2 to 3 years after finishing the treatment, in order to confirm a durable remission. Patients who have undergone treatment and are planning pregnancy need information regarding the risk of disease progression during pregnancy, the possibility to treat the disease during pregnancy and the potential fetal side effects of the treatments.<sup>33</sup>

### Discussion

The relationship between leukemia and pregnancy is not well understood, and to comprehend it, it is necessary to evaluate all the areas that impact the disease and that involve the pregnancy as the emotional aspect, health, as well as the molecular mechanism involved, to determine what is better for the mother and the child. Pregnancy presents many physiological and metabolic changes, many of the symptoms associated with these changes are common also in leukemia, so the diagnosis can be delayed.

The therapeutic approach of leukemia during pregnancy is an ethical-medical decision with a lot of controversy. Doctors and patients should work together to take the best decision for the mother and fetus, the type and stage of the disease is crucial to take the best treatment decision. Each case is specific; it should be evaluated the trimester, the mother's general health condition, the access to different treatment to decide the best therapeutic decision. Actually, there are reports of cases in which a viable product has been obtained despite the use of chemotherapy, but this depends on the trimester, during the first trimester the risk of fetal or obstetric complications increases and it is recommended to conclude the pregnancy because chemotherapy is associated with serious malformations, the earlier the diagnosis of leukemia in pregnancy, the higher perinatal mortality. For some drugs data exist only for animal models, but almost all chemotherapeutic agents are teratogenic. Cancer treatment knowledge advances more rapidly than the safety chemotherapy data in pregnancy, before new agents are used caution should be warranted, even if the drug used is from the same class as other agents with demonstrated safety.

Postpartum both the baby and the mother should be monitored to rule out the adverse effects of chemotherapy or treatment sequelae. Leukemia during pregnancy is not so well known, the available data are limited and contradictory, more studies are necessary to better understand the behavior of pregnancy al leukemia together, and make possible more successful cases.

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### Conflicts of interest

None.

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