Chemotherapy and Pharmacology for Leukemia in Pregnancy

Guidelines and Strategies for Best Practices

Carolina Witchmichen Penteado Schmidt
Kaléu Mormino Otoni
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Preface

One of our great challenges as health professionals in hematology is that we already work with a particular group of patients that requires specialized knowledge. This group of hematological patients is already individualized among the various hematological diseases. Even when we identify the type of leukemia in patients, their genetic conditions, and the risk group they belong to, they can yet be part of an even more restricted group: that of pregnant patients.

Professionals who work with leukemia diagnosis and treatment race against time, and when a patient requires greater care, the lack of widely defined and well-standardized protocols makes the work of these professionals difficult, and it reflects in the health of both patients: mother and fetus. As there is little data on the treatment of leukemia during pregnancy, Kaléu and I decided to edit this book to save time for professionals involved in the care of pregnant women with leukemia. We gather a great team that includes pharmacists in pediatrics, oncology, hematology, clinical pharmacy, and pharmacovigilance; physicians in hematology, obstetrics, gynecology, infectious diseases, and palliative care; in addition to researchers. Our team of specialists gathered and curated the available information in addition to making it as transparent and practical as possible for daily use.

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Author of the Springer books: *Hematopoietic Stem Cell Transplantation for Pharmacists: The Gold Standard to Practice*; *Pediatric Oncologic Pharmacy: A Complete Guide to Practice*; *Chemotherapy in Neonates and Infants: Pharmacological Oncology for Children Under 1 Year Old*; and *Drug Therapy and Interactions in Pediatric Oncology: A Pocket Guide*. Author of various children's books about cancer, including the award-winning *Chubby's Tale: The true story of a teddy bear who beat cancer* and the best-selling book *Bald is Beautiful: A letter for a fabulous girl*.

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Chapter 1
Introduction

Gustavo Alves

1.1 Introduction

Statistics on the frequency of malignant diseases in pregnant women points to 1 in 1000 cases. The incidence of leukemia in pregnant women can vary from 1 in 75,000 to 1 in 100,000 cases, and acute leukemia represents the majority of leukemia cases during pregnancy. Immediate treatment is essential for acute leukemia cases, even with the risks involving pregnancy; if not treated immediately, the risk of maternal mortality is increased [5]. In summary, avoiding the risks of chemotherapy in the first trimester and postponing postpartum treatment is not a preferable strategy [1–4].

From the physiological point of view, a pregnant woman's body naturally undergoes changes during pregnancy, which makes the diagnosis of leukemia even more difficult. There is a great risk that this diagnosis may be delayed or even neglected for some time, as some common symptoms of pregnancy may be mistaken for symptoms of leukemia. We can highlight fatigue, shortness of breath, and weakness in general as the most important symptoms. In addition, anemia and leukocytosis may be present in pregnancy at the same time as they are considered common findings in leukemia [6]. All the time lost in effective diagnosis can cause a great loss in the treatment and quality of life of the patient.

As previously stated, the diagnosis of leukemia is not simple, requiring morphological, immunophenotypic, and cytogenetic evaluations of bone marrow samples. A bone marrow biopsy is performed safely under local anesthesia only in pregnant

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women, a simple procedure performed without causing any harm to the fetus, obviously being careful not to pose a risk of infection [6].

1.2 Ethical Dilemmas

Many ethical dilemmas can be observed in issues related to the treatment of any disease in a pregnant woman, starting with the safety of the drugs used, since in most cases, teratogenic events are only recognized and evaluated after the occurrence of damage caused. In general, some choices must be made, always aiming at the preservation of human dignity and considering the presence of one or more fetuses. Using a drug with potent antitumor action on a pregnant woman will trigger unmanaged and managed consequences.

1.3 Multidisciplinary Team

The Leukemia during pregnancy is in itself a medical emergency, due to its progression and rapid progress, and requires redoubled attention. The work of the multidisciplinary team is important because in addition to neonatologists and pediatricians, it will gather oncologists, hematologists, social workers, psychologists, and pharmacists, among others. Since diagnosis to treatment, the patient plays a fundamental role in deciding [7] whether to adopt a more conservative therapy or risk all the more for therapeutic success.

1.4 Statistics and Concept

1.4.1 United States of America

In the United States, monitoring of disease-related indices and other health impact indices are very effective, often serving as a basis for epidemiological studies and assessments, even to other countries. Regarding the number of new cases and mortality rates per 100,000, the following numbers were calculated:

The number of new cases of leukemia was 14.1 per 100,000 men and women per year. The rate of deaths was 6.5 per 100,000 men and women per year. These rates are age-adjusted and based on 2012–2016 cases and deaths. Approximately 1.6% of men and women will be diagnosed with leukemia at some point during their lifetime, based on 2014–2016 data. Prevalence of Leukemia: In 2016, there were an estimated 414,773 people living with leukemia in the United States [8].

In Brazil (INCA 2018) [9]:

- Estimates of new cases: 10,800
- 5940 men
- 4860 women
- Number of deaths: 6837
- 3692 men
- 3145 women

Leukemia is a disease of unknown origin with white blood cells of malignant character. Its main feature is the accumulation of leukemic cells in the bone marrow, replacing normal cells. In the bone marrow, cells are produced, giving rise to white and red blood cells. In patients with leukemia, these blood cells that have not yet matured will mutate into cancer cells. There is then a process of gradual replacement of normal cells with cancer cells [9].

In a pregnant woman, the damage caused by leukemia, regardless of type, is enormous, even greater than in an adult individual. This process occurs because homeostasis, common in pregnant women, is a balance point for metabolism, energy expenditure and cell multiplication. Any damage in this physiological condition brings exponential damage that may also extend to the fetus.

1.4.2 Risk Factors for Leukemia

It is not possible to clearly and accurately determine all risk factors as well as causes for leukemia; however, it is known, that benzene and ionizing radiation are determining environmental factors for acute leukemia. Although without defined causes, the association of some elements may increase the risk of developing some specific types of leukemia [9]:

- Exposure to substances used in agricultural management, such as pesticides, diesel, solvents, and dust: leukemias.
- Chemotherapy: acute myeloid leukemia and acute lymphoid leukemia.
- Smoking: acute myeloid leukemia.
- Ionizing radiation (X-rays and gamma rays) from radiotherapy: acute myeloid leukemia and acute lymphoid leukemia. The degree of risk will depend on age, radiation dose, and exposure to agents.
- Exposure to formaldehyde, which is a product used in the textile, chemical industry, and also used in hospitals, laboratories, clinics as a solvent, histological fixative, disinfectant, and antiseptic, can cause leukemia.
- Rubber production: leukemia.
- Down syndrome and other hereditary factor-related diseases: acute myeloid leukemia.
- Family history: acute myeloid leukemia and chronic lymphoid leukemia.
- Myelodysplastic syndrome and other blood disorders: acute myeloid leukemia.

- Benzene: substance widely used in the chemical industry and in the composition of fuels such as gasoline – acute and chronic myeloid leukemia and acute lymphoid leukemia.
- Age: the risk of acquiring leukemia increases with age, except for acute lymphoid leukemia, which is more common in children. All others mostly affect the elderly.

We can correlate many of the above situations with the occurrence of leukemia, manifesting in the gestational period. Many women prefer to have children later in life. Although the number of smokers worldwide has decreased, still the number of female smokers is large. And we must not forget the factors linked to occupational contamination and family inheritance (hereditary).

1.5 General Aspects of Treatment

The most commonly diagnosed cancers in pregnant women are cervix, breast, melanoma, lymphoma, and leukemia [16].

In 1856, Rudolph Virchow, considered the father of modern pathology, described the first scientific work on leukemia, precisely in a pregnant woman. He already claimed that this disease caused molecular or structural changes in cells. Since Virchow's discovery until 1995, more than 500 cases of leukemia have been reported in pregnant women [6], most of them being acute and predominantly myeloid [10].

Acute leukemia in pregnant women causes anemia, thrombocytopenia, and neutropenia; and infections may occur due to bone marrow failure caused by the malignancy of the disease [7]. The risk of increased susceptibility to infections increases with leukemia, as well as cytopenia and autoimmune phenomena. Infections are a serious maternal and fetal risk problem, and it is important to remember that not all antibiotics can be used during pregnancy. It is essential to assess the presence of herpes virus and cytomegalovirus during leukemia due to the increased risk of reactivation [11].

Cytopenias can cause infections and bleeding, which are considered very serious events during gestational period. In the spinal cord failure caused by leukemia, red blood cell and platelet transfusions are used to maintain hemoglobin levels of approximately 10 g/dL and platelet counts in the range >50–100 × 109/L (with close monitoring of platelet level) at delivery [12].

Pregnant women with acute promyelocytic leukemia (ALI) require special vigilance and care, as the most common manifestations of ALI include medical emergencies such as pancytopenia, intravascular coagulation, and hyperfibrinolysis [13]. Chemotherapy in the first trimester of pregnancy significantly increases the risk of miscarriage, fetal malformation, and fetal death [14].

As for the diagnosis of leukemia in pregnant women, it will be the same as in nonpregnant women; however, certain radiological evaluations that may affect the fetus may not be performed in pregnant women [7]. Although biopsy can be

performed during pregnancy, it should be avoided; however, for accurate confirmation, techniques such as peripheral blood microscopy, flow cytometry or molecular analysis are required [10].

When the diagnosis of leukemia is made in the first trimester of pregnancy, termination of pregnancy may be considered [15, 18]. During the second and third trimesters, chemotherapy treatment will rarely cause congenital malformations, but the risk of prematurity, *fetal growth restriction*, neonatal neutropenia, and sepsis should be considered [15].

The treatment of a cancer patient during pregnancy is challenging, mainly due to the effects that can be caused to the fetus. The effects will be influenced by factors such as time and frequency of drug exposure and the ability of drugs to cross physiological barriers such as the blood-brain barrier and the placental barrier. Other issues to be evaluated include diagnosis and gestational period [17].

For ethical and moral reasons, no studies have been performed on pharmacokinetic profiles of chemotherapy drugs in pregnant women. Thus, the doses that pregnant women receive from chemotherapy are exactly the same as those of nonpregnant women. In pregnancy, the blood volume increases by up to 50%, and the same occurs with the renal clearance rate that also increases; therefore, the serum concentration of the drug can be reduced. In a pregnant woman, the hormonal and metabolic changes associated with pregnancy should be considered [15].

Chemotherapy in leukemia inhibits placental trophoblast migration and proliferation in the first trimester of pregnancy, which may partially explain the lower birth weights of newborns whose mothers received chemotherapy [19]. The trophoblast is the outer layer of the blastocyst and contributes to endometrial implantation and placental formation. It is essential to mention that chemotherapy drugs disrupt vital cell functions during some phases of the cell cycle [15, 20].

Table 1.1 describes and the consequences of chemotherapy in the treatment of leukemia during the first, second, and third trimesters of pregnancy.

At King Faisal Hospital and Research Center in Riyadh, the capital of Saudi Arabia, a research was conducted on 32 patients who developed leukemia during pregnancy, with long-term follow-up. The types of primary hematologic malignancies were CML (11 patients), acute promyelocytic leukemia (ALI) (5 patients), and non-M3 AML (8 patients). Spontaneous abortions occurred in 14 patients and therapeutic abortions in 2 patients, while 16 live births were delivered at

Table 1.1 Chemotherapy in pregnancy [21]

Leukemia (type)	First trimester of pregnancy	Second trimester of pregnancy	Third trimester of pregnancy
Acute leukemia	Abortion	Cytarabine and doxorubicin induction therapy	Induction of labor and initiation of therapy
Acute promyelocytic leukemia	Abortion	Doxorubicin and trans retinoic acid	Induction of labor and initiation of therapy
Chronic myeloid leukemia (CML)	Interferon-alpha	Interferon-alpha or imatinib	Interferon-alpha or imatinib

30–41 weeks of gestation. Regarding the results obtained from the mothers, this research found that 19 patients were dead; 7 patients lost follow-up, and only 6 patients were alive. Of the 32 patients evaluated, 19 underwent hematopoietic stem cell transplantation (HSCT) to control their primary hematologic malignancies. At long-term follow-up, 14 transplant recipients were dead and only 5 transplant patients survived. Negatively, we can conclude from this case that the long-term prognosis of pregnant women with leukemia is poor, even with HSCT in high-risk patients [22].

In another study conducted in Japan, 16 patients with leukemia during pregnancy were evaluated between 2001 and 2011. Of the 16 patients evaluated, 9 had chronic myeloid leukemia (CML), 5 had acute lymphoid leukemia (ALL), and only 2 had developed acute myeloid leukemia (AML). Almost half of CML patients received treatment with imatinib, which was discontinued in three patients after the first trimester and one after the second trimester. Of these nine CML patients, six were treated with hydroxyurea and/or interferon, while the remaining three patients had no complementary treatment following the use of imatinib. Anemia was developed in four patients and thrombocytopenia in one patient. Acute leukemia was diagnosed in seven patients: two during the first trimester, two during the second trimester of pregnancy, and three during the third trimester of pregnancy. Two ALL patients had therapeutic abortion. Four ALL patients received chemotherapy in the first trimester of pregnancy. All patients with acute leukemia had thrombocytopenia, while four patients developed febrile neutropenia. At birth, the average gestational age was 32 weeks, with two reported perinatal deaths. In this study, it was possible to conclude that fetal and maternal morbidity is high in pregnant women with acute leukemia, while in pregnant women with chronic leukemia, fetal and maternal prognosis may be more favorable and management of complications is easier compared to acute leukemia [23].

Vertical transmission of leukemia from mother to fetus is rare and uncommon, thanks to the placental barrier and the immune system of the fetus. Chemotherapeutic agents have low molecular weight, so most of them can cross the placental barrier and reach the fetus. When treating a pregnant woman with antineoplastic drugs, we should consider the physiological changes that occur in the woman's body and the potential changes in drug metabolism and excretion. Increased renal clearance and hepatic oxidation of drugs occur during pregnancy, which may negatively influence the outcome of the protocols, as well as reducing the safety of these drugs [7].

Some medicines used to treat leukemia may be harmful in pregnancy:

- Imatinib: it is a tyrosine kinase inhibitor which blocks proliferation and induces the apoptosis process. This is related to some fetal abnormalities and abortion and is shown to be teratogenic in mice. Some studies claim that it can be safely used throughout pregnancy, but studies are lacking to prove its safety in the first trimester of pregnancy [11, 24].
- Nilotinib: it is a tyrosine kinase inhibitor which blocks proliferation and induces the apoptosis process [24]. Animal studies suggest that the use of this drug in pregnancy is related to mortality, miscarriage, and reduced gestational weight at

a dose of 300 mg/kg/d. Other authors suggest that nilotinib has no teratogenic action, determining successful pregnancies in patients [24].

- Trans retinoic acid: it participates in the regulation of transcription of target genes that control cell proliferation, differentiation, and apoptosis. According to studies, this drug causes teratogenic effects, such as craniofacial alterations, neural tube defects, cardiovascular malformations, and thymic aplasia, mainly in the first trimester of pregnancy. Spontaneous abortions occur in 40% of cases. In the second and third trimesters of pregnancy, there is less risk of teratogenic effects [19, 25].
- Hydroxyurea: it inhibits DNA synthesis [26]. In rats, the use of hydroxyurea has been shown to increase the risk of teratogenic effects. Some studies report that it can cause miscarriage, intrauterine growth retardation, and congenital malformation without specifying exactly which trimester is most at risk [19, 27].
- Cytarabine: this is an antimetabolite, acting as a false substrate for reactions necessary for DNA replication and RNA synthesis. The recommendation is to avoid the use of cytarabine throughout pregnancy. During the first trimester, it can cause severe limb malformations, and its use in the second and third trimesters is related to transient cytopenias, intrauterine fetal death, intrauterine growth retardation, and neonatal death from sepsis and gastroenteritis [19, 28].
- Methotrexate: this is an antimetabolite which acts as a false substrate for reactions necessary for DNA replication and RNA synthesis. Similar to most drugs, it should also be avoided during the first trimester of pregnancy. If really needed, it can be used in the second and third trimesters of pregnancy. Studies do not specify exactly which complications may occur for the mother and the fetus [19, 28].
- Rituximab: the mechanisms of this drug are antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis induction [29]. It has a low risk of teratogenicity compared to other drugs but should be avoided during the first trimester of pregnancy. Some studies and research indicate that rituximab can be safely used in the second and third trimesters of pregnancy [19].
- Thalidomide and Lenalidomide: they have anti-inflammatory activity, are immunomodulatory, and inhibit anti-apoptosis effects. They trigger antiangiogenic effects and inhibit the production, release and signaling of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and lead to cytotoxicity mediated by T30 cells. They may cause teratogenic effects and should be avoided during pregnancy [19].

Like drugs, some of the tests used to diagnose leukemia during pregnancy may not be safe [15]:

- Excisional biopsy and bone marrow biopsy: safe in pregnancy.
- Ultrasound: safe in pregnancy.
- Computed tomography and PET scan: may cause carcinogenic, teratogenic effects or miscarriage during pregnancy.
- Magnetic resonance imaging (MRI) and use of gadolinium: MRI can be safely used during the second and third trimesters of pregnancy only if there is a strong

reason for it, as it poses a risk to the fetus. The use of gadolinium as a contrast is dangerous because it crosses the placenta and affects the development of the fetus, producing malformations and restricting growth. The use of iodinated contrast agents is not recommended as they can cross the placenta and cause depression of thyroid function.

1.6 Postpartum Effects of Chemotherapy on Mothers with Leukemia

At the end of pregnancy, chemotherapy should not be administered as it may lead to childbirth without bone marrow recovery. Some common complications occur during childbirth; however, thrombocytopenia, characteristic of leukemia, can lead to excessive bleeding in caesarean section or normal delivery. Severe anemia can complicate delivery of oxygen to the fetus. Obstetric infections can become very serious if neutropenia is present [30]; hence, chemotherapy should be discontinued 3 weeks before delivery for fetal placental excretion of drugs, which reduces the risk of neonatal myelosuppression [15].

Planning all chemotherapy sessions is critical, so that the risks are minimized. A caesarean section may be required in a patient with leukemia, neutropenia, or thrombocytopenia. After childbirth, it is recommended that breastfeeding begin 2 weeks after the last administration of chemotherapeutic agents because of the risk of toxicity involved. Even in small concentrations, drugs can be secreted into breast milk and cause significant harm to the fetus. Following chemotherapy in a leukemia patient, it is recommended to wait between 6 months and 2–5 years to allow oocytes to recover from possible drug damage during treatment [31].

1.7 Leukemias During Pregnancy

1.7.1 Acute Myeloid Leukemia in Pregnancy

Acute Myeloid Leukemia in Pregnancy is a type of cancer of the white blood cell myeloid line, characterized by the rapid proliferation of malignant and abnormal cells, the blasts, which do not mature without performing their functions and accumulate in the bone marrow. As a result, it interferes with the production of other cells [32]. AML occurs quite frequently in young adults and the elderly. Thus, more data are available for the management of AML in pregnant women [6, 10]. AML has no aggressive malignancy, but delayed initiation of chemotherapy has adverse consequences for the mother. Therefore, careful evaluation should be performed to find a balance between the consequences of intensive chemotherapy on the fetus and mother. Also, check the consequences of postponing treatment to the mother [6, 10].

The possibility of long-term consequences of chemotherapeutic cytotoxicity on the mother's future fertility should be considered [10, 33].

There are therapeutic regimens and protocols for the treatment of AML, and these include the use of anthracyclines (daunorubicin, idarubicin, doxorubicin), antimetabolites (cytarabine), topoisomerase II inhibitors (etoposide), monoclonal antibodies (gemtuzumab), and multikinase inhibitors [10]. AML induction regimens are based on a combination of cytarabine and anthracycline, while other combinations of intensive chemotherapies are used in consolidation therapy [6, 7]. There are sufficient data on the use of cytarabine and anthracyclines during pregnancy, except in the first trimester; however, there is a lack of information on the administration of gemtuzumab and multikinase inhibitors in pregnant women with AML [6, 10]. Experience with the use of anthracyclines in pregnancy is limited to the administration of doxorubicin and daunorubicin, since idarubicin, being more lipophilic, may be related to higher rates of fetal complications [7, 33].

There are many reports of successful management of AML in pregnancy and few reports of vertical transmission of acute leukemia from mother to fetus [34, 35]. Spontaneous remission of acute leukemia after pregnancy has been reported and the following rare forms of AML have been reported: erythroleukemia, AML with granulocytic sarcoma causing spinal cord compression, and AML mimicking HELLP (hemolysis, elevated liver enzymes and low platelet counts) syndrome [36].

Although AML is a rare event during pregnancy, there is a clear risk to life for both mother and fetus. AML diagnosed during pregnancy should be treated immediately, as higher maternal mortality is associated with delayed initiation of treatment. However, the decision regarding the choice of treatment for AML in pregnancy will depend on the case. If AML is diagnosed during the first trimester of pregnancy, termination of pregnancy should be discussed and chemotherapy should be initiated [34, 35, 37–40].

Management of AML diagnosed during the second and third trimesters of pregnancy is often difficult because simply delaying the initiation of chemotherapy sessions entails significant risk for the mother, and administration of antineoplastic drugs induces fetal death, prematurity, malformations, and congenital infections [39]. Some studies state that chemotherapy may be safe during the second and third trimesters of pregnancy, and that chemotherapy with cytarabine and idarubicin in AML in the second trimester of pregnancy may be associated with fetal heart malformations. These are conflicting issues which, as a rule, run into the risk to the fetus, most likely in the first trimester of pregnancy. The choice of chemotherapy, specifically in the first trimester of pregnancy, will always be a challenge for the multidisciplinary team. As mentioned earlier, ethical issues are important and the lack of accurate information on the pharmacokinetic behavior of chemotherapy in pregnant women is a serious technical obstacle [34, 40].

Constant fetal evaluation is required using cord blood samples (cordiocentesis) and ultrasounds because intrauterine exposure to chemotherapy drugs represents a significant risk of unfavorable outcomes such as low birth weight, fetal death, and intrauterine fetal death [38, 41].

1.7.2 Acute Promyelocytic Leukemia in Pregnancy

Acute promyelocytic leukemia is characterized by the presence of t-translocation (chromosomes 15 and 17) involving the retinoic acid receptor α (RAR-α) on Chromosome 17 and the promyelocytic leukemia gene on Chromosome 15. APL comprises about 5% of AML in the United States. In recent decades, anthracyclines, all-trans retinoic acids (ATRAs), and arsenic trioxide (ATO) have been used in the treatment of ALI with excellent long-term survival results proven in many studies [42–44].

The treatment of APL in pregnancy represents major challenges regarding the optimal management of the complications of the disease, as maternal and fetal well-being must be prioritized. It is considered that the thrombohemorragic and infectious risk may be higher during pregnancy, while the identification of differentiation syndrome may be more complicated. Diagnosis of APL in pregnancy is quite uncommon, and there is a lack of information on the treatment of early-onset APL during pregnancy. Even the non-systemic use of retinoids can lead to significant embryo/fetal teratogenicity, especially in the organogenesis phase, in the first trimester of pregnancy [45]. The clinical phenomenon of disseminated intravascular coagulation (ICD) often accompanies ALI; hence, sequelae of ICD in pregnant women are potentially threatening to both mother and fetus [46, 47].

Acute promyelocytic leukemia reaches higher proportions in young adults when compared to other types of AML. The average age of diagnosis is 47 years, which is much lower than the AML, that is, 66 years. Therefore, APL is more common in pregnancy than the other AML subtypes. However, there are other subtypes of AML more common than APL in the general population [48, 49].

It is very difficult to estimate the value definitively, but the number of acute leukemia cases is greater than the total number of chronic leukemia cases in pregnancy, similar to AML which is more common than lymphocytic leukemia in pregnancy [6, 50].

There is uncertainty about the pathogenesis of ALP differing from a pregnant woman to a nonpregnant woman. It is believed that there are hormonal and immunological changes during pregnancy that may create a state of cellular immunosuppression and inflammatory process, which may predispose to malignant diseases and alter the behavior of tumors [51, 52].

The diagnosis of ALI in the first trimester of pregnancy resulted in greater difficulties, with risks to the fetus and a high rate of spontaneity or therapeutic abortion, regardless of ATRA use. These findings show that current therapy is effective in pregnant women with ALI, but diagnosis and treatment may be associated with a high risk of obstetric and fetal complications. Until recently, the obstetric complications of APL therapy had been poorly understood, as they stemmed from individual case reports. Currently, it is possible to recognize high rates of fetal and obstetric complications in ALI, especially when the diagnosis occurs in the first trimester of pregnancy, regardless of the type of chemotherapy [53].

Patients diagnosed with APL during pregnancy represent an unusual challenge, requiring the approach of a hematologist, an obstetrician, and a neonatologist. But it is important to note that the treatment of APL depends essentially on the trimester of pregnancy in which the disease was diagnosed [56, 57].

The use of ATRA in the first trimester of pregnancy is associated with a high risk of teratogenicity and miscarriage [54]. The safety of anthracycline and cytarabine use has been well evaluated in some cases with follow-up. Use of cytarabine ($n = 93$) was associated with approximately 4% risk of limb malformations if used in the first trimester, 6% risk of intrauterine fetal death, 2% risk of neonatal mortality, and 13% of delayed intrauterine growth. Many of these adversities were noted with the combination of cytarabine with thioguanine and daunorubicin [55].

During the second and third trimesters of pregnancy, ATRA may be used, but arsenic-derived substances are contraindicated because they are highly embryotoxic [56, 57].

In women diagnosed with ALI in the second and third trimesters of pregnancy, the two main options available are as follows [56]:

1. Induction of ATRA remission only with postponement of chemotherapy administration until delivery.
2. Simultaneous administration of ATRA and chemotherapy as it is performed in nonpregnant women at the time of diagnosis.

Immediate administration of ATRA and chemotherapy provides the best chance of cure but is accompanied by an increased risk of miscarriage, prematurity, low birth weight, neonatal neutropenia, and sepsis; hence, induction of labor between cycles should be considered [56, 57]. Patients treated with ATRA alone, compared with patients treated with ATRA plus chemotherapy, have similar remission rates but higher rates of hyperleukocytosis and higher relapse rates. Patients treated with ATRA alone need continuous monitoring by RT-qPCR after remission induction to monitor for relapse pending delivery. Patients who are newly combined with ATRA and chemotherapy require strict fetal monitoring with a specific emphasis on cardiovascular functions [56, 57].

1.7.3 Acute Lymphoblastic Leukemia (ALL) in Pregnancy

Cervical and breast tumors are the most commonly diagnosed tumors during pregnancy, followed by melanoma, leukemia, and lymphoma. The treatment of malignancies during pregnancy has been updated, and the participation of the multidisciplinary team is important. Chemotherapy should be avoided during the first trimester as it has harmful effects on the fetus during the period of organogenesis. Even with the administration of chemotherapy during the second and third trimesters, there are cases of fetal growth restriction, intrauterine death and neonatal death, prematurity and myelosuppression [58].

Cases of ALL are relatively rare in adults: only 21 cases of this type of leukemia have been reported since 2009. Thus, there is little information and data about ALL, which precludes better recommendations for treatment during pregnancy [6, 7, 10].

The incidence of ALL is 1.3 per 100,000, with a slight male predominance. In nonpregnant adults, the complete remission rate reaches 80% of cases. Approximately 40% of adults are cured by modern treatment strategies, which gives an average 10-year survival. In the last 20 years, there has been a significant technological advance and the basic principle of all treatments has been chemotherapy: induction, consolidation, and maintenance therapy [59].

In the first trimester of pregnancy, the teratogenic effects of chemotherapy may occur in the treatment of ALL [60]. In the second and third trimesters of pregnancy, chemotherapy can cause a greater number of stillbirths, growth retardation, prematurity at birth, and maternal and fetal myelosuppression. Treatment during pregnancy seems to have no impact on the child's future growth and development. However, much of the scientific literature deals with acute myeloblastic leukemia rather than ALL. In ALL patients, pancytopenia, sudden intrauterine death and severe eclampsia have been reported. Acute leukemia requires immediate treatment regardless of gestational period. Acute leukemia does not have its course altered by pregnancy, but the outcome is much worse if initiation of treatment is delayed. Pregnant women should receive doses similar to nonpregnant women and because of the high risk of teratogenic effects of chemotherapy in the treatment of leukemia in the first trimester, termination of pregnancy should be considered [55, 61–63].

The structural basis of ALL's remission induction regimens is based on the use of vinca alkaloids, anthracyclines, cytarabine, and steroids. Vinca alkaloids have no teratogenic effects. In a group of 28 reported cases of ALL treated with anthracyclines after the first trimester of pregnancy, 21 had no complications. Cytarabine may produce limb abnormalities if used in the first trimester. The Cytarabine treatment was reported in 88 cases in all trimesters, with 6 intrauterine fetal deaths and 2 neonatal deaths [55].

Acute lymphoblastic leukemia chemotherapy regimens include cytarabine, cyclophosphamide, L-asparaginase, anthracyclines, corticosteroids, and vincristine [6].

Different chemotherapy induction regimens are used to treat ALL worldwide. It is important to remember the degree of malignancy of this type of leukemia and the need for immediate initiation of treatment. In the same country, several schemes can be used, such as CALGB, CCG, and DFCI in the United States and FRALLE, LALA, and GRAALL protocols in France. These treatment regimens undergo total modification or replacement as new protocols emerge. Even with the development of various induction regimes, it is still not possible to claim that there is a better treatment for ALL. The drugs constituting these therapeutic regimens are basically the same with different doses and dosing schedules [64–66].

In recent years, more intensified ALL pediatric treatment regimens have been used in patients aged 15–40 years. This is because many studies have shown that adolescents and young adults treated with adult chemotherapy regimens performed worse compared to patients in the same age group treated with pediatric protocols.