ACUTE LEUKEMIA IN PREGNANCY: FROM THE EXPERIENCE OF THE SUUB HEMATOLOGY CENTER

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Abstract

The occurrence of acute leukemia during pregnancy is a rare pathologic situation and requires a multidisciplinary approach that includes at least a hematologist, gynecologist, neurologist, or psychotherapist and sometimes even intensive care unit care. The difficulties in caring for such a patient are many, from determining the risk associated with continuing the pregnancy, to choosing diagnostic tools and therapy appropriate for such a situation, to considering the patient's wishes and preferences.

Below, we present the approach for cases of acute leukemia in pregnancy diagnosed and treated at the Emergency University Hospital of Bucharest (SUUB), Hematology Department, between January 1, 2017 and December 31, 2022, during a 6-year period.

Keywords: *pregnancy, acute leukemia, special care.*

Rezumat

Apariția leucemiei acute în timpul sarcinii este o situație patologică rară și necesită o abordare multidisciplinară care trebuie să includă cel puțin un hematolog, ginecolog, neurolog sau psihoterapeut și, uneori, chiar și îngrijiri de terapie intensivă. Dificultățile în îngrijirea unei astfel de paciente sunt multe, de la determinarea riscului asociat continuării sarcinii, la alegerea instrumentelor de diagnostic și a terapiei adecvate unei astfel de situații, până la luarea în considerare a dorințelor și preferințelor pacientei.

Vă prezentăm mai jos abordarea cazurilor de leucemie acută în sarcină diagnosticate și tratate la Spitalul Universitar de Urgență București (SUUB), Secția Hematologie, în perioada 1 ianuarie 2017 – 31 decembrie 2022, pe o perioadă de 6 ani.

Cuvinte cheie: *sarcină, leucemie acută, îngrijire specială.*



Internal Medicine

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Introduction

Oncohematologic diseases represent 25% of all cancers diagnosed during pregnancy[1,2,3]. Acute leukemia (AL) is reported in one of 75,000 to one of 100,000 pregnancies[4,5] and presents multiple medical and ethical challenges.

Acute myeloid leukemia (AML) accounts for two-thirds of all cases, while acute lymphoid leukemia, chronic leukemia or myelodysplastic syndrome are rarely described[6,7].

AL is usually reported during the second and third trimesters of pregnancy, accounting for 37% and 40% of the cases respectively[1,2,8]. In the first trimester the incidence is generally estimated around 23%, even if an underreporting bias caused by spontaneous pregnancy termination could not be excluded.

The clinical presentation of acute leukemia in pregnancy is broadly similar to that in the nonpregnant, although pregnancy may obscure some of the clinical signs. During pregnancy, some of the early signs of acute leukemia, such as fatigue and shortness of breath, or changes in peripheral blood count, such as anemia and thrombocytopenia, may be interpreted as pregnancy-related symptoms, leading to delayed diagnosis and inappropriate therapy.

If left untreated, the disease is likely to lead to maternal and fetal mortality[9] and a decision to delay the start of induction chemotherapy negatively affects the likelihood of remission[10]. Data suggest that maternal outcomes in acute leukemia after chemotherapy are similar to those in nonpregnant patients, so delaying the start of treatment should be avoided[11].

The therapeutic approach depends on the type of leukemia and the gestational age. The first trimester is defined as before the end of week 12 and the third trimester is after week 27 of pregnancy.

Guidelines for the diagnosis and management of acute leukaemia in pregnancy[12], specify the following:

- When a diagnosis of acute leukemia is made in the first trimester, a successful pregnancy outcome is unlikely, and spontaneous abortion in this situation is associated with significant risks to the mother. The reasons for and against elective abortion should be discussed with the patient.
- If the pregnancy is more than 32 weeks, it may be advisable to deliver the foetus before starting chemotherapy.
- Between 24 and 32 weeks, the risks of foetal chemotherapy exposure must be weighed against the risks of preterm delivery after elective delivery at this stage of pregnancy.

- The risk-benefit ratio must be carefully considered before using any drugs in pregnancy.

Experience - hematology department S.U.U.B.

Because S.U.U.B. is a multidisciplinary hospital (with hematology, obstetrics, neonatology and anesthesiology teams), the addressability of pregnant patients with hematologic pathology was higher compared with other hematology centers. Our service diagnosed and treated pregnant women with various hematologic pathologies: hemolytic anemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic 3 purpura, chronic myeloid leukemia, Hodgkin's and non-Hodgkin's lymphomas and acute leukemias.

During the period from January 2017 to December 2022, 4 cases of acute leukemia in pregnancy were diagnosed and treated in the Hematology Department of S.U.U.B.: two cases of acute myeloblastic leukemia and two cases of acute lymphoblastic leukemia (1 case with B-lineage precursor and 1 case with T-lineage precursor).

The diagnosis was established following specific investigations: morphological, cytological, immunophenotypic, cytogenetic and molecular. The classification of the AL subtype was based on the French-American-British (FAB) criteria and the revised World Health Organization (WHO) criteria, 2016.The diagnosis AL requires at least 20% blasts among no erythroid cells in bone marrow or blood.

Diagnosis requires certain investigations (including imaging) that may affect the fetus. For this reason, the guidelines specify certain precautions for their use (Table 1).

The therapeutic approach for AL in a pregnant patient is a real challenge. The efficacy of leukemia treatment (i.e., achieving complete remission) must be weighed against the toxic risks that such treatment poses to the fetus and mother. It must also be taken into account that, after chemotherapy severe aplasia occurs, which increases the risk of infection, bleeding or hypoxia in the mother and fetus.

Chemotherapy administered in the first trimester is associated with the greatest risk of miscarriage, fetal death, and congenital malformations, ranging from 10 to 20%[14].

It is generally believed that the risk of fetal malformations in the second and third trimesters decreases as the pregnancy progresses. Chemotherapy exposure after the first trimester results in an increased incidence of intrauterine growth retardation (which is also influenced by maternal nutritional status throughout pregnancy), preterm birth, and fetal death, but no increase in the incidence of congenital anomalies[15] and, in particular, no documented increase in childhood malignancies or adverse neurologic development, although the latter persists throughout pregnancy[16,17].

Treatment in the third trimester generally results in the fewest complications, but the exact timing of chemotherapy must be carefully planned to avoid inducing pancytopenia immediately before delivery. Early delivery may be considered if the leukemia occurs sufficiently late in pregnancy. If chemotherapy is considered mandatory, it is important to anticipate the myelosuppressive effects of chemotherapy on the fetus and to plan supportive treatment after delivery, which should preferably coincide with recovery of the maternal blood count.

In addition, a longer period between chemotherapy administration and fetal birth



Internal Medicine

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Radiological Study	Effects on Pregnancy
Core Needle or Excisional Biopsies and Bone Marrow Biopsy	Safe
Ultrasonography	Safe
Computed Tomography (CT) and Positron Emission Tomography (PET)	Carcinogen, teratogen or spontaneous abortion
Magnetic Resonance Imaging (MRI) and Gadolinium	(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

Table 1. *The investigations and radiological studies and its effects on pregnancy*[13]

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

Table 2. *Effects of chemotherapy during pregnancy*[13]

	CASE 1	CASE 2	CASE 3	CASE 4
AGE OF PATIENT	19 years	33 years	25 years	34 years
GESTATIONAL AGE AT DIAGNOSIS	Week 21	Week 28	Week 11	Week 25
HEMATOLOGICAL DIAGNOSIS	Acute myeloblastic leukemia with minimal maturation (WHO 2016) / LAM 1-2 FAB, FLT3 negative, with recurrent genetic abnormalities (translocation 10 and 11, trisomy 19)	Acute myeloblastic leukemia with minimal maturation M1-M2 FAB,FLT3 negative No other genetic or molecular changes	Pre B acute lymphoblastic leukemia, CALLA positive, BCR-ABL negative, MLL negative	T-cell acute lymphoblastic leukemia
THE RISK OF HEMATOLOGICAL DISEASE	Intermediate-high risk	Standard risk	Intermediate risk (WBC, BCR-ABL, CALLA)	High risk
ONSET OF THE DISEASE	- physical asthenia, fever - right lower leg edema (thrombosis) - ascites - suprahepatic vein thrombosis (Sdr Budd Chiari) - mediastinal tissue mass (68/110 mm)	-asymptomatic - laboratory changes during a routine control during pregnancy	-vaginal bleeding and abdominal pain -without other symptoms of hematological disease	-dyspnea - facial paresis right - pleura effusion, mediastinal tissue block 93/70 mm, generalized adenopathies Clostridium difficilae infection, ascites
BLOOD COUNT ON DEBUT	WBC - 66.000/mmc Hb - 11.7 g.dl PLT - 29.000/mmc PBS with 35% Blasts	WBC -11.400/mmc Hb -10.5 g/dl PLT - 276.000/mmc PBS with 56% Blasts	WBC - 59.700/mmc Hb -7.4 g/dl PLT - 28.000/mmc PBS with 47% blasts	WBC - 168.000/mmc Hb -11.8 g/dl PLT - 53.000/mmc PBS with 73% blasts
THE DECISION TO INTERRUPT THE PREGNANCY	YES - maternal and fetal risk - Therapeutic delivery in week 21-22 (miscarriage) - Postabortion: placenta without missing cotyledons, minimal intrauterine content, favorable evolution	NOT - Cesarean section at 28 weeks .Live fetus, weight 1200 g ; No hemorrhagic or infectious complications for mother ; Infant was sent home from the neonatal unit at approx. 7 weeks after birth.	YES - fetal risk - spontaneous abortion the day after admission	YES - maternal risk -delivered spontaneously 3 weeks after the initiation of chemotherapy -live fetus 600g that dies after 3 days of birth

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	CASE 1	CASE 2	CASE 3	CASE 4
TREATMENT OF HEMATOLOGICAL DISEASE	Induction type "5+2" with Cytosar + Idarubicin initiated at diagnosis	Initiated 14 days postpartum Induction type 5+2 (reduced doses considering the recent caesarean section and the risks of aplasia). Well tolerated	Treatment according to the CALGB protocol initiated after spontaneous abortion	Treatment according to the UKALL XII protocol initiated in emergency mode immediately after establishing the hematological diagnosis
EVOLUTION	10 months after diagnosis: RCM but with MRD positive, Decision : haplo alloSCT (paternal donor	3 months after diagn : PR the patient dies due to an infectious complication in severe post-chemotherapy aplasia	-after phase 1 of induction, RCM was achieved but later the patient discontinues the treatment, disappears from the records of the clinic	- died 5 weeks after the diagnosis, with septic shock in severe aplasia

Table 3. *Characteristics and evolution of pregnant patients with leukemia from our case report RCM = complete morphological remission, PR = partial remission; MRD = minimal residual disease, alloSCT = allo stem cells transplant , PBS = peripheral blood smear*

allows for excretion of the drug across the placenta, which may counteract the difficulty of fetal excretion of toxic metabolites due to immaturity of the fetal liver and kidneys. To minimize risks for mother and fetus, a near term cesarean delivery (>35–37 weeks) remains the main goal.

Survival following delivery at or beyond 28 weeks gestation are >90% in most large centers, but even higher (>95%) if the delivery was at or beyond 32 weeks gestation. (18) Considering all these aspects, we approached our patients a shown in Table 3.

Disccusion

The literature does not provide much current data on the frequency of acute leukemias in pregnant women and their development and

pregnancy. The prevalence of such pathology is based on estimates (approximately 1 case per 10,000 pregnancies) because there is no database in which they are reported. However, considering the increase in the incidence of acute leukemias in the adult population, an increase in leukemia cases in pregnancy is also estimated. 2/3 of cases are acute myeloblastic leukemia and 1/3 are acute lymphoblastic leukemia.

From the case history of our service from 2017-2022, out of 300 new cases diagnosed with adult acute myeloid leukemia two cases were diagnosed during pregnancy and out of the total 50 new cases of acute lymphoblastic leukemia two cases were pregnant women. Of the four pregnant patients with acute leukemia, one patient was diagnosed with hematologic disease in the first trimester of pregnancy (< 12 weeks), two patients were diagnosed with hematologic disease in the second trimester of pregnancy (< 27 weeks) and one patient in the third trimester(>27 weeks). Therapeutic approaches to leukemia during pregnancy may depend on several variables, including gestational age at diagnosis, clinical and biological disease characteristics, and potential toxicity of drugs to mother and child.

Of the four patients, one is still alive, one is no longer in the records, and two died after chemotherapy from infectious complications. Of the four pregnancies, two resulted in the birth of live fetuses (one 600 g and one 1200 g), of which only one fetus survived.

The two patients who died due to infectious complications were in the second and third trimesters of pregnancy, respectively, and delivered live fetuses. It is possible that immunosuppression was also increased after delivery and promoted the infectious complications that occurred in aplasia after chemotherapy.

Conclusion

The management of leukemia in pregnancy remains challenging and requires consideration of the nature of the disease, the stage of leukemia, the need for intervention, and careful assessment of maternal and fetal risk. There is little evidence-based data, and concerted efforts are needed to increase the number of clinical trials and basic research.

Conflict of interest

The authors have no conflicts of interest to declare related to this manuscript.

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