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Maternal and Perinatal Outcomes in Pregnancy with Leukemia: A Tertiary Institution Experience of 12 Pregnancies for 5 Years

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Pregnancy with Leukemia is a rare but serious condition, with a global prevalence of about 1 in 75,000 to 100,000 pregnancies. The simultaneous occurrence of pregnancy and leukemia presents a complex therapeutic dilemma for patients, hematologists, and obstetricians. This study is a serial case study that collected data on pregnant patients with leukemia treated at dr. Soetomo Teaching Hospital. The data includes demographic characteristics, types of leukemia, age at diagnosis, age during pregnancy, as well as clinical and laboratory manifestation and their maternal and perinatal outcomes. Of the 12 identified cases, 8 cases (66.7%) were Chronic Myeloid Leukemia (CML), 2 cases (16.7%) were Acute Myeloid Leukemia (AML), and 2 cases (16.7%) were Acute Lymphocytic Leukemia (ALL) and there were no cases of Chronic Lymphocytic Leukemia (CLL). The average age of patients at diagnosis was 23 years, and age during pregnancy was 25 years. The prevalence of pregnancy with leukemia at dr. Soetomo Teaching Hospital is 1 in 482 deliveries, possibly due to the hospital's status as a tertiary referral center with adequate cancer services in East Java Province. The worst maternal and perinatal was AML, whereas all pregnant women with AML has died. The best maternal and perinatal outcome was CML. Chronic Leukemia showed better maternal and perinatal outcomes compared with acute leukemia. This study highlights the importance of proper management and coordination between hematology and obstetricians to achieve optimal outcomes for both the mother and the fetus.
Keywords: Pregnancy with Leukemia, Acute Leukemia, Chronic Leukemia,

Maternal and Perinatal Outcome.

1. Introduction

Leukemia during pregnancy is an extremely rare condition. The coexistence of pregnancy and leukemia creates a complex therapeutic challenge for patients, hematologists, and obstetricians alike1. Due to the limited experience in treating pregnant women with leukemia, despite advances in leukemia treatment that have significantly improved survival rates and made cures possible in many cases, the rarity of leukemia in pregnancy and the potential underreporting of cases have hindered a comprehensive understanding of effective management during pregnancy. In Indonesia, no large-scale studies on pregnancy complicated by leukemia have been conducted. The available data are mostly limited to individual case reports, with no case series published so far2. Thus, the author aims to present a 5-year case series from Dr. Soetomo Teaching Hospital focusing on the management of leukemia during pregnancy and the resulting maternal and perinatal outcomes. It is hoped that this will add valuable information to the existing knowledge on managing leukemia in pregnant patients.

2. Research Methodology

This study is a serial case that collected data on pregnant patients with leukemia treated at Dr. Soetomo Teaching Hospital. The data includes demographic characteristics, types of leukemia, age at diagnosis, age during pregnancy, as well as clinical and laboratory manifestation and maternal and perinatal outcomes. To provide data about maternal and perinatal outcomes in pregnancy with leukemia in a tertiary hospital and compare the results between acute and chronic leukemia.

3. Results and Discussion

From 2019 to May 2024 at Dr. Soetomo Teaching Hospital Surabaya Acute lymphoblastic leukemia (ALL) was diagnosed in two cases (16.7%), acute myeloid leukemia (AML) in two cases (16.7%) and chronic myeloid leukemia (CML) in eight cases (66.7%). Of the cases of acute leukemia, two patients with ALL were primigravida and diagnosed before pregnancy and had been treated for ALL before and were known to relapse in the second trimester of pregnancy. Two patients with AML were diagnosed during pregnancy. One patient was primigravida and diagnosed in trimester one, meanwhile, 1 patient was multigravida and diagnosed in the third trimester of pregnancy. Of eight patients with CML, seven were diagnosed with CML before pregnancy and 6 were on imatinib therapy 1 was on hydroxyurea and 1 patient was newly diagnosed during the first trimester. The average age of patients at diagnosis was 23 years, and age during pregnancy was 25 years. The prevalence of pregnancy with leukemia at Dr. Soetomo Teaching Hospital is 1 in 483 deliveries, possibly due to the hospital's status as a tertiary referral center with adequate cancer services in East Java Province.

One patient with AML was diagnosed in the first trimester (patient no.1) and had severe clinical manifestations. The patient was given supportive care but died during pregnancy caused by respiratory failure and induction chemotherapy was not performed yet. One AML patient was diagnosed in the third trimester (patient no. 2) in 31/32 weeks gestational age. The pregnancy was continued until 33/34 wga and the baby was given lung maturation injection. Baby born preterm by cesarean delivery 1900 g/ 43 cm/ Apgar score 3,5 and 7. The patient died of febrile neutropenia before chemotherapy started. Two patients with ALL were diagnosed before pregnancy and with a history of chemotherapy before. Both patients were known to be pregnant in the second trimester (21/22 wga and 16 wga). one patient was having a spontaneous abortion and one patient underwent a therapeutic abortion. Both patients were given chemotherapy after abortion and discharged alive. Of eight pregnant women with CML, six were treated with imatinib mesylate when they became pregnant, with treatment being interrupted in the first trimester and 4 patients switched to Hydroxyurea, two patients stopped leukemia medication (one from this two patients died because of leukemia was progressively become blastic crisis phase. The patient died caused by septicemia. One patient was treated with Hydroxyurea before pregnancy and the treatment was continued during pregnancy. One patient was diagnosed during pregnancy and treated with hydroxyurea, but the patient died during pregnancy caused by febrile neutropenia. Maternal outcome from 8 pregnancies with CML was 2 patients died and 6 patients alive. The pregnancy outcomes of eight patients were 4 aterm deliveries and 1 preterm delivery with healthy babies without congenital anomaly, 2 therapeutic abortions and 1 patient died while pregnancy on progress.

Case 1

YUI/24 y.o/ AML-M1

A 24-year-old primigravida was diagnosed with Acute Myeloid Leukemia in 9/10 WGA. Come to the hospital at Nganjuk because of dyspnea, fever, and vaginal bleeding suspected of threatened abortion. Laboratory results show severe anemia (Hb 4.5 g/dl), thrombocytopenia (Plt 15,000/□l), and hyperleukocytosis (WBC 109,000/□l). Peripheral Blood Smear showed normochromic normocytic anemia, leukocytosis with dominant myeloblasts without maturation, and thrombocytopenia. Impression: Suspected AML with Little Maturation (AML-M1). The patient was then referred to dr. Soetomo Hospital at 10/11 WGA. The clinical manifestation was getting worse and the patient lost of consciousness. The Bone Marrow Apiration can't be done due to thrombocytopenia and the patient died before starting chemotherapy.

Case 2

NUR/ 34 y.o/ AML

A 34-year-old multigravida (G3P2) was diagnosed with Acute Myeloid Leukemia in 31/32 WGA. The patient came to the Hospital in Lumajang complaining of fatigue, headache, gum bleeding, and skin lesions. Laboratory results showed severe anemia (Hb 5.5 g/dl), leukocytosis (Plt 17,000/□l), and severe thrombocytopenia (Plt 7800/□l). The patient was referred to Dr. Soetomo General Hospital, then did the Peripheral Blood Smear and the result was normochromic normocytic anemia with anisopoikilocytosis, leukocytosis with 85%

blasts, and thrombocytopenia. The patient was given red blood cell and thrombocyte concentrate transfusion, the baby was delivered by cesarean on 33/34 WGA. Baby born alive 1900 g/ 43 cm/ apgar score 3,5 and 7 without congenital anomaly. The chemotherapy was planned after delivery, but the patient's condition got worsened, and died of sepsis caused by febrile neutropenia before the chemotherapy started.

Case 3

RIA/ 21 y.o/ ALL-L1

A 21-year-old primigravida was diagnosed with Acute Lymphocytis Leukemia-L1 at 13 years old. The patient has undergone multiple c hemotheraphy before. The patient got pregnant after being married for 6 months and still in chemotherapy. The patient came to dr. Soetomo Hospital and known to be pregnant in 21/22 WGA. The patient complained fatique and looked pale. The laboratory results showed pancytopenia (Hb 4.4 g/dl; WBC 1500/□l, Plt 108,000/□l), hypokalemia (K 2.5) and hypoalbuminemia (Alb 2.55). Peripheral Blood Smear showed normochromic microcytic anemia with anisocytosis, leukopenia, and thrombocytopenia (Pancytopenia). Bone Marrow Apiration showed normocellular (indicative of ALL-L1). The patient was given red blood cell and thrombocyte concentrate transfusion, then having spontaneous abortion and induction chemotheraphy (Vincristine-Prednisone) started immediately. The patient was discharged alive but died in other hospitals after 7 months discharged from dr. Soetomo Hospital.

Case 4

GAB/ 29 y.o/ ALL-L2

A 29 years old primigravida was diagnosed with Acute Lymphocytic Leukemia-L2 at 27 y.o. patient have undergone chemotherapy Vincristine and Vincristine-Danaurubycin since 27 y.o and got pregnant after being married for 9 months. The patient is known to be pregnant in 16 WGA. The patient was complaining of fatique. Laboratory results showed anemia (Hb 9.0 g/dl), leukocytosis (WBC 33,640/□l) and thrombocytopenia (Plt 44,000/□l). the patient underwent therapeutic abortion and chemotheraphy Vincristine-Danaorubicine started immediately after pregnancy termination. The patient was discharged in stable condition.

Case 5

CHI/ 20 y.o/ CML

A 20 years later primigravida was diagnosed with Chronic Myeloid Leukemia at 19 years old and took Imatinib therapy routinely. The patient was got pregnant after married for a year. There were no symptoms during pregnancy and was in the chronic phase of CML. Imatinib was stopped when the patient was known to be pregnant in 21/22 WGA. Laboratory results showed anemia (Hb 10.2), and hyperleukocytosis (WBC 219,690/□l). The cytogenetic BCR-ABL was positive. Pregnancy was continued until term and delivered vaginally at a private hospital in 38/39 WGA. Baby born 2850 g/51 cm healthy baby without congenital anomaly.

Case 6

SUY/ 36 y.o

A 36-year-old multigravida (G2P1) was diagnosed with Chronic Myeloid Leukemia at 30 years old and took Imatinib routinely. This pregnancy was the third pregnancy. Two pregnancies before were diagnosed with leukemia. The patient had no symptoms during pregnancy and laboratory results showed a normal limit (Hb 12.3; WBC 9,450/□l; Plt 151.000/□l). The cytogenetic BCR-ABL was positive. The patient was known to be pregnant in 18/19 WGA and Imatinib was stopped and the patient received Hydroxyurea. Pregnancy was continued until term. Patient was delivered at a Private Hospital in 39/40 WGA. Baby born 3200 g/ 35 cm, healthy baby without congenital anomaly.

Case 7

MAY/ 26 y.o

A 26-year-old multigravida (G2P2) was diagnosed with Chronic Myeloid Leukemia at 24 years old and took Imatinib routinely and stopped in 26/27 WGA and switched to hydroxyurea. This was the second pregnancy, patient was in a chronic phase and complaining of fatigue and an enlarged spleen. Laboratory results showed anemia (Hb 10.3 g/dl) and leukocytosis (WBC 79.050/□l). The cytogenetic BCR-ABL was positive. Pregnancy was continued until 37/38 WGA and terminated vaginally through misoprostol induction at dr. Soetomo Hospital. Baby born 3500 g, 50 cm, Apgar score 8 dan 9, healthy baby without congenital anomaly.

Case 8

DEK/ 29 y.o

A 29-year-old multigravida (G4P2A1) was diagnosed with Chronic Myeloid Leukemia at 23 years old and took Imatinib routinely. This was the fourth pregnancy and the patient was known to be pregnant in 9/10 WGA. The patient was referred from Kediri Hospital complaining of fatigue, headache, nausea, and enlarged spleen. Laboratory results showed anemia (Hb 6.5 g/dl) and Hyperleukocytosis (WBC 287,540/□l). Peripheral Blood Smear showed normochromic normocytic anemia, anisopoikilocytosis, and leukocytosis with 14% myeloblast (accelerated phase CML). The cytogenetic BCR-ABL was positive. Pregnancy was terminated with abortion induction in 9/10 WGA. The patient got red bood cell and thrombocyte concentrate transfusion, Hydroxyurea and leukapheresis. Patient was discharged in stable condition.

Case 9

ERA/ 19 y.o

A 19 year old primigravida was diagnosed with Chronic Myeloid Leukemia at 16 years old and took Imatinib routinely. Got pregnant after being married for 6 months. The patient was complaining of fatique and looked pale. Laboratory results showed anemia (Hb 8.2 g/dl) and hyperleukocytosis (WBC 478.080/□l). The cytogenetic BCR-ABL was positive. Pregnancy was continued, imatinib was stopped and switched to Hydroxyurea and the patient was in labor in 34 WGA at Jombang Hospital due to premature rupture of membrane. Baby born 1920 g, 45 cm, healthy baby without congenital anomaly

Case 10

ROH/ 28 y.o

A 28-year-old multigravida (G2P1) was diagnosed with leukemia during pregnancy, before this the patient was diagnosed with essential thrombocytosis. The patient complained fatique and fever. Laboratory results showed anemia (Hb 102 g/dl), leukocytosis (WBC 26,640/□l), and thrombocytosis (Plt 2.174.000/□l). Peripheral blood smears showed normochromic normocytic anemia, anisopoikilocytosis, leukocytosis with 2% myeloblast 2%, and thrombocytosis. The patient was diagnosed in a chronic phase. The cytogenetic BCR-ABL has not been performed yet. Pregnancy was terminated with curettage and sterilization. The patient was treated with Hydroxyurea but died during admission because of febrile neutropenia.

Case 11

MAI/ 22 y.o

A 22-year-old primigravida was diagnosed with Chronic Myeloid Leukemia at 21 years old and took Imatinib routinely. The patient was got pregnant after married for a year. The patient was known to be pregnant in 18/19 WGA and stopped all leukemia medication. Patient control to dr. Soetomo Hospital while having complained of fatigue, fever, and enlarged spleen. Laboratory results showed severe anemia (Hb 4.7 g/dl), leukocytosis (WBC 45.950/□l), and severe thrombocytopenia (Plt 4000/□l), Peripheral blood smear showed normochromic normocytic anemia with anisocytosis, leukocytosis with 93% lymphoblasts, and thrombocytopenia. The patient stated as blastic crisis of CML and suspected of transforming to ALL. The cytogenetic BCR-ABL was positive. The patient died during admission caused of sepsis.

Case 12

LAI/ 24 y.o

A 24-year-old primigravida was diagnosed with Chronic Myeloid Leukemia 23 years ago and took Hydroxyurea routinely. The patient got pregnant after being married for a year. Laboratory results showed hyperleukocytosis WBC 144,140/□l) and thrombocytosis (Plt 591,000/□l). Peripheral blood smear showed normochromic normocytic anemia with anisopoikilocytosis, leukocytosis with 5% myeloblasts, immature granulocytes (+), eosinophilia and basophilia, and thrombocytosis. The patient stated in the chronic phase of CML The cytogenetic BCR-ABL was positive. The patient was known to be pregnant in 18 WGA and the Hydroxyurea continued taken. Pregnancy was continued until 37/38 WGA. Delivery was induced by misoprostol. Baby born 2300 g, 47 cm apgar score 8 and 9, healthy baby without congenital anomaly.

Table 1. Patient Characteristics, Clinical and Laboratory Manifestations

Leukemia	Year	Age when diagnosed (year)	Age while get pregnant (year)	Parity	BC/ NBC	Clinical Manifestation	BMA	Peripheral Blood Smear	Cytogenetic
AML	2021	24	24	Primigravida	NBC	Shortness of breath Weakness Vaginal bleeding Decreased consciousness	Not done yet	Normochromic anemia Normocytic, leucocytosis, with myeloblast predominance without	Not done

						Anemia Thrombocytopenia Hyperleukocytosis		maturation, thrombocytopenia.	
AML	2022	34	34	Multigravida	NBC	Fatique Headache Gum bleeding Anemia Thrombocytopenia Leukocytosis	Not done yet	Normochromic anaemia normocytosis anisopoikilocytosis, leucocytosis with 85% blast, thrombocytopenia	Not done
ALL-L1	2023	13	21	Primigravida	BC	Pancytopenia Abdominal pain Splenomegaly	Normocellular	Microcytic normochromic anaemia, Anisocytic, leucopenia, thrombocytopenia.	Not done
ALL-L2	2024	27	29	Primigravida	BC	Fatique Anemia Leukocytosis Thrombocytopenia	Hypercellular	Normocytic normochromic anaemia, lymphocytosis with 84% lymphoblasts and thrombocytopenia.	Not done
CML Chronic Phase	2020	19	20	Primigravida	BC	Anemia Hyperleukocytosis	Not done	Normocytic normochromic anaemia with normoblasts (+), leucocytosis with granulocyte immature	BCR-ABL Positive
CML Chronic Phase	2020	30	36	Multigravida	BC	Asymptomatic	Not done	Normochromic anaemia, Anisocytotic (-) leucocytosis with immature granulocytes (+)	BCR-ABL Positive
CML Chronic Phase	2021	24	26	Multigravida	BC	Fatique Leukocytosis Splenomegaly	Not done	Normocytic normochromic anaemia, thrombocytopenia.	BCR-ABL Positive
CML Accelerated Phase	2023	23	29	Multigravida	BC	Fatique Aaemia Splenomegaly Hyperleukocytosis	Hypercellular	Normochromic anemia, anisopoikilocytic, leukocytosis with myeloblast 14%	BCR-ABL Positive
CML Chronic Phase	2023	16	19	Primigravida	BC	Anemia Leukocytosis Thrombocytosis Hyperleukocytosis	Hypercellular	Anemia normochromic, normocytic, anisopoikilocytosis, polychromated cells (-), myeloblasts (-), leukocytes increased predominantly segmental neutrophils, atypical lymphocytes (-), immature granulocytes (+), metamielocytes, blasts (-), platelets impression increased, giant platelets (+)	BCR-ABL Positive
CML Chronic Phase	2023	27	28	Multigravida	BC	Fatique Fever Anemia Thrombocytosis Leukocytosis	Not done	Normochromic anemia, anisopoikilocytic, leukocytosis with 2% myeloblast, thrombocytosis	Not done yet
CML Blastic Crisis Phase	2023	22	22	Primigravida	BC	Fatique Fever Anemia Thrombocytopenia Leukocytosis Splenomegaly	Not done yet	normochromic anemia, anisocytosis, leukocytosis with 93% lymphoblasts and thrombocytopenia. Currently impressive blastic lymphoid crisis (ALL)	BCR-ABL Positive
CML Chronic Phase	2024	22	24	Primigravida	BC	Leukocytosis Thrombocytosis	Not done	Normocytic normochromic anemia, anisopoikilocytosis, leukocytosis with 5% myeloblasts and immature granulocytes (+), thrombocytosis	BCR-ABL Positive

BC: Booked Case; NBC: Non Booked Case

Table 2 Laboratory Characteristics, Maternal Therapy, and Maternal Perinatal Outcomes

Leukemia	Hb	WBC	Platelet	Leukemia Diagnosed	Therapy before pregnancy	Therapy during pregnancy	Fetal Outcome	Congenital anomaly	Maternal Outcome
AML	**4,5**	**148.200**	**87.000**	During Pregnancy TM 1	No treatment yet	PRC and TC Transfusion	Died while pregnant	-	Death e.c. Respiratory Failure
AML	**8,5**	**17.380**	**7.000**	During Pregnancy TM 3	No treatment yet	PRC and TC Transfusion	Preterm live birth 1900 g/43 cm/ AS 3,5,7	No	Meninggal e.c Febrile Neutopenia
ALL-L1	**7,6**	**1.590**	**30.000**	Before Pregnant, relapsed during pregnancy TM2	Induction chemotherapy 3 cycles (Metrotrexat 12 mg, Vincristine 2 mg, Dexamethasone 7-6-6 Tablets, HD-Metrotrexat 1000 mg + Leucovorin 15 mg, Daunorubicin 30 mg + Cyclo 1600 mg, Citarabin 100 mg, L. Aspiraginase 7500 iu, MP 70 mg) (2014-2016), Vincristin chemotherapy 4x (2022)	PRC and TC Transfusion Vincristine-Prednison Chemotheraphy	Spontaneous abortion	-	Hidup
ALL-L2	**9,0**	**33.640**	**44.000**	Before Pregnant, relapsed during TM2	Vincristine, Vincristine-Danaurubycin Chemotherapy	PRC and TC Transfusion Vincristine-Prednison Chemotheraphy	Therapeutic Abortion	-	Alive
CML Chronic Phase	11,3	6.620	234.000	Before Pregnancy	Imatinib 0-0-400 mg Hydroxyurea 0-0-1 g	TM 1 Imatinib TM 2 No treatment	Aterm live birth 2850 g/51 cm Healthy baby (other hospital)	No	Alive
CML Chronic Phase	12,3	9.450	151.000	Before Pregnancy	Imatinib 0-0-400 mg	TM1 Imatinib TM2 Hydroxyurea	Aterm live birth 3200 g/ 35 cm, healthy baby (other hospital)	No	Alive

CML Chronic Phase	10,3	**79.050**	258.000	Before Pregnancy	Imatinib 0-0-300 mg	TM 1 Imatinib TM 2 Hydroxyurea 0-0-1 g	Aterm live birth 3500 g/ 50 cm AS 8 dan 9	No	Alive
CML Accelerated Phase	**6,5**	**287.540**	376.000	Before Pregnancy	Imatinib 0-0-100 mg	Imatinib PRC Transfusion Leukafaresis, Hydroxyurea	Abortion Therapeutic	-	Alive
CML Chronic Phase	**8,2**	**478.080**	448.000	Before Pregnancy	Imatinib 0-0-200 mg	TM 1 Imatinib TM 2 Hydroxyurea 0-0-1 g	Aterm live birth 1920 g/ 45 cm, healthy baby	No	Alive
CML Chronic Phase	10,2	**26.640**	**2.174.000**	During Pregnancy TM1	Hidroxyurea 0-0-1 g	Hidroxyurea 0-0-1 g Allopurinol 1x100 mg	Abortion Therapeutic	-	Died e.c Febrile Neutropenia
CML Blastic Crisis Phase	**4,7**	**45.950**	**4.000**	Before Pregnancy	Imatinib 0-0-400 mg	Imatinib 0-0-400 mg	Died while pregnant	-	Died e.c sepsis
CML Chronic Phase	11,8	**21.600**	436.000	Before Pregnancy	Hydroxyurea 0-0-1 g	TM 1 Hidroxyurea 0-0-1 g TM 2 Hidroxyurea 0-0-1,5 g	Aterm live birth 2300 g/ 47cm/ AS 8 dan 9, BS 37 mgg LS p10-25%	No	Alive

Discussion

The prevalence of pregnancy-associated leukemia worldwide is approximately 1 case per 75,000 to 100,000 pregnancies. This rare occurrence hinders the conduct of large prospective studies to analyze the diagnosis, management, and pregnancy outcomes2. At dr. Soetomo Hospital, this is the first case study on leukemia during pregnancy. However, at dr. Soetomo Hospital Surabaya, the incidence of leukemia during pregnancy is relatively high compared to the global population. Data collected from 2019 to May 2024 revealed 12 patients out of 5789 deliveries, with case distribution as follows: 8 cases (66.7%) were CML, 2 cases (16.7%) were AML, 2 cases (16.7%) were ALL, and no cases of CLL were found. Roughly, this translates to 1 case per 482 deliveries at dr. Soetomo Hospital. This is due to RSDS being a tertiary referral hospital, providing adequate cancer care in East Java Province.

The age range at leukemia diagnosis was from 13 years (the youngest) to 34 years (the oldest), and the age range during pregnancy and follow-up at dr. Soetomo Hospital was from 19 years (the youngest) to 36 years (the oldest). The average age of patients at leukemia diagnosis at dr. Soetomo Hospital was 23 years, and during pregnancy, the average age was 25 years. The median age in China, Hong Kong, India, the Philippines, Singapore, South Korea, Thailand, and Malaysia ranges between 36-55 years. Indonesia has a similar situation, with a median age of 34-35 years (average 36 years) and a male-to-female ratio of 1.5:1. Data from dr. Cipto Mangunkusumo General Hospital show an average (SD) age of diagnosis of 39 years with a standard deviation of 13 years. A previous study conducted

between 2003 and 2008 revealed comparable findings, with a median age at diagnosis of 37 years and a male-to-female ratio of 1.2:1. The data at dr. Cipto Mangunkusumo General Hospital and Indonesia resemble trends in Asia3. The age of pregnant patients with CML in this case series ranged from 19 to 36 years, and almost all CML patients were diagnosed before pregnancy.

Leukemia impacts the physiology of pregnant women. General catabolism occurs in all patients with malignancies, both the underlying disease and the anorectic effects of chemotherapy agents lead to reduced nutrition for the mother and fetus. Possible mechanisms causing intrauterine growth retardation in babies born to mothers with acute leukemia include decreased maternal hemoglobin concentration, which can directly result in decreased oxygen transfer to the fetus. Leukemic cell aggregates in the uteroplacental circulation can reduce blood flow. Disseminated intravascular coagulation, which can occur in ALL, can cause vascular disturbances in the uteroplacental circulation. Furthermore, because normal white blood cells are replaced by leukemic infiltrates, white blood cell function is suppressed, and maternal resistance to infection is greatly reduced. Preterm labor, whether medically induced or spontaneous, is common in acute leukemia, and the primary cause is unknown. Maternal death during previous pregnancies was a leading cause of fetal death. Many chemotherapy agents used in the treatment of acute leukemia are known to cross the placenta. Because their effectiveness in cancer treatment is related to their ability to damage and destroy dividing cells, it is not surprising that many have been shown to cause developmental anomalies in animal and human studies. Concerns have been raised regarding the potential long-term effects of chemotherapy on the fetus, including poor growth, poor intellectual function, loss of reproductive capacity, impaired immunological status, and the development of secondary malignancies4. In this case series, no fetuses were exposed to chemotherapy agents in patients with acute leukemia, so the effects of chemotherapy on the fetus cannot be assessed. Meanwhile, 5 out of 8 successful pregnancies with CML did not show growth disturbances in the fetus.

Pregnancy can potentially affect the course of leukemia or other malignancies in various ways: it can increase or decrease its incidence, improve or delay diagnosis, limit therapeutic options, or affect cure rates. Pregnancy is a condition with a reduced immune response. Given that one function of the immune system is to detect and destroy cancer at an early stage. The diagnosis of new leukemia cases during pregnancy is more complicated compared to non-pregnant women, as anemia and thrombocytopenia are common in pregnant women. If neutropenia is detected, it should raise suspicion and require close monitoring. If blasts are found in the blood circulation, a bone marrow biopsy should be performed. The diagnostic criteria for diagnosing leukemia in pregnant women are the same as in the general population. During pregnancy, some early symptoms of acute leukemia, such as fatigue and shortness of breath, or changes in peripheral blood counts, like anemia, leukocytosis, and thrombocytopenia, might be interpreted as pregnancy-related symptoms, leading to delayed diagnosis and inappropriate therapy. If not treated promptly, this disease can result in rapid maternal and fetal death. Additionally, delaying induction chemotherapy negatively impacts the likelihood of patient remission5. In this case series, three patients were diagnosed with new leukemia during pregnancy. Two of the patients were diagnosed with acute leukemia, specifically AML, and both exhibited severe clinical manifestations. Patient 1 was diagnosed

with acute leukemia in the first trimester (at 9/10 weeks of gestation) and showed symptoms of shortness of breath, weakness, anemia, vaginal bleeding, and decreased consciousness. Laboratory results indicated severe anemia, thrombocytopenia, and hyperleukocytosis (Hb 4.5 g/dl; WBC 148,200/µl; Plt 87,000/µl). The clinical condition of this patient deteriorated rapidly, and she died within 48 hours of being treated. A bone marrow biopsy (BMA) was not performed on this patient due to thrombocytopenia and a tendency to bleed. The diagnosis was based solely on routine blood tests and a Peripheral Blood Smear (PBS), which showed normochromic normocytic anemia, leukocytosis with a predominance of myeloblasts without maturation, and thrombocytopenia. The patient died from ARDS before chemotherapy could be administered. Patient 2 was also a new case of acute leukemia during pregnancy, with AML and severe clinical manifestations, including weakness, headache, bleeding gums, and skin abscesses. Laboratory results indicated anemia, severe thrombocytopenia, and BMA was not performed on this patient due to thrombocytopenia. The diagnosis was made based on routine blood tests and a Peripheral Blood Smear, which showed normochromic normocytic anemia with anisopoikilocytosis, leukocytosis with 85% blasts, and thrombocytopenia. Chemotherapy had not been administered yet, and the patient's condition was being stabilized in relation to severe anemia and thrombocytopenia, with plans for BMA in the future. Of the eight CML patients in this case series, seven were diagnosed before pregnancy and were already undergoing treatment. The clinical manifestations of CML patients varied depending on the phase of the disease, with milder symptoms in the chronic phase and more severe symptoms in the accelerated or blast crisis phases. Regardless of the severity of the symptoms, laboratory findings showed anemia, leukocytosis, and thrombocytopenia/thrombocytosis. Of the 12 patients in this case series, only four had BMA data: patients 3 and 4 (ALL), patient 8 (accelerated phase CML), and patient 9 (chronic phase CML). BMA in the ALL patient (patient 4) and two CML patients showed hypercellularity, while BMA in one ALL patient (patient 3) showed normocellularity, as it was performed in 2022 during an evaluation. No BMA data were available at the initial diagnosis of ALL in 2015.

This case series presents four cases of acute leukemia during pregnancy, showing that perinatal outcomes tend to be better if the onset of acute leukemia occurs in the third trimester compared to the first or second trimesters, and with induction chemotherapy leading to better maternal outcomes. Two of the four acute leukemia cases showed good maternal outcomes (patients 3 and 4) after receiving immediate induction chemotherapy, although the fetal outcomes were spontaneous abortion (patient 3) and therapeutic abortion (patient 4). The other two patients (patients 1 and 2) died before chemotherapy could begin, resulting in poor maternal outcomes. Perinatal outcomes were better in third-trimester pregnancies (patient 2), where pregnancy termination was performed at 33/34 weeks of gestation, while the other three patients ended in abortion in the first trimester (patient 1) and second trimester (patients 3 and 4). According to the literature, in acute leukemia, elective delivery can be scheduled based on fetal maturity, and a gestational age of 32 weeks or more is usually acceptable. Although delaying induction chemotherapy is generally associated with poor outcomes for the mother, a slight delay in treatment to allow for delivery first may be considered for patients diagnosed in late pregnancy (>30 weeks). There are several reasons to consider this, including the potential risks of hematopoietic suppression, growth restriction, intellectual impairment, and reduced fertility in babies exposed to chemotherapy

in the third trimester. Additionally, the administration of cytotoxic chemotherapy agents after 30 weeks may trigger labor during a period of bone marrow suppression, increasing the risk of infection and bleeding. If a patient is diagnosed with acute leukemia after 30 weeks of gestation, delivering the baby first can minimize chemotherapy exposure to the fetus while maintaining a high neonatal survival rate6. If possible, normal delivery is preferred over cesarean section to reduce the risk of bleeding7.

Two patients with AML in this case series, one was diagnosed in the first trimester, and the other was diagnosed with leukemia during the third trimester of pregnancy. The clinical manifestations in the AML patients in this case series included shortness of breath, weakness, anemia, vaginal bleeding, thrombocytopenia, and hyperleukocytosis (Hb 4.5 g/dl; WBC 148,200/µl; Plt 87,000/µl) in patient number 1. The patient felt very weak due to severe anemia. The patient experienced threatened abortion with symptoms of vaginal spotting, likely related to thrombocytopenia. Patient number 2 showed clinical manifestations of weakness, headache, gum bleeding, anemia, leukocytosis, and severe thrombocytopenia (Hb 8.5 g/dl; WBC 17,380/µl; Plt 7,000/µl). The patient felt weak due to anemia and had gum bleeding due to severe thrombocytopenia. Both patients received PRC and TC transfusions related to anemia and thrombocytopenia. Patient 1 died within less than 24 hours of care at RSDS and had not yet undergone chemotherapy. In patient 2, pregnancy was terminated at 33/34 weeks of gestation, within two weeks of hospitalization before termination. The baby was born preterm, 1900 g, with a length of 43 cm, and Apgar score of 3, 5, and 7. Induction chemotherapy was delayed for 2 weeks after the diagnosis was made. The patient died before induction chemotherapy could begin. This aligns with the study by Greenlund et al. in the UK, which found that pregnancy itself may not affect chemotherapy outcomes in AML, but delayed treatment in AML patients can worsen maternal outcomes without improving pregnancy outcomes8. In this case series, there were two patients with ALL. The patients were diagnosed with ALL-L1 and ALL-L2. Both patients were diagnosed with leukemia before pregnancy, at the ages of 13 and 27. Patient number 3 had undergone several rounds of chemotherapy from 2014 to 2022 and had a relatively good therapeutic response previously. However, during the first trimester of pregnancy in 2023, the patient relapsed and experienced a spontaneous abortion. Patient number 4 had also undergone several rounds of induction chemotherapy, and at the age of 29, became pregnant, leading to a therapeutic abortion at 18 weeks of gestation. The clinical manifestations of these two patients during relapse were very clear, including feelings of weakness, pallor, pancytopenia (anemia, leukopenia, thrombocytopenia), hypokalemia, and hypoalbuminemia. Vincristine and Prednisone chemotherapy were administered after the abortion. Patient number 3 survived during care but was found to have died 7 months after being discharged from the hospital. Patient number 4 is still alive to this day and is still undergoing chemotherapy.

The effects of chemotherapy on fetal development depend on the point in pregnancy at which the chemotherapy is administered. During the pre-embryogenesis stage (from fertilization to 17 days after conception), rapid cell division occurs. Damage to most of the conceptus cells is likely to result in miscarriage, but if the damaged cells are replaced, there is unlikely to be any long-term effect. Organogenesis occurs during the embryonic period (2-8 weeks after conception), and if organ damage (heart, neural tube, and limbs) is induced by chemotherapy during this time, the effects are likely to be permanent. During the fetal period

(8-38 weeks after conception), the growth and differentiation of the digestive and renal systems and the cerebral cortex continue and remain vulnerable to chemotherapy-induced toxicity. As a result, chemotherapy administered in the first trimester is associated with the highest risk of miscarriage, fetal death, and congenital malformations, ranging from 10% to 20%. Chemotherapy also inhibits trophoblast migration and proliferation, which may contribute to low birth weight in newborns. However, this data is limited as it is based on rare case reports and a small number of retrospective studies7. Patients who delayed chemotherapy experienced a tendency for higher mortality rates compared to those who received timely chemotherapy, and initiating chemotherapy as soon as possible can increase the rate of complete remission6,9-13.

CML occurs in up to 10% of leukemia cases during pregnancy. The course of CML does not appear to be affected by pregnancy7. In this case series, there were 8 patients with CML. Of these 8 patients, 7 were long-standing cases already under treatment before pregnancy, and 1 was a new case of CML, where the patient had a history of thrombocytosis for the past 8 months and was only diagnosed with CML during the first trimester of pregnancy. This delay in diagnosis was due to the prominent laboratory manifestation of thrombocytosis, while anemia and leukocytosis were not significant (Hb 10.2; WBC 26,640/µl; Plt 2,174,000/µl), leading to a late diagnosis and the patient's death due to febrile neutropenia. Six were in the chronic phase, 1 in the accelerated phase, and 1 in the blast crisis phase. Regarding maternal outcomes in chronic phase cases, 5 of the 6 patients survived, while 1 patient died during treatment due to complications from thrombocytosis (Plt 2,174,000). The patient in the accelerated phase (patient number 7) survived, undergoing a therapeutic abortion at 9/10 weeks of gestation followed by sterilization and leukapheresis (WBC 287,540 at the time) and was subsequently treated with Hydroxyurea. One patient in the blastic crisis phase died during treatment. This patient had severe anemia, thrombocytopenia, and leukocytosis, with a tendency to transform into ALL, as peripheral blood smear results showed 93% lymphoblasts. The patient had been diagnosed with CML a year before pregnancy and was receiving Imatinib 4x100 mg, which was discontinued upon pregnancy and died while the pregnancy in progress

Among the 8 CML patients, 2 pregnancies ended with therapeutic abortions, 1 patient died in the first trimester, 1 pregnancy ended in preterm delivery, and 4 pregnancies resulted in aterm deliveries. Six out of the 8 patients regularly consumed Imatinib before pregnancy. This supports data that Imatinib tends not to affect female fertility. Data on the effects of Imatinib on ovarian function is indeed still limited. One publication reported ovarian failure in a 30-year-old CML patient who received Imatinib for 2 years. Another case report on a 17-year-old Asian woman showed low ovarian response to gonadotropins while on Imatinib, with ovarian response returning to normal after Imatinib was discontinued. However, many other case reports show that pregnancies frequently occur in patients taking Imatinib14. Five deliveries involving CML patients showed good perinatal outcomes, with no signs of fetal growth restriction or congenital abnormalities. All mothers who gave birth with CML had been exposed to Imatinib in the first trimester before pregnancy was confirmed, and 4 out of 5 were treated with Hydroxyurea after Imatinib was discontinued until delivery. None of the babies born with any congenital abnormalities. This case series aligns with several studies in various countries, such as Brazil15. In CML, conception should be planned, and TKI therapy

should be discontinued in women during pregnancy. The use of Imatinib during pregnancy falls under FDA Category D. Women should be clearly informed about the potential risks to the fetus if Imatinib is used during pregnancy or if they become pregnant while on the drug. Mammalian ovaries express c-kit, c-abl, and platelet-derived growth factor, which are inhibited by TKIs, and these are important in the growth and maturation of oocytes and follicles. When CML is diagnosed in the first trimester, termination of pregnancy is considered not to harm the mother; however, TKIs are associated with fetal malformations if used in the second trimester. Typical congenital abnormalities have occurred following the administration of Imatinib early in pregnancy, including exomphalos, omphalocele, pulmonary hypoplasia, duplex kidneys, renal agenesis, skeletal malformations (craniosynostosis, shoulder anomalies, and scoliosis), and spontaneous abortion16. In cases where conception occurs while using Imatinib, ideally, Imatinib should be discontinued, and close monitoring of fetal development should be carried out to detect fetal abnormalities, regardless of maternal age16.

In this study, all pregnancies with CML were unplanned, and all patients who were previously on Imatinib had their therapy discontinued upon pregnancy confirmation. Hydroxyurea is a cytotoxic drug that inhibits DNA synthesis. This treatment is not curative. Hydroxyurea is generally used in AML at diagnosis, especially in cases of hyperleukocytosis, to control leukemic proliferation until chemotherapy regimens are initiated. Preclinical models have shown that Hydroxyurea is teratogenic in all animal species. Congenital anomalies of the heart, central nervous system, skeleton, and neural tube defects have been described. In humans, cases of Hydroxyurea exposure during pregnancy in patients with chronic myeloid leukemia have been recently reviewed. Despite severe teratogenicity in animals, no reports have shown chromosomal abnormalities in newborns or malformations. Only one woman experienced a spontaneous miscarriage. However, Hydroxyurea should not be a treatment choice during pregnancy17,18. In this case series, 4 out of 5 successful pregnancies ended in live births, despite exposure to Hydroxyurea during pregnancy, with no congenital abnormalities in the babies born. In this case series, 2 patients were asymptomatic during pregnancy (patients 4 and 5), for patient 4, Imatinib was immediately discontinued once pregnancy was confirmed, and no therapy was given during pregnancy. The patient remain stable until the end of the pregnancy with a good perinatal outcome, delivering a aterm baby 2859 grams. For patient 5, pregnancy was known in the second trimester (18/19 weeks), the patient was exposed to Imatinib during the first trimester. This aligns with the literature stating that patients with CML in the chronic phase during the first trimester may not require treatment if the white blood cell count is below 100,000/µl and the platelet count is below 500,000/µl19. One patient (patient 10) who was initially in the chronic phase of CML but progressed to blastic crisis at the beginning of pregnancy, which is an aggressive phase of the disease with a poor prognosis. The patient was first diagnosed with chronic-phase CML in November 2022 (five months before becoming pregnant) and received imatinib therapy. Imatinib was discontinued once pregnancy was confirmed. The blastic crisis phase represents the progressive transformation of CML into a phase resembling acute leukemia. Patients with chronic-phase CML generally progress to blast crisis at a rate of 1% per year; thus, most patients will have a known prior diagnosis of CML. The blast crisis phase can last several months without treatment and presents with symptoms of acute leukemia, with at least 20% blasts in the bone marrow or

peripheral blood. Management recommendations are similar to those for patients with acute leukemia during pregnancy19. The progression from the chronic to blastic crisis was likely due to the discontinuation of imatinib16. Women with CML who wish to become pregnant should wait until achieving a major molecular response (MMR) and maintain this condition for at least two years. Imatinib can be discontinued immediately before ovulation, possibly at the time of menstruation. The duration of time without medication before conception should be limited because this period will be added to the duration of pregnancy as the total time without treatment; six months may be acceptable, although this can be extended if sequential RT-qPCR analysis for BCR-ABL1 transcripts shows no increase from baseline values. For women with a less deep or short-lived response, consideration may be given to using IVF techniques to achieve a quick pregnancy or storing embryos for reimplantation after further treatment. Although there are reported cases where patients continued therapy throughout pregnancy without problems for the baby, it is not recommended to use TKIs during pregnancy16. chronic lymphocytic leukemia (CLL This aligns with the literature, which states that CLL concurrent with pregnancy is extremely rare, primarily due to the fact that the median age at diagnosis of this disease is 72 years, with only about 10% of CLL patients being under 55 years old20.

This case series showed the best maternal and perinatal outcomes were seen in patients with CML, while AML and ALL showed poor outcomes, and there were no patients with CLL, so the authors could not further discuss pregnancy outcomes with CLL. Four cases of acute leukemia showed poor fetal outcomes if the leukemia occurred or relapsed in the first and second trimesters. Fetal outcomes were better when leukemia occurred in the third trimester. Among the two patients with AML, both showed poor maternal outcomes, with both patients dying during treatment. Chemotherapy had not yet been administered, and the causes of death were respiratory failure and febrile neutropenia, respectively. The ALL patients in this case showed better maternal outcomes compared to AML. One ALL patient had a spontaneous abortion, and one patient underwent a therapeutic abortion in the second trimester, allowing chemotherapy to begin in both patients after the abortion. During treatment, these patients showed relatively good outcomes and were discharged from the hospital alive; however, one patient died during a follow-up seven months after discharge. The cause of death is unknown as it occurred in another hospital. The eight CML patients showed better maternal and perinatal outcomes compared to acute leukemia. Eight CML patients consisted of six patients in the chronic phase, one patient in the accelerated phase, and one patient in the blast crisis phase. Seven of the eight CML patients were diagnosed before pregnancy and became pregnant while undergoing therapy. Before pregnancy, five patients received Imatinib only, two received Hydroxyurea only, and one received both Imatinib and Hydroxyurea. All pregnancies in this case series were unplanned, so all patients on Imatinib were exposed to it in the first trimester, but once pregnancy was confirmed, Imatinib was discontinued. Five of the eight patients received Hydroxyurea during pregnancy due to leukocytosis. Four of the five fetuses exposed to Hydroxyurea during pregnancy showed good fetal outcomes, with live births and good Apgar scores without congenital abnormalities. Compared to a study at Anderson Cancer Center, USA, from 1999 to 2005 on 18 patients with 19 pregnancies from 10 female patients and 8 pregnancies from male partners of women with leukemia who became pregnant while on Imatinib, one patient had a therapeutic abortion, three patients had spontaneous abortions, seven patients delivered

at term, and seven patients delivered preterm. Only one baby was born with hypospadias; the other babies were born healthy without congenital abnormalities21. One CML patient in the blast crisis phase died, one patient in the accelerated phase underwent therapeutic abortion and survived after leukapheresis and Hydroxyurea therapy, and one patient in the chronic phase died during treatment due to febrile neutropenia. In this patient, therapy was discontinued during pregnancy. Upon returning for follow-up, thrombocytosis and neutropenia were detected, but the patient died before plateletpheresis could be performed. This case series shows similar results to a study by Nomura et al. A 10-year retrospective study conducted from 2001 to 2011 in Brazil22.

4. Conclusion

Chronic Leukemia showed better maternal and perinatal outcomes compared to acute leukemia, diagnosed of acute leukemia in the third trimester showed better outcome compared to the first and second trimesters and chronic phase of CML patients showed the best maternal and perinatal outcomes compared to accelerated and blastic crisis phase of CML. Although almost all successful pregnancies in this case series exposed to imatinib during the first trimester deliver healthy babies without congenital anomalies, the use of TKIs is not recommended in pregnancy because of the risk of teratogenicity from other studies. Patients who wish to conceive should be advised to interrupt TKIs, with the recommendation that they achieve a stable and deep molecular response or at least a stable MMR before discontinuation. Hydroxyurea is a safe option for patients with hyperleukocytosis during pregnancy.

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