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Update on Leukemia in Pregnancy

Khalid Ahmed Al-Anazi

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Abstract

Leukemia is a rare event in pregnancy. Acute leukemia represents 90% of leukemias occurring during pregnancy with AML accounting for two thirds of these cases. During the first trimester of pregnancy, standard chemotherapy has a teratogenicity rate of up to 20% depending on the specific agent employed. Exposure to cytotoxic agents during the second and third trimesters is not teratogenic but may predispose the fetus to growth retardation, premature delivery and bone marrow suppression. Additionally, the mother and the fetus are at risk of thromboembolism and sepsis. Only absolutely necessary radiologic work-up is justified during the first trimester of pregnancy as exposure to radiation during the first 2 weeks of pregnancy is usually lethal. Thereafter, radiation predisposes to congenital malformations, growth retardation and malignancy in the newborn. Although most infants exposed to multi-agent chemotherapy seem to suffer no long-term detrimental consequences, studies have shown that: (1) cytotoxic chemotherapy can cross the placenta and cause teratogenicity, (2) there is a potential risk of adult cancer after intrauterine exposure to radiation, and (3) cytotoxic chemotherapy and radiotherapy increase genetic defects in germ cells. In the first trimester, the termination of pregnancy should seriously be considered if the disease is aggressive and if intensive chemotherapy is needed. In the second and third trimesters, standard chemotherapy can safely be administered without resorting to pregnancy termination. The choice of specific regimens depends upon several factors that include: the gestational age, the clinical status of the patient, the specific type of leukemia and the anticipated toxicity of the cytotoxic agents employed. The decision is often difficult and confounded by several concerns, but the management of each pregnant patient with leukemia has to be individualized and should have a multidisciplinary approach. Vaginal delivery is preferable while caesarean section is reserved for certain obstetric complications. It is preferable to time delivery between 32 and 36 weeks of gestation to ensure optimal

fetal maturation and it is recommended to avoid maternal bone marrow suppression prior to delivery.

The management of chronic leukemia in pregnancy is generally easier than that of acute leukemia. However, certain precautions should be taken as some targeted therapies need to be avoided and they may need to be replaced by alternative therapies that are less effective in controlling chronic leukemia. Pregnancy in patients with chronic myeloid leukemia on tyrosine kinase inhibitors requires proper planning as it is essential to have optimal control of the disease for 2 to 3 years prior to having pregnancy in order to avoid acceleration of the disease during pregnancy.

Leukemia diagnosed during pregnancy can be considered a poor clinical prognostic factor owing to the less than average long-term disease-free survival due to high relapse rates and high incidence of refractoriness to chemotherapy. Countries should have registries for mothers and children exposed to chemotherapy and radiotherapy and it is essential to have guidelines on the management of various types of leukemia during pregnancy.

Keywords: Acute leukemia, pregnancy, cytotoxic chemotherapy, chronic leukemia, abortion, teratogenicity

1. Introduction

During pregnancy, the body of the mother undergoes certain physiological changes that may make the diagnosis of leukemia more challenging. Thus the diagnosis of leukemia may be delayed as non-specific manifestations of leukemia such as fatigue, weakness and dyspnea may be attributed to gestation. Additionally, pregnancy itself may be associated with anemia and leukocytosis which are also common laboratory findings in patients with leukemia [1].

The diagnosis of leukemia requires morphologic, immunophenotypic and cytogenetic examination of bone marrow samples. However, bone marrow biopsies can be safely performed under local anesthesia in pregnant females without any harm to the fetus [1]. Leukemia itself often presents as a medical emergency that requires prompt initiation of appropriate therapy. Also, the diagnosis of leukemia in pregnancy is a rather exceptional event that can generate complex ethical and therapeutic dilemmas. Therefore a multidisciplinary team that includes hematologists, obstetricians, neonatologists, psychologists and social workers in addition to the patient should all be involved in making therapeutic decisions [2].

The decision to initiate chemotherapy during pregnancy must be weighed against the consequences of delaying treatment on maternal survival. In general, therapeutic decisions must be made on data obtained from prospective clinical trials, but unfortunately the available data in the literature on the management of most leukemias diagnosed during pregnancy are derived from retrospective case reports, case series and few meta-analyses [1].

This literature review will cover the following: the consequences of maternal and fetal exposures to cytotoxic chemotherapy, radiotherapy and targeted therapies; the detailed description of coexistence between various types of leukemia and pregnancy; and the specific data obtained from the major studies and the important case reports on pregnancy in different types of leukemia.

2. Physiological and hematological alterations in pregnancy

Pregnancy is associated with the following physiological changes that may alter drug metabolism: (1) slow gastric emptying, (2) increase in plasma volume by 50%, (3) increase in plasma proteins and decrease in serum albumin, (4) enhanced hepatic oxidation, and (5) increase in glomerular filtration and renal plasma flow [3]. Also, pregnancy is associated with several hematological complications that include: (1) anemia with iron deficiency, due to blood loss and nutritional causes, being the commonest hematological disorder; (2) thrombocytopenia which can be: gestational, due to idiopathic thrombocytopenic purpura, microangiopathic hemolytic anemia, pre-eclampsia, antiphospholipid antibody syndrome or systemic lupus erythromatosis evolving during pregnancy; (3) pancytopenia due to: acute fatty degeneration of the liver, bone marrow failure caused by aplastic anemia or congenital causes, leukemia, lymphoma or metastatic cancer evolving during pregnancy; (4) inherited or acquired bleeding disorders such as von Willebrand disease; and (5) venous thromboembolism [4-6].

3. Maternal exposures during pregnancy

Maternal exposure to the following agents during pregnancy may increase the risk of leukemia in the newborn infants: alcohol intake by the mother, cigarette smoking, antibiotic use, benzene exposure, exposure to estrogens, diethylstilbestrol and other hormones, bacterial infections, food-related or respiratory maternal IgE and *Helicobacter pylori* immunoglobulin G [7-14]. However, intake of the following by pregnant women may have protective effect against the development of leukemia in the newborn: vitamin supplements, folate supplements and diet rich in vegetables [15-17].

4. Exposure to diagnostic and therapeutic radiation

The association between in utero irradiation and the increased risk of childhood malignancies has been studied since the 1950s [18]. The potential deleterious consequences of ionizing radiation on the fetus include the following: (1) pregnancy loss; stillbirth or miscarriage, (2) congenital malformations, (3) disturbances in growth or development; growth and mental retardation, and (4) mutagenic and carcinogenic effects [19]. Radiotherapy given during the first trimester is associated with teratogenic effects and an increase in the risk of childhood

malignancy [20]. Radiotherapy given during the second and third trimesters of pregnancy is associated with: (1) an increased risk for the development of leukemia and solid tumors within the first decade of life, and (2) an increased risk of neurodevelopmental delay [20].

Diagnostic irradiation of the mother during pregnancy increases the risk of childhood acute lymphoblastic leukemia (ALL). Also, there is some evidence that exposure of the father to abdominal X-rays or intravenous pyelograms, prior to conception, increases the incidence of ALL in the offspring [21]. Prenatal X-ray exposure is associated with 40-80% increase in childhood cancers [22]. Prenatal exposure to ionizing radiation has been associated with a statistically significant increase in the incidence of all cancers and specifically leukemia in newborn infants [18]. However, the average radiation dose from individual diagnostic and therapeutic procedures has historically declined owing to the improvements in technology and equipment safeguards [18]. Postnatal X-ray exposure is also linked to a small elevation in the risk of all cancers in childhood [22]. At doses < 0.05 Gy there is no evidence of increased risk of: intellectual disability, fetal anomalies, loss of pregnancy or growth retardation [19]. During the first 14 days after fertilization: intact survival or death is the most likely outcome of radiation exposure ≥ 0.05 Gy (5 Rads). A conservative estimate of the threshold for intrauterine fetal death is > 1 Gy (10 Rads) [19]. After the first 14 days of gestation, radiation exposure ≥ 0.5 Gy may be associated with increased risks of congenital malformations, growth retardation and intellectual disability [19]. A total of 10-20 Gy of radiation, when given during organogenesis is considered to be the threshold dose for severe congenital malformations [20].

There are no reports of adverse fetal effects from diagnostic doses of radioactive iodine. However, radioactive iodine should not be administered to pregnant women because there is a concern that it may induce thyroid cancer in the offspring [19]. Antenatal ultrasound exposure is not associated with an increase in the risk of childhood cancer, so it is safe during all stages of pregnancy [19,22,23]. Magnetic resonance imaging (MRI) is generally preferred to other imaging modalities that involve ionizing radiation. However, gadolinium is not recommended for use in pregnant women [19]. Computed axial and positron emission scans are contraindicated during pregnancy, particularly in the first two trimesters. Both procedures can be performed after delivery but caution should be taken in breast-feeding women [23].

5. Exposure to cytotoxic chemotherapy in utero

The effects of cytotoxic chemotherapy on the developing fetus are dependent on the time of gestation at which such treatment is administered. In the pre-embryonic phase that extends from fertilization till 17 days after conception, significant damage to the conceptus cells results in miscarriage [24]. In the embryonic or organogenesis phase which occurs between 2 to 8 weeks following conception, chemotherapy may cause irreversible damage to the newly formed fetal body organs, while in the fetal phase which extends between the 8th and the 38th weeks after conception the gastrointestinal and renal tracts as well as cerebral cortex remain susceptible to chemotherapy-induced toxicity [24].

In a retrospective study that included 84 mothers with various hematological malignancies who had received cytotoxic chemotherapy during gestation, 38 fetuses were exposed to cytotoxic chemotherapy in utero during the first trimester of pregnancy [25]. The delivered children were followed up for a median time of 18.7 years (range 6-29 years). No cancer or acute leukemia was reported in the children who had been exposed to chemotherapy in utero so pregnant females having aggressive hematological malignancies including leukemia can receive cytotoxic chemotherapy at full doses even during the first trimester of pregnancies [25]. In another retrospective study that included 21 pregnancies in 18 patients with hematological malignancies, 8 babies were exposed to cytotoxic chemotherapy in utero [26]. Out of the 4 babies exposed to chemotherapy during the first trimester of gestation, 3 had low birth weight and one was born healthy but died three months later because of gastroenteritis. The fourth baby had been exposed to chemotherapy during the 3 trimesters of pregnancy, the baby was born prematurely and subsequently died of intracranial hemorrhage. Out of the 3 babies exposed to chemotherapy during the second and third trimesters of pregnancy: one died in utero, one had low birth weight and one was born alive but died of pulmonary hemorrhage later on. [26]. The adverse effects of cytotoxic and targeted therapies in pregnant females and newborn infants are summarized in Table 1 [3,27-30]. The adverse effects of cytotoxic chemotherapy and radiotherapy in pregnant mothers and fetuses are included in Table 2 [30]. The genotoxic and teratogenic effects of various cytotoxic agents are shown in Table 3 [31-33]. The recommended therapies that are relatively safe in treating pregnant females with leukemia are summarized in Table 4 [1,2,20,23,34-39].

Drug (class)	Common adverse effects in pregnant mothers	Common adverse effects in newborn infants	Teratogenic effects
Cytarabine (pyrimidine analogue)	<ul style="list-style-type: none"> - Myelosuppression - Diarrhea - Skin rashes - Fever - Hepatotoxicity 	<ul style="list-style-type: none"> - Myelosuppression - Infections - Hepatopathy - Meningeal hemorrhage - Respiratory distress symptoms -Chromosomal abnormalities: Down's syndrome and inversion of chromosome 9. - Growth defects and congenital malformations. 	<ul style="list-style-type: none"> - Teratogenic in animals. - Expected to penetrate the blood placental barrier. - No measurements performed in human placenta.
Daunorubicin (anthracycline)	<ul style="list-style-type: none"> - Myelosuppression - Acute and chronic cardiotoxicity - Mucositis - Alopecia - Nausea and vomiting 	<ul style="list-style-type: none"> - Myelosuppression; pancytopenia and anemia. - Hepatopathy and elevated CK level - Seizures and respiratory tract infections 	<ul style="list-style-type: none"> - Teratogenic in mice - Less teratogenic than doxorubicin

Drug (class)	Common adverse effects in pregnant mothers	Common adverse effects in newborn infants	Teratogenic effects
		- Spontaneous abortions, premature delivery and still birth. -Chromosomal abnormalities and congenital malformations	
Idarubicin (anthracycline)	- Myelosuppression - Acute and chronic cardiotoxicity - Mucositis - Alopecia - Nausea and vomiting	- Myelosuppression - Cardiomyopathy - Hepatopathy and elevated CK level - Acrocyanosis and hyperbilirubinemia - Intrauterine fetal death and growth retardation - Congenital malformations: short limbs and macrognathia	- Idarubicin is more lipophilic than other anthracyclines so it may increase the concentration crossing the placenta
Doxorubicin (anthracycline)	- Myelosuppression - Cardiotoxicity - Mucositis and alopecia - Nausea and vomiting	- No major side effects. - Transient myelosuppression - Hyaline membrane disease - Meningeal hemorrhage - Premature delivery & fetal distress - Imperforate anus and rectovaginal fistula	- Crosses the placenta - Can distribute into fetal tissues including liver, lung and kidneys.
Etoposide (topoisomerase inhibitor)	- Myelosuppression - Prolongation of PT and INR - Hypotension - Fever and alopecia	- Transient pancytopenia - Leucopenia - Hearing loss	- Decreased serum albumin level - Potential of elevated free drug levels and increase in drug toxicity.
Mitoxantrone (anthracenedione)	- Cardiotoxicity - Hepatotoxicity - Alopecia	- No major adverse effects reported - Pancytopenia	- Teratogenic in animals: fetal growth retardation and premature delivery.
Fludarabine (purine analogue)	- Myelosuppression - Autoimmune effects - JC virus-induced progressive multifocal leukoencephalopathy.	- No fetal adverse effects reported	- Teratogenic in rats and rabbits. - Increased incidence of skeletal malformations in rats.
Cyclophosphamide (alkylating agent)	- Hemorrhagic cystitis - Cardiotoxicity - Myelosuppression	- Myelosuppression - Low birth weight, still birth and growth retardation	- Teratogenic in animals - May cross placenta in mice

Drug (class)	Common adverse effects in pregnant mothers	Common adverse effects in newborn infants	Teratogenic effects
	- Alopecia, nausea and vomiting	- Imperforate anus and rectovaginal fistula, facial abnormalities, single left coronary artery and hernias.	- Teratogenic in mice, rats and rabbits.
Vincristine (vinca alkaloid)	- Neurotoxicity - Alopecia - SIADH	- Anemia and severe pancytopenia - Left shift in leukocytes and mild infections - Hyaline membrane disease - Low birth weight, spontaneous abortions, hydrocephalus and cleft lip	- Vincristine is highly protein bound. - Penetration into barriers such as blood placental barrier may be limited.
Hydroxyurea (antimetabolite)	- Myelosuppression	- Still birth without gross abnormalities - Premature delivery without congenital defects - Intrauterine fetal death and growth retardation	- None reported
Methotrexate (antimetabolite)	- Myelosuppression - Acute renal failure	- Spontaneous abortions low birth weight - Pancytopenia - Aminopterin-type syndrome	- None reported
ATRA (PML-RARA targeted therapy)	- Hemorrhage - Differentiation syndrome - DIC - Fever	- Miscarriage and fetal death - Pulmonary hyperplasia and respiratory distress - Thrombocytopenia - Intrauterine growth retardation	- When give during first trimester: severe neurological and cardiovascular complications. - Teratogenicity risk: 85%
Interferon alpha	- Fatigue - Flu-like illness - Intertility	- Fetal malformations in 1 case out of 8 patients reported (concurrent with use of hydroxyurea).	--
Imatinib (TKI; first generation)	- Fatigue - Fluid retention	- Elective abortions done due to congenital malformations. - Exophthalmos and brain abnormalities - Cardiac and renal anomalies - Hypospadias and bone abnormalities	- Teratogenic in animals: exencephaly, encephalocele, absent or reduced frontal or parietal bones
Dasatinib	- Fluid retention	- Spontaneous abortions	--

Drug (class)	Common adverse effects in pregnant mothers	Common adverse effects in newborn infants	Teratogenic effects
(second generation TKI)		- Elective abortions	
Rituximab (Anti-CD20 monoclonal antibody)	- Infusion related reactions - Myelosuppression	- Few reports show safety in all -- trimester of pregnancy - Transient β -cell depletion has been reported	

Table 1. shows adverse effects of cytotoxic and targeted therapies reported in pregnant females and newborn infants

(A) cytotoxic chemotherapy given during the first trimester of pregnancy			
Drug		Estimated risk of congenital malformations	
Cytosine arabinoside		1:8	
Cyclophosphamide		1:6	
Methotrexate		1:4	
Chlorambucil		1:2	
Busulfan		1:9	
(B) effects of radiation on pregnancy and fetus			
Dose of radiation		Effects on the fetus	
Gy	Rad		
< 0.1	< 10	No major effect	
0.1-0.15	10-15	Increased risk	
2.5	250	Malformations in most cases	
> 30	> 300	Abortion	
(C) adverse effects of radiation in relation to gestational age			
Gestational age		Adverse effects	
Conception till day 10		Lethal	
2 to 6 weeks		Teratogenesis and growth retardation	
12 to 16 weeks		Microcephaly, mental and growth retardation	
20 weeks till delivery		Sterility, malignancy and genetic defects	

Table 2. Adverse effects of chemotherapy and radiation on pregnancy and fetus

High risk [> 80%]	Intermediate risk [20% - 80%]	Low risk [< 20%]	Unknown risk
- Therapeutic radiation to ovaries	- Anthracyclines	- Methotrexate	- Tyrosine kinase inhibitors

High risk [> 80%]	Intermediate risk [20% - 80%]	Low risk [< 20%]	Unknown risk
- Alcohol	- Cytosine arabinoside	- 5 fluorouracil	- Monoclonal antibodies
- Retinoic acid	- Cisplatinum	- 6 mercaptopurine	- Taxanes
- Valproic acid	- Carboplatin	- Etoposide	- Bleomycin
- Cyclophosphamide and ifosfamide		- Fludarabine	
- Thalidomide		- Vinca alkaloids	
- Busulfan		- Actinomycin D	
- Melphalan			
- Chlorambucil			
- Decarbazine and procarbazine			
- Thiotepa			
- Stem cell transplantation			
- Doxorubicin			

Table 3. Genotoxic and teratogenic agents in human classified according to the risk levels

Type of leukemia	First trimester	Second trimester	Third trimester
Non-M3 Acute myeloid leukemia	- Termination of pregnancy	- Cytarabine + doxorubicin - High dose cytarabine - Cytarabine + daunorubicin	- Cytarabine + doxorubicin - High dose cytarabine - Cytarabine + daunorubicin
Acute promyelocytic leukemia	- Termination of pregnancy	- ATRA + anthracyclines: daunorubicin, idarubicin or doxorubicin	- ATRA + anthracyclines: daunorubicin, idarubicin or doxorubicin
Acute lymphoblastic leukemia	- Termination of pregnancy - Corticosteroids	- Modified ALL-induction regimens of chemotherapy including methotrexate and corticosteroids.	- Standard induction regimens of chemotherapy.
Chronic myeloid leukemia	- Interferon - α - Hydroxyurea - Leukapheresis	- Interferon - α - Hydroxyurea - Leukapheresis - TKIs such as imatinib	- Interferon - α - Hydroxyurea - Leukapheresis - TKIs such as imatinib
Chronic lymphocytic leukemia	- Leukapheresis - Corticosteroids	- Leukapheresis - Corticosteroids - Chlorambucil - Cyclophosphamide - Rituximab	- Leukapheresis - Corticosteroids - Chlorambucil - Cyclophosphamide - Rituximab

Type of leukemia	First trimester	Second trimester	Third trimester
Hairy cell leukemia	- Splenectomy	- Splenectomy	- Splenectomy
	- Interferon	- Interferon	- Interferon
		- Cladribine	- Cladribine
		- Rituximab	- Rituximab

Table 4. Recommended therapies and relatively safe medications during pregnancy

6. Leukemia in pregnancy

The annual incidence of leukemia in pregnancy is approximately 1:100,000 pregnancies. This low incidence can be explained by the fact that leukemia usually spares childbearing ages as follows: (1) ALL occurs predominantly in childhood and acute myeloid leukemia (AML) occurs most frequently in late adulthood, and (2) chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) predominantly affect individuals belonging to age groups older than childbearing age [2]. The majority of cases of leukemia in pregnancy are acute leukemia with AML representing two thirds of cases and the vast majority of chronic leukemias diagnosed during pregnancy are CML [1,2].

Virtually all cytotoxic agents can cross the placenta and reach the fetus and almost all chemotherapeutic agents have been reported to be associated with congenital malformations in animal models [1,2]. In humans, chemotherapy administered during the first trimester of pregnancy in humans may increase the risk of spontaneous abortion, fetal death and major malformations, but the risk of teratogenesis following cancer therapy appears to be lower in humans than in animals [1,2]. Exposure to chemotherapy during the first trimester of pregnancy is associated with 10-20% risk of major malformations, but this risk is usually lower when single agent chemotherapy is administered and when antimetabolites are excluded. Hence, if the administration of cytotoxic chemotherapy during the first trimester of pregnancy is essential, therapeutic abortion will become strongly recommended [1,2]. The administration of chemotherapy during the second and third trimesters of pregnancy is not associated with congenital malformations, but increases the risk of intrauterine fetal death, growth retardation and low birth weight. Delivery should be planned to occur 2-3 weeks after the last session of chemotherapy to allow bone marrow recovery [1,2]. Pregnant females or mothers with terminated pregnancies receiving cytotoxic chemotherapy require supportive care with: fluids for hydration and nutritional supplements, safe antimicrobials to treat various infectious complications, growth factors to shorten the periods of neutropenia, and blood product transfusions as needed [1].

The data and results of 2 major studies on leukemia in pregnancy are described below [40,41]. At King Faisal Specialist Hospital and Research Center in Riyadh, 32 patients who had developed leukemia during pregnancy were reported and their long-term follow up was provided [40]. The primary hematological malignancies were as follows: CML (11 patients), 5 patients with acute promyelocytic leukemia (APL), and non-M3 AML (8 patients). Spontane-

ous abortions occurred in 14 patients, therapeutic abortions were performed in 2 patients and 16 live births were delivered at 30-41 weeks of gestation [40]. At the end of the study, the outcomes of mothers were as follows: 19 patients (59.4%) were dead, 7 patients (21.9%) lost follow up and only 6 patients (18.8%) were alive. Five of the living patients had already received HSCT. Out of the 32 patients included in the study, 19 patients (59.4) were subjected to HSCT to control their primary hematological malignancies [40]. On long-term follow up, 14 transplanted patients (73.7%) were dead and only 5 transplanted patients (26.3%) were alive. The conclusion that can be drawn from this study is that the long term prognosis of pregnant females having leukemia is poor even if HSCT is performed for high-risk patients [40]. In another retrospective study from Japan, 16 patients with leukemia in pregnancy were reported between 2001 and 2011 [41]. Out of the 16 patients reported: 9 (56.3%) had CML, 5 (31.3%) had ALL and 2 patients (12.5%) had AML. Out of the 9 patients with CML, 4 received imatinib therapy which was subsequently interrupted (3 in the first trimester and 1 in the second trimester). Out the 9 CML patients, 6 patients required treatment with hydroxyurea and/or interferon while the remaining 3 patients required no treatment after stopping imatinib [41]. Anemia developed in 4 patients and thrombocytopenia was reported in 1 patient. Regarding fetal outcomes, no perinatal deaths or fetal abnormalities were reported. The diagnoses of acute leukemia in the 7 patients reported were made in 2 patients during the first trimester, in 2 patients during the second and in 3 patients during the third trimester of pregnancy [41]. Therapeutic abortion was performed in 2 patients with ALL. Chemotherapy was administered during the second trimester in 4 patients and 1 patient with ALL received chemotherapy after delivery. All patients with acute leukemia developed thrombocytopenia and 4 patients developed febrile neutropenia. Mean gestational age at delivery was 32 weeks and 2 perinatal deaths were reported [41]. The authors concluded that: (1) maternal and fetal morbidity is high in pregnancies complicated by acute leukemia, and (2) in pregnancies complicated by chronic leukemia, fetal and maternal prognoses appear to be more favorable and management of complications is easier compared to acute leukemia [41].

7. Acute leukemia in pregnancy

Virchow described the first case of leukemia in a pregnant woman in the year 1856 [2]. Between 1856 and 1995, more than 500 cases of leukemia in pregnancy were reported [1]. It is estimated that 23% of acute leukemias are diagnosed during the first trimester, 37% during the second trimester and 40% during the third trimester of pregnancy [2]. The majority of leukemias diagnosed in pregnancy are acute and predominantly myeloid as the incidence of ALL is more common in childhood and adolescence [1,2,24]. The presentation of acute leukemia in pregnancy is broadly similar to that in nonpregnant females although pregnancy may obscure the diagnosis of leukemia as pregnant ladies often describe nonspecific symptoms such as fatigue and tiredness [1,24]. Pregnant females with leukemia particularly acute leukemia present with anemia, thrombocytopenia and neutropenia in addition to recurrent infections due to bone marrow failure caused by the aggressive malignancy [2]. The diagnostic work up of pregnant females should be the same as their nonpregnant counterparts apart from the avoidance of

certain radiological procedures due to their adverse effects on the fetus [2]. Although a bone marrow aspirate and a trephine biopsy may be performed safely in pregnancy, these can be avoided if confirmation is clear possibly by means of peripheral blood microscopy, flow cytometry and molecular analysis [24].

If the disease is left untreated, it will likely result in maternal and fetal mortality. A decision to delay initiation of induction chemotherapy negatively impacts on the likelihood of remission [24]. There are no prospective studies that compare the outcome of pregnant ladies with their nonpregnant counterparts [2]. However, data suggest that maternal outcomes for AML following chemotherapy are analogous to nonpregnant females and consequently delay in commencing chemotherapy is to be avoided. The therapeutic approach to the management of acute leukemia in pregnancy, regardless the subtype, is generally similar [24].

Vertical transmission of leukemia to the fetus is exceptionally rare due to the placental barrier and the fetal immune system [2]. Cytotoxic agents have a relatively low molecular weight and most of them can cross placental barrier and reach the fetus [2]. When treating a pregnant woman with chemotherapy, it is essential to consider many gestational physiological changes that can potentially alter the effectiveness of chemotherapeutic agents by changing their metabolism and clearance [2]. During pregnancy, plasma volume is increased leading to enhancement of renal clearance and hepatic oxidation of drugs. Lower plasma drug exposures to doxorubicin, epirubicin and carboplatin have been described during pregnancy [2]. However, the physiological changes in pregnancy have their effects on drug exposure, drug effectiveness and drug toxicity and all these factors make management of acute leukemia in pregnancy a rather difficult task [2].

The data and the results of 5 major studies on acute leukemia in pregnancy are summarized below [42-46]. In March 1993, a questionnaire was sent to 362 gynecology and obstetrics centers in Japan and answers were obtained from 260 centers [42]. A total of 103 patients with acute leukemia in pregnancy were reported in that study, 39 of them were obtained from the questionnaire survey and 64 patients were reported from literature review [42]. The following conclusions and results were made: (1) maternal survival was longer in patients treated between 1985 and 1993 compared to patients treated between 1975 and 1984, (2) survival was significantly longer in patients in whom induction chemotherapy was commenced before delivery compared to patients in whom chemotherapy was started after delivery, (3) treatment of acute leukemia during pregnancy should be started as soon as possible after establishing the diagnosis of leukemia with carefully selected chemotherapeutic regimens, and (4) the time of delivery should be selected considering maternal and fetal circumstances after consultation with obstetricians [42].

In a Canadian study, 7 patients with acute leukemia were included and 51 additional patients, reported between 1975 and 1987, were added [43]. Out of the 58 pregnant women reported, 53 patients received chemotherapy for acute leukemia during pregnancy. Forty nine pregnancies results in birth of 50 infants, 28 of them were prematurely delivered and 4 had low birth weights [43]. Cytopenias at birth were encountered in 39% of newborn infants who had been exposed to cytotoxic medications in the last month of pregnancy. One child had congenital malformations, neuroblastoma arising from the adrenal gland and papillary thyroid cancer

[43]. Long-term follow-up (ranging between 1 and 17 years) of the 7 Canadian patients showed normal growth of babies and no malignancies were encountered in the children born. The authors recommended having a central registry in order to document long-term complications in children exposed to chemotherapy in utero [43].

In a French retrospective study, 37 patients with acute leukemia (31 AML patients and 6 ALL patients) were reported [44]. The diagnosis of leukemia was made in: 9 patients in the first trimester, 10 patients in the second trimester and 18 patients in the third trimester of pregnancy. Cytogenetic analysis results were favorable in 10 patients, unfavorable in 6 patients and intermediate in 12 patients [44]. The outcomes of the pregnancies were as follows: 15 pregnancies ended in abortions (2 spontaneous and 13 therapeutic) and 22 deliveries (13 spontaneous vaginal deliveries and 9 cesarean sections) were reported. Out of the 23 healthy babies delivered, 22 of them had been exposed to chemotherapy during gestation [44]. Disease outcomes were as follows: 34 patients (92%) achieved complete remissions (CRs) of their leukemias, 2 patients (5.4%) had refractory disease, 1 patient (2.7%) had toxic death and 11 patients developed severe nonhematological complications [44]. HSCT was performed in 11 patients (6 autologous and 5 allogeneic). Disease-free survival was 65% at 3 years and 54% at 5 years, while overall survival was 64% at 3 years and 46% at 5 years. Follow-up showed death of 12 patients (32.4%) at 3.4 years and relapse of 10 patients (27%) at 11.9 months [44]. The authors concluded that: (1) although pregnancy, in general, does not affect the outcome of acute leukemia, relapse rate in pregnant ladies with acute leukemia is relatively high; (2) chemotherapy during the first trimester of pregnancy requires the termination of pregnancy to allow appropriate therapy to be administered; and (3) chemotherapy administration during the second and third trimesters of pregnancy does not require termination of pregnancy [44].

In a survey that had been performed at 24 institutions in Japan over 11 years, 11 cases of acute leukemia during pregnancy were reported [45]. Out of the 11 patients with acute leukemia, 8 patients had AML and 3 patients had ALL. The diagnosis of acute leukemia was made in 6 patients in the first trimester, 1 patient in the second and 4 patients in the third trimester [45]. Infant outcomes were as follows: 5 out of 6 patients had abortions before chemotherapy and 1 elective abortion was performed after chemotherapy, while all the patients diagnosed in the second and third trimester of pregnancy delivered live births. Four of the mothers diagnosed in the first trimester achieved CR of their leukemias, while 2 patients died of recurrent leukemia. Four of the mothers diagnosed in the second and third trimesters had CR and remained in remission, while 1 patient died of sepsis following cesarean section [45]. The authors concluded that careful surveillance and monitoring of the fetus in addition to close co-operation between hematologists, gynecologists and pediatricians are essential to successfully treat pregnant women with acute leukemia [45].

A retrospective study included 10 pregnancies in 8 patients with acute leukemia (6 patients with AML and 2 patients with ALL) [46]. The diagnoses of acute leukemia were made in 6 pregnancies in the first trimester, 3 pregnancies in the second trimester and 1 patient in the third trimester. Three pregnancies ended in spontaneous abortions, 3 in intra-uterine fetal death and 3 in therapeutic abortions [46]. One spontaneous abortion and one intrauterine fetal death were encountered during combination chemotherapy (cytarabine and daurorubicin) given for AML. Only 1 baby survived and that baby was never exposed to chemotherapy [46]. The conclusions from this study included the following: (1) while none of the mothers had obstetric

complications, 5 out of 8 pregnant women with acute leukemia died because of primary disease, and (2) fetal outcome was very poor, thus the diagnosis of acute leukemia particularly during early pregnancy carries poor outcome for both the fetus and the mother [46].

8. AML in pregnancy

AML occurs more frequently in young adults and in elderly individuals. Consequently, more data are available on the management of AML in pregnancy [1,24]. As AML is an aggressive malignancy, delaying chemotherapy has adverse consequences on the mother so a balance between having the consequences of intensive chemotherapy on both the mother and the fetus as well as the negative impact of postponing chemotherapy on the mother must be carefully evaluated [1,24]. Also, the possibility of long-term consequences of cytotoxic chemotherapy on future fertility of the mother has to be taken into consideration [24,27]. Clinical studies and recent research suggest: (1) a similar prognosis for women treated during pregnancy as compared to nonpregnant patients, and (2) most modern remission induction chemotherapeutic regimens used in the treatment of acute leukemia do not induce sterility [24].

The existing therapeutic protocols or regimens including modern agents that are utilized in the management of AML include: anthracyclines such as daunorubicin, idarubicin and doxorubicin; antimetabolites such as cytarabine; topoisomerase II inhibitors such as etoposide; monoclonal antibodies such as gemtuzumab (myelotarg, anti-CD33 monoclonal antibody); and multikinase inhibitors [24]. The induction regimens of AML consist of a combination of cytarabine and an anthracycline, while various combinations of intensive chemotherapies are used in the consolidation therapy [1,2]. Enough data is available on the use of cytarabine and anthracyclines during pregnancy, except in the first trimester, but there is a lack of data on the use of modern therapies such as gemtuzumab and multikinase inhibitors in pregnant females having AML [1,24]. Cytarabine therapy in pregnancy carries a significant risk to the fetus, so its use is not advocated in the first trimester of pregnancy [2]. The administration of cytarabine, alone or in combination with other chemotherapeutic agents such as anthracyclines, during the first trimester is associated with the development of congenital malformations, miscarriage, low birth weight and fetal death, while embryonic exposure to etoposide is associated with genomic instability and mixed-lineage leukemia (MLL) rearrangement [2,24]. The unfavorable experiences of chemotherapy in the first trimester of pregnancy have resulted in the recommendation for therapeutic abortion and the decision to treat AML in the first trimester with a regimen containing an antimetabolite must be accompanied by careful counseling of the mother [1,24]. So, in pregnant females with AML presenting during the first trimester, termination of pregnancy is strongly recommended then intensive chemotherapeutic regimens that include cytarabine and anthracyclines should be commenced [1,2].

The experience with the use of anthracyclines during pregnancy is limited mostly to doxorubicin and daunorubicin as idarubicin which is more lipophilic may be associated with higher rates of fetal complications [2,27]. Three major studies that included more than 200 patients with various cancers including hematological malignancies (at least 60 of them were treated

during the first trimester of pregnancy with doxorubicin, daunorubicin, cytarabine and other chemotherapeutic agents) reported the following complications: pre-eclampsia, premature deliveries, stillbirths, miscarriages, congenital malformations, intrauterine fetal death, growth retardation and neonatal sepsis. These studies confirmed that doxorubicin is more effective and safer than other anthracyclines in treating leukemia during pregnancy. However, it is still unknown whether exposure to anthracyclines is cardiotoxic to the developing fetus [2].

The administration of cytotoxic chemotherapy including cytarabine in the second and third trimesters of pregnancy is associated with intrauterine fetal death and growth retardation, pre-term deliveries in addition to neonatal cytopenias that may cause deaths due to severe infections, but no increase in congenital malformations, unfavorable neurological development or childhood malignancy [1,24,27]. In patients presenting during the second or third trimesters of pregnancy, induction chemotherapy with cytarabine and either daunorubicin or doxorubicin should be instituted promptly [1,24]. In AML relapsing during pregnancy, the termination of pregnancy should be performed as treatment of AML in relapse includes: high dose chemotherapy followed by HSCT or experimental therapy all of which cannot be delivered during pregnancy [1,2].

Adequate supportive care should be given to mothers as aggressive chemotherapy may cause infections, nausea, vomiting and variable cytopenias [1]. Regular surveillance for the development of congenital abnormalities and monitoring of fetal cardiac function are essential [1,24]. Delivery should be electively planned after the 32nd week of gestation and it should be done 2-3 weeks after the last session of chemotherapy to allow recovery of bone marrow function [2].

In a large systematic review that included 83 pregnant females with AML diagnosed and treated between January 1969 and June 2014, 85 fetuses were exposed to cytotoxic chemotherapy during pregnancy [27]. During the first trimester of pregnancy 8 mothers were treated and all achieved CR, 61 mothers were treated during the second trimester and 81% of them achieved CR, while 14 patients with AML were treated during the third trimester and 67% of them achieved CR of their AML. Fetal deaths and/or spontaneous abortions occurred in 37.5% of cases in the first trimester, 9.7% of cases in the second trimester and 0.0% of cases in the third trimester of pregnancy [27]. All fetuses were exposed to cytarabine, 47 fetuses were exposed to daunorubicin and only 8 fetuses were exposed to idarubicin. In fetuses exposed to cytarabine and daunorubicin, fetal defects occurred in 8.5% of cases and fetal deaths were encountered in 6.4% of cases, while in fetuses exposed to cytarabine and idarubicin, fetal defects occurred in 28.6% of cases and fetal deaths occurred in 12.5% of cases [27]. The following conclusions were made: (1) treatment during the second and third trimesters of pregnancy resulted in fewer fetal complications than in the first trimester, (2) delaying treatment of AML may adversely affect the outcomes of pregnant mothers, (3) induction chemotherapy administered during pregnancy resulted in CR rates comparable to those obtained in nonpregnant females, and (4) the choice of anthracycline is unclear but the decision should be made with careful consideration, weighing the outcomes of both the mother and the fetus [27].

In a retrospective study that was published in 1977 the outcomes of 32 pregnant mothers with AML and their offspring were reported [47]. Out of the 32 pregnancies with AML reported

between 1905 and 1976, the outcomes of 27 mothers were known and only 1 of these mothers was alive and the survival rate was 3.7% for 6 months postpartum. Approximately 43% of fetuses were either delivered normally or were premature live births, while 53% of them were dead due to abortion, stillbirth or intrauterine fetal death [47]. The chemotherapeutic regimens that were used to treat AML included: corticosteroids, adrenocorticotropic hormone and 6-mercaptopurine. Hence, the recent improvement in fetal and maternal outcomes of AML in pregnancy is due to improvements not only in supportive care, but also in specific anti-leukemic therapies [47].

There are numerous reports of the successful management of AML in pregnancy and few reports of vertical transmission of acute leukemia from the mother to the fetus [48-50]. The spontaneous remission of acute leukemia after the termination of pregnancy and the following rare forms of AML have been reported: erythroleukemia, t(8,21) AML with granulocytic sarcoma causing spinal cord compression, and AML mimicking HELLP (hemolysis, elevated liver enzymes and low platelet counts) syndrome [50-53].

Although acute leukemia is a rare event in pregnancy, it may be associated with life-threatening complications to both the mother and the fetus [49]. Therefore, acute leukemia diagnosed during pregnancy should be treated promptly as delay in treatment is associated with higher maternal mortality, but decision on the choice of treatment for acute leukemia during pregnancy should be case-dependent [50,54]. If AML is diagnosed during the first trimester of pregnancy, the immediate termination of pregnancy should be considered then standard induction chemotherapy should be commenced [48,55-57]. Without the termination of pregnancy, combination chemotherapy is associated with an unacceptable high incidence of fetal abnormalities and/or fetal loss [55]. The management of AML diagnosed during the second and third trimesters of pregnancy is often difficult because delay in administration of chemotherapy implies significant risk to the mother, and administration of chemotherapy may induce: fetal death, prematurity and congenital malformations [55]. There are reports that chemotherapy can be safely given during the second and third trimesters of pregnancy and that induction chemotherapy using cytarabine and idarubicin for AML in the second trimester of pregnancy may be associated with fetal abnormalities including cardiac malformations [48,57]. Close monitoring of the fetus and the mother should be considered when chemotherapy is administered during the second trimester of pregnancy, [58]. However, the administration of standard chemotherapy including idarubicin during the third trimester of pregnancy may increase the chances of CR of AML without adversely affecting fetal outcome or increasing the risk of leukemia in the offspring [55,59]. In selected AML patients presenting in late pregnancy, it is possible to offer leukapheresis and blood product transfusions and to plan early delivery [55].

As in utero exposure to chemotherapy carries a significant risk of unfavorable outcome including low birth weight, fetal death and intrauterine fetal death, the fetus should be regularly evaluated by sonograms and umbilical blood sampling through cordocentesis [54,60]. Unfortunately, AML diagnosed during pregnancy may be associated with poor outcome including maternal death, even if chemotherapy or HSCT are offered [57].

9. APL in pregnancy

APL is recognized to occur infrequently during pregnancy. APL is characterized by an onset at young age and life-threatening bleeding diathesis attributed to disseminated intravascular coagulation (DIC)-like coagulopathy [61,62]. The discovery of all trans-retinoic acid (ATRA) has changed the course of APL treatment by reducing the onset of DIC and inducing complete and durable remissions in more than 90% of patients [61]. The prognosis is good for APL with modern treatment that includes ATRA which specifically targets the causative retinoid acid receptor oncoprotein (PML-RARA) [63].

The use of daunorubicin therapy in pregnancy was first reported in 1976. The patient was in the 23rd week of gestation and despite the use of daunorubicin, she gave birth to a normal full term baby [64]. Thereafter, daunorubicin has been successfully used in the second and third trimesters of pregnancy without adversely affecting the offspring of pregnancy. Additionally, there are reports of using daunorubicin in the first trimester of pregnancy without causing fetal adverse events [64].

ATRA alone or combined with chemotherapy has been safely and successfully used in the treatment of APL during the second and third trimesters of pregnancy [65-67]. ATRA has been reported to ameliorate coagulation parameters and to induce remissions of APL in pregnant females [65-67]. However, close monitoring for fetal cardiac complications throughout pregnancy is mandatory and long-term follow up of children born to mothers treated with ATRA during pregnancy is warranted [65].

The management of APL in pregnant females requires special considerations [68]. Patients diagnosed to have APL during pregnancy pose a distinct challenge requiring a team approach involving a hematologist, an obstetrician and a neonatologist [68]. Nevertheless, the management of APL depends to a large extent on the trimester of pregnancy during which APL is diagnosed [68,69].

During the first trimester of pregnancy, both ATRA and arsenic trioxide (ASO) are contraindicated as both of them are highly teratogenic [68,69]. The critical factor in determining the line of management in women with APL in the first trimester of pregnancy is whether the pregnancy will be electively terminated once the patient is hemodynamically stable [68]. If the patient plans to terminate the pregnancy then conventional treatment with ATRA and chemotherapy can be commenced. If the elective termination of the pregnancy is unacceptable to the patient, the only available therapeutic option is the administration of chemotherapy such as daunorubicin [68]. In patients with APL, chemotherapy alone compared to ATRA and chemotherapy is associated with inferior response rates and progression-free survival but higher relapse rates and risk of bleeding due to coagulopathy. If chemotherapy alone is chosen, daunorubicin is the anthracycline of choice in pregnant females as there is greater experience with it and there are concerns over the lipophilic nature of idarubicin that may increase its fetal transfer and consequently fetal toxicity [68]. If the remission of APL is achieved with chemotherapy alone, ATRA may then be added in the second and third trimesters. After delivery, breast feeding is contraindicated during treatment with chemotherapy or ATO [68].

During the second and third trimesters of pregnancy, ATRA can be used but arsenic derivatives are contraindicated as they are highly embryotoxic [68,69]. In women diagnosed to have APL in the second or third trimesters of pregnancy, two main options are available: (1) induction of remission with ATRA alone with postponement of chemotherapy administration until after delivery, and (2) simultaneous administration of ATRA and chemotherapy as given in patients who are not pregnant at the time of diagnosis [68]. The immediate administration of combined ATRA and chemotherapy offers the best chance of cure but is accompanied by an increased risk of spontaneous abortion, premature delivery, low birth weights, neonatal neutropenia and sepsis so induction of labor between cycles of chemotherapy should be considered [68,69]. Patients treated with ATRA alone, compared to patients treated with ATRA and chemotherapy, have similar rates of remission, but higher rates of hyperleukocytosis and higher rates of relapse [68]. Patients treated with ATRA alone require frequent monitoring by real time-quantitative-polymerase chain reaction (RT-q-PCR) after induction of remission to monitor them for relapse while awaiting delivery, but patients receiving combined therapy with ATRA and chemotherapy require stringent fetal monitoring with particular emphasis on cardiac function [68,69]. For deliveries before 36 weeks of gestation, antenatal corticosteroids before preterm delivery are recommended to reduce the risk of morbidity and mortality associated with respiratory distress syndrome [69]. Vaginal delivery is generally preferred since it is associated with a reduced risk of bleeding [68]. After successful delivery, breast feeding is contraindicated if chemotherapy or ATO are required [69]. Female patients with APL should be advised against conceiving whilst exposed to ATRA or ATO for consolidation or maintenance therapy [69].

In an English literature review on APL in pregnancy that included 35 studies, 42 females with APL were reported between January 1972 and May 2008 [70]. Twelve cases of APL in pregnancy were reported in the first trimester, 21 cases in the second trimester and 9 cases in the third trimester. Thirty five patients (83%) achieved CR and the most commonly administered drugs were ATRA, anthracyclines and antimetabolites [70]. Fetal outcomes with ATRA and chemotherapy were as follows: spontaneous abortions and fetal malformations were encountered during the first trimester, while relatively favorable outcomes were encountered in the second and third trimesters [70]. The following conclusions were made: (1) the management of pregnant patient with APL is a real challenge; (2) the immediate treatment of APL is critical as APL is an oncologic emergency associated with high risks of morbidity and mortality due to DIC; (3) the administration of chemotherapy and differentiating agents in pregnancy is controversial because of the potential teratogenic effects; (4) the management of a pregnant woman with APL should include discussion about pregnancy termination particularly if APL is diagnosed during the first trimester of pregnancy; (5) if the patient and her family refuse pregnancy termination, then appropriate chemotherapeutic regimens need to be determined; and (6) frequent fetal monitoring and aggressive management of potential APL-related complications are essential to allow for optimal maternal and fetal outcomes [70].

In another study that included literature review of 23 cases of APL in pregnancy, 8 patients received chemotherapy and 3 patients received ATRA in late pregnancy [62]. There was one spontaneous abortion and one therapeutic abortion. Eleven patients had spontaneous vaginal

delivery, 8 patients required cesarean section and 1 patient needed low forceps delivery while the mode of delivery was unknown in 1 pregnancy [62]. Sixteen patients (72%) achieved CRs of their APLs, 1 patient achieved partial remission and 2 patients showed no response while no information was obtained on the treatment given to 2 patients. Ten mothers (43.5%) died, while outcomes of newborn infants were as follows: 19 infants were born alive, 1 infant was gravely ill at birth and 2 infants had intrauterine fetal death [62]. The following conclusions were made: (1) pregnancy in APL requires special consideration to maximize the probability of survival of both the mother and the fetus, and (2) proper management of a pregnant female with APL usually results in a live birth with CR of the mother's leukemia despite the potentially devastating consequences of DIC, which is present at the time of diagnosis of APL in most patients [62].

A third study performed in Russia between 1998 and 2013 included 9 patients with APL and 6 patients were having APL during pregnancy [71]. The diagnosis of APL was made in 1 patient in the first trimester, 3 patients in the second trimester and 2 patients in the third trimester. Management was tailored according to the trimester of pregnancy: the termination of pregnancy was performed for patients presenting in the first trimester, chemotherapy then delivery for patients presenting in the second trimester while delivery followed by chemotherapy was offered to patients presenting in the third trimester [71]. Out of the 6 patients of APL diagnosed in pregnancy, 5 received AIDA (ATRA and idarubicin) regimen of treatment while one patient received 3+7 chemotherapy in addition to ATRA. Late recurrences were encountered in 33% of patients with APL and 44.4% of patients were alive with a median overall survival of 26 months while the median relapse-free survival was 17.5 months. The authors concluded that APL treatment in pregnancy, which is aimed at saving lives of both mothers and infants, is effective and results in a reasonable outcome [71].

Three patients with APL in pregnancy were reported from Italy [61]. The authors concluded that despite the rare occurrence of APL in pregnancy, the management of these patients raises many therapeutic and ethical dilemmas and requires careful clinical case evaluation of fetal and maternal risk, coagulation status, parents' wishes and therapeutic options [61]. Another study that included 3 patients with APL diagnosed during pregnancy concluded that: (1) management of APL in during pregnancy is complex because there are a number of possible therapeutic strategies that have varying implications for the mother and the fetus, and (2) response to treatment is subject to stringent monitoring by RT-q-PCR for the PML-RARA transcript [63]. Finally, 2 cases of APL in pregnancy were reported in Japan [72]. The first patient was diagnosed in the 14th week of gestation and she presented with pancytopenia and bleeding diathesis. She was treated with a combination of chemotherapeutic drugs that included daunorubicin [72]. Pregnancy ended in intrauterine fetal death at week 19 of gestation and the baby was found to be anemic with hypoplastic bone marrow [72].

A number of rather exceptional cases of APL in pregnancy have been reported [73-78]. Pregnancy has been reported after successful treatment of secondary APL following multi-agent chemotherapy and radiotherapy for lymphoma [73]. ATRA or differentiation syndrome has been reported in a pregnant patient with APL treated with ATRA and the respiratory failure induced by ATRA was successfully treated with non-invasive ventilation and corticosteroid therapy

[74]. Cesarean section was performed for a pregnant woman with untreated APL having DIC after active treatment of coagulopathy and close collaboration between hematologists and obstetricians [75]. Fetal arrhythmias and fetal growth retardation have been reported following the use of ATRA in treating pregnant females having APL [76]. APL has been diagnosed after management of placental abruption causing prolonged DIC [77]. Also, APL with t (15,17) and variant PML-RARA fusion transcript has been reported in pregnancy [78].

10. ALL in pregnancy

ALL is relatively rare in adults [1,2]. Only 21 cases of ALL in pregnancy had been reported prior to the year 2009 [1,2]. Subsequently, limited data on the treatment of ALL in pregnancy impedes absolute recommendations on the management of ALL in pregnant females [1,24].

As ALL is a highly aggressive malignancy, it is essential to administer adequate and appropriate chemotherapy immediately after diagnosis of ALL to control the disease [1,2]. Worldwide, different induction regimens of chemotherapy are utilized in the treatment of ALL [79-81]. Even in the same country, various chemotherapeutic protocols may be used such as CALGB, CCG and DFCI in the United States of America and FRALLE, LALA and GRAALL protocols in France [79-81]. Also, these therapeutic regimens undergo modifications or total replacement as new data evolve or whenever results of large studies are published [79-82]. Despite the development of multiple induction regimens, still there is no best regimen for induction therapy in ALL. However, the constituents of these chemotherapeutic regimens are almost similar with different dosing and schedules [79-82]. Recently, the more intensified pediatric ALL treatment regimens have been used in patients belonging to the age-group 15 to 40 years having ALL because several studies had shown that adolescents and young adults treated with adult ALL regimens of chemotherapy have poorer outcome compared to patients belonging to the same age-group treated with pediatric protocols [79,81,83]. Certain cancer centers are currently treating ALL patients between 1 and 50 years of age with the same chemotherapeutic protocols and are incorporating novel agents such as nelarabine and rituximab in the treatment of ALL [80,81]. Thus, unlike the situation in AML, the use of different treatment regimens in ALL makes it very difficult to adopt strong recommendations or to establish strict guidelines for the management of ALL in pregnancy [79-83].

Studies have shown that in patients in whom induction chemotherapy is commenced before delivery, survival is longer than in those treated after delivery [2]. The risk of congenital malformations diminishes as pregnancy advances [1,2]. The absence of autopsy data on fetuses delivered by terminations could result in a decrease in the incidence of congenital malformations in the fetuses delivered [24]. High-dose methotrexate is a crucial component of most of the ALL intensification protocols of chemotherapy but unfortunately the drug is highly teratogenic and its administration during the first trimester of pregnancy is associated with the development of aminopterin syndrome and a high risk of miscarriage [1,2,24].

When the diagnosis of ALL is made during the first trimester of pregnancy, the termination of pregnancy is strongly recommended in order to commence standard induction chemother-

apy [1]. Chemotherapeutic regimens have included: cytarabine, cyclophosphamide, L-asparaginase, anthracyclines, vincristine and corticosteroids [1,24]. The second trimester of pregnancy can be roughly divided into two parts: (1) part one, before the 20th week of gestation: management resembles that in the first trimester of pregnancy, so the termination of pregnancy should be considered, followed by the administration of adequate or standard ALL induction chemotherapy, and (2) part two, after the 20th week of gestation: bridging chemotherapy or modified ALL regimens of chemotherapy without methotrexate can be given till the third trimester of pregnancy, although possible damage to the fetus should be taken into consideration [1,2,24]. Several chemotherapeutic regimens that exclude the use of methotrexate have been suggested, but the experience with these modified therapies is extremely limited, so these therapeutic regimens should be used as short bridging treatments till the third trimester starts [1,2,24].

A brief period of treatment with prednisolone alone for 1-2 weeks may allow the patient to enter the period of gestation beyond the 20 weeks in order to receive more intensive chemotherapy thereafter. A similar approach with prednisolone alone can be recommended for patients presenting close to 32 weeks of gestation [24]. For patients presenting in the third trimester of pregnancy, they can be treated with the same chemotherapeutic protocols that are used to treat their nonpregnant counterparts [2,24]. The outcome of ALL is stratified according to a number of risk factors: (1) patients with a good prognosis can be treated with less intensive chemotherapeutic approaches, and (2) patients with more aggressive features will require interventions according to the pace of the underlying disease [24]. Close obstetric care and close monitoring of the mother and the fetus are essential to ensure the best possible outcome [2]. Elective delivery after 32 weeks of gestation should be planned but timing of delivery should avoid periods of pancytopenia to prevent further complications [2,24].

Acute leukemia develops in 1:750,000 pregnancies and ALL accounts for 11-28% of acute leukemia in pregnancy [84,85]. Although ALL is rare in pregnancy, it can be rapidly fatal if left untreated. Thus, it requires immediate therapy irrespective of the gestational age [85,86]. Advances in the management of leukemia have led to improved survival and emphasized the importance of initiation of cytotoxic chemotherapy in the antepartum period [85]. Several case reports, case series and retrospective studies have shown successful treatment of ALL in pregnancy using several combinations of the following cytotoxic agents: prednisolone, cytarabine, cyclophosphamide, vincristine, daunorubicin or doxorubicin, L-asparaginase, 6-mercaptopurine and intrathecal methotrexate [85]. However, the choice of specific chemotherapeutic regimen depends on the gestational age and clinical status of the pregnant female as well as the anticipated toxicities of the cytotoxic agents [85].

The basic principle of ALL treatment is combination chemotherapy with the sequential administration of induction, consolidation and maintenance therapy and this holds true for ALL in pregnancy [86]. Thus, the management of ALL during pregnancy requires high-dose chemotherapy that can pose risks to both the mother and the fetus [84]. In order to limit fetal exposure to chemotherapy and to provide optimal care to the mother, particular attention should be paid to: the chemotherapeutic regimen to be administered, the doses of the cytotoxic agents to be used and the gestational age at the time of chemotherapy administration [84].

During the first trimester of pregnancy, chemotherapy used in the treatment of ALL is associated with teratogenicity, stillbirths and abortions, so the termination of pregnancy should be considered and the risks of chemotherapy administered during this part of pregnancy should be discussed with the pregnant mother [84,86]. During the second and third trimesters of pregnancy, the administration of chemotherapy has been widely practiced, although the following adverse events have been reported: intrauterine fetal death and growth retardation, premature delivery, low birth weight, maternal as well as fetal myelosuppression and pre-eclampsia of pregnancy [84,86].

Some of the rather exceptional case reports include: (1) relapse of ALL in pregnant females; (2) presentation of ALL in pregnancy with extra-medullary disease involving the central nervous system, breast and ovaries; and (3) successful treatment of ALL during the second and third trimesters of pregnancy with combination therapy or single agents such as corticosteroids [87-97].

In a literature review that included 17 patients with ALL treated during pregnancy the following maternal and fetal outcomes were reported: 9 mothers (53%) achieved CRs of their ALLs while 8 patients (47%) either died (5 patients) or had relapse of their leukemia (3 patients) [84]. Thirteen babies (76%) were alive, 4 babies (24%) were dead and 6 babies were delivered by cesarean section. The authors also concluded that: doxorubicin was the safest anthracycline employed in pregnant females and they highlighted the importance of long-term follow up of children exposed to chemotherapy in utero [84].

Pregnant females can achieve CR of their leukemia but the decisions on future conception need to be individualized because of unpredictable outcome [98]. Although the literature is modestly positive on the prognosis of ALL in pregnancy, this may not be entirely true particularly in aggressive forms or high-risk ALL presenting during pregnancy where termination of pregnancy should be performed in order to allow the administration of intensive chemotherapy that may be followed by HSCT [86].

11. CML in pregnancy

CML accounts for 15% of adult leukemias, but only 10% of cases are diagnosed during childbearing age as the median age at the diagnosis of CML is the sixth decade of life [1,24]. CML occurs in 10% of all pregnancy-associated leukemias and the annual incidence ranges between 1 in 75000 and 1 in 100000 pregnancies [2,24]. The diagnosis of CML during pregnancy may be made more complicated as the physiological changes, including those in hematological parameters which accompany pregnancy, may mask the symptoms of CML [24]. However, the diagnostic approach of CML in pregnant females is identical to that in non-pregnant patients [2].

Previously, there was a suggestion of an increase in the rates of miscarriage, low birth weight and premature babies in mothers having CML, but this is no longer apparent in the more recent years. Reassuringly, the course of CML does not appear to be adversely affected by pregnancy

[24]. Due to the excellent clinical outcome with tyrosine kinase inhibitors (TKIs), the expectations of a relatively normal life style inclusive of parenting children is increasing. Therapeutic approaches to CML diagnosed during pregnancy include: leukapheresis, hydroxyurea, α -interferon and imatinib [24]. There are numerous case reports describing the use of leukapheresis and plateletpheresis in pregnant women having CML but unfortunately, apheresis technology is not universally available [24].

There are several studies and literature reviews including relatively large numbers of patients with CML diagnosed during pregnancy [29,99-101]. The studies and reviews that included the largest numbers of cases are described below. In a literature review that included 265 pregnant ladies with CML treated with imatinib, the outcomes of pregnancies were known in 210 pregnancies while the outcomes of 55 other pregnancies were unknown [99]. Pregnancies that ended in the delivery of normal live infants were 128 (60%), elective terminations of pregnancy were described in 43 patients (20%), spontaneous abortions occurred in 24 cases (11%) and fetal abnormalities were described in 15 cases (7%) [99]. A second study reported 217 pregnancies in 215 women with CML. The number of fetuses exposed to imatinib was 217 [29]. Out of the 217 pregnancies, 46 had therapeutic or elective abortions and 5 out of the 46 aborted fetuses had congenital malformations. Out of the 217 pregnant females, 171 women decided to continue pregnancy. Only 85 pregnancies were carried out till term after being exposed to imatinib for some time during pregnancy. One out of 85 pregnancies ended in a stillbirth with meningocele and 84 pregnancies ended in delivery of live births of these: 73 were normal healthy babies, 9 were having congenital malformations and 2 had low birth weights [29]. Regarding the outcome of pregnancies, 24 pregnancies ended in spontaneous abortion, 62 had unknown outcomes and 109 had known outcomes. Among the 109 pregnancies with known outcomes, 36 (33%) resulted in complications. Regarding the 43 out of 84 babies who were carried to term and were exposed to imatinib throughout pregnancy, 22 babies were born without abnormalities and 2 were reported to have low birth weights [29]. A third review, over 10 years, included 180 pregnant females who had been exposed to imatinib [100]. However, data on outcomes were available for 120 patients (69% of cases). In this review, 50% of pregnancies ended in delivery of normal infants and 28% of pregnancies underwent elective terminations, 3 of them were done after identification of fetal abnormalities of the delivered infants, 18 had abnormalities identified, 3 of them were complex malformations [100]. The authors concluded that although most pregnancies exposed to imatinib are likely to yield successful outcome, there remains a risk that imatinib exposure during pregnancy may result in spontaneous abortions and serious fetal malformations [100]. A fourth study from China reported 16 pregnancies in patients with CML [101]. Out of the 16 pregnancies, 7 ended in deliveries and 9 ended in therapeutic abortions during the first and second trimesters of pregnancy. Out of the 9 patients with CML who required therapeutic abortions: 4 lost follow-up, 1 died 3 years after the diagnosis of her disease and 4 were alive at 5-72 months. Out of the 4 patients alive, 1 had HSCT, 2 were back on imatinib and one was given hydroxyurea [101]. Maternal outcome for the 7 pregnancies that ended in deliveries: 2 lost follow-up, 2 died and 3 were still alive. In these 7 pa-

tients, fetal outcome was as follows: 2 lost follow-up, and 5 babies had normal development and they were reported to be alive at 4 months to 9 years of follow up [101].

11.1. Planning an elective pregnancy in CML patients

Female patients with CML who wish to become pregnant should be advised to wait until they have achieved major molecular response (MMR) or better responses and sustained these responses for at least 2 years [24,99,102]. Imatinib can be discontinued shortly before ovulation and perhaps at the onset of menstruation. The duration of interruption of imatinib therapy should be limited to 6 months. However, if the RT-q-PCR analyses of BCR-ABL transcripts do not show a rise from the baseline, the duration of interruption can be extended further. RT-q-PCR monitoring in addition to complete blood count (CBC) should be performed every 2-3 months while imatinib therapy is on hold [24,99]. In females with CML achieving complete hematological response (CHR) or better responses, oocytes should be collected for future assisted conception, TKIs should be stopped at the onset of the menstrual cycle, in vitro fertilization medications should be commenced 7 days after stopping TKIs and TKI therapy should be resumed after oocyte collection [24,99].

The interruption of imatinib therapy in pregnant patients having CML should be considered seriously and replacement of imatinib by alternative therapies such as interferon, hydroxyurea or leukapheresis can be taken into consideration [100,102,103]. There are different opinions regarding the use of interferon in pregnancy. Although it is generally safe during pregnancy, some believe that it should be avoided unless the potential benefits justify the potential risks to the fetus [1,100,102]. After cessation of imatinib, treatment with interferon- α is effective to sustain the complete molecular response achieved in CML patients with low Sokal score, while patients with high Sokal score usually fail interferon- α therapy, relapse quickly and lose their CHR [102]. Decisions on the interruption of TKI therapy, replacement by alternative treatments and planning of delivery should all be made after counseling the patient and her family and after involvement of obstetricians and neonatologists [100,103]. There is no evidence that a brief exposure to imatinib therapy during conception and pregnancy adversely affects the developing fetus. Unfortunately, after interruption of imatinib therapy, most patients lose their achieved responses particularly those with high Sokal score [99,102].

In a study which tested the interruption of imatinib therapy in pregnant females with CML that included 7 patients, the results were as follows: in patients who achieved optimal responses prior to interruption of imatinib therapy during pregnancy, maintenance of optimal responses was achieved after delivery and resumption of imatinib, while in patients who had suboptimal responses before the interruption of imatinib during pregnancy, failure to achieve optimal responses years after delivery and resumption of imatinib therapy was encountered [105]. Therefore, the interruption of imatinib treatment should be considered in patients who achieved optimal responses well before planned pregnancy or interruption of TKI therapy [24,102,105].

11.2. Imatinib in CML post-stem cell transplantation

A single report of a female patient with CML who received reduced intensity conditioning (RIC) allogeneic HSCT for her CML was documented [106]. The patient was resumed on imatinib on day 100 post-HSCT for 30 months. Seven months after withdrawal of imatinib and all transplant-related medications, the patient was found to be pregnant. She had uneventful pregnancy and she delivered 2 full-term babies. No relapse of her CML was reported till 5 years post-HSCT [106].

11.3. Experience with second generation TKIs

The experience with dasatinib and nilotinib in pregnant females having CML is very limited [107-110]. Three spontaneous abortions and 4 successful pregnancies in CML patients exposed to dasatinib have been reported. In one additional patient, CML was diagnosed during pregnancy and the patient was treated with dasatinib but unfortunately she developed serious complications that lead to the termination of pregnancy [107-109]. A patient with CML had 2 pregnancies; no treatment was required for the first one but nilotinib was used during the second pregnancy, which ended in a successful delivery without maternal or fetal complications [110].

11.4. The use of leukapheresis in pregnancy with CML

Leukapheresis has been successfully utilized in the upfront management of CML patients during the 3 trimesters of pregnancy [24,111,112]. At least 12 cases have been reported and in few cases it was used as the sole management of CML in pregnant females. It was successfully used for up to 15 sessions per pregnancy and no adverse outcomes were encountered in the vast majority of cases [24,111,112]. However, one baby was delivered with myelomeningocele and talipes equinovarus to a patient with CML who received leukapheresis in addition to hydroxyurea during pregnancy [24].

12. CLL in pregnancy

CLL is very rare in pregnancy and only 7 cases of CLL were reported between 1996 and 2014 [1,2,24,113-116]. The following complications of CLL have been reported in pregnant females: autoimmune phenomena, anemia requiring blood transfusions, hyperleukocytosis and repeated infections [1,2,35,115,117]. The following therapeutic modalities have been reported to be safe in pregnant females having CLL, at any stage of pregnancy: (1) leukapheresis for hyperleukocytosis, (2) corticosteroids for autoimmune hemolytic anemia and autoimmune thrombocytopenia, and (3) certain antimicrobials for the treatment of infectious complications of CLL [1,2,35].

Chlorambucil is contraindicated during the first trimester of pregnancy because of its teratogenic effects and fludarabine should be avoided in pregnancy and can be used to treat CLL after delivery [2]. During the second and third trimesters of pregnancy, the following drugs can be safely used: rituximab, chlorambucil and cyclophosphamide [2].

13. HCL in pregnancy

Hairy cell leukemia (HCL) is rare in young women and it is exceptional in pregnancy [1,2,39]. Only 6 cases of HCL were reported in pregnant females between 1987 and 2008 and few additional cases have been added since the year 2008 [1,2,38,39]. All the reported cases of HCL in pregnancy ended in uncomplicated deliveries [2]. If HCL is diagnosed during pregnancy, management depends on whether the termination of pregnancy is considered or not. In case the termination of pregnancy is done or treatment is postponed till after delivery, the following therapeutic options are safe: splenectomy, interferon, cladribine, rituximab and other new therapeutic modalities [1,2,36-39]. If the termination of pregnancy is not undertaken, the following options are available: (1) splenectomy and interferon have been safely reported in all trimesters of pregnancy, and (2) cladribine can be safely used in the second and third trimesters [1,2,36-39]. However, due to the limited number of HCL in pregnancy reported, no definitive conclusions should be made [1,2,36-39].

14. Other therapeutic measures during pregnancy

14.1. Corticosteroids in pregnancy

Prednisolone, methylprednisolone and hydrocortisone are extensively metabolized in the placenta; therefore; they are preferred over dexamethasone and betamethasone [1,2]. Corticosteroids are indicated for treating: (1) ALL in pregnancy, and (2) autoimmune complications of CLL during pregnancy. In animal studies, steroids are associated with development of cleft palate and altered neurological development resulting in complex behavioral abnormalities [1]. Corticosteroids have the following effects on pregnant women: (1) premature rupture of membranes, and (2) exacerbation of gestational diabetes mellitus and hypertension [1]. They also have the following effects on newborn infants: (1) intrauterine growth retardation, (2) low birth weight, (3) increased infant morbidity, (4) hyperactivity in the newborn infant, and (5) risk of adrenal insufficiency and infectious complications [1].

14.2. Growth factors in pregnancy

Granulocyte-colony-stimulating factor (G-CSF, filgrastim) is the most commonly used colony stimulating factor. It is usually used (1) in patients with neutropenia to reduce the incidence of infectious complications, and (2) for mobilization of stem cells in donors of autologous and allogeneic HSCT [118]. The administration of G-CSF in pregnant women who serve as donors for HSCT is generally safe as data from 5 studies that included HSCT donors including pregnant females did not show any evidence of increased risk of leukemogenicity [118]. Also, data from 8 studies that included 96 pregnant females having hematological malignancies showed delivery of 94 healthy babies, but one fetal death as the mother was exposed to idarubicin and cytarabine during pregnancy in addition to one birth of a child with low intelligence and malignancy [118].

14.3. Leukapheresis in pregnancy

Leukapheresis has been used in both acute and chronic leukemia in order to rapidly reduce high white blood counts (WBCs) in patients with an impending vascular occlusion due to leukostasis induced by hyperleukocytosis [2]. Although the experience is limited, the procedure has been successfully used as a short-term measure to rapidly control hyperleukocytosis at the presentation of acute and chronic leukemia [1,2,40].

14.4. Drugs and breast feeding after delivery

Chemotherapeutic agents differ in their concentrations that are found in breast milk [1,24]. Definitive neonatal toxicity during lactation has not been precisely delineated. However, it is advisable to avoid breast feeding for at least 2 weeks after the administration of cytotoxic chemotherapy [1,24]. Hydroxocobalamine is excreted in breast milk and should be avoided during lactation. Interferon- α is probably excreted in breast milk and should be avoided during lactation. TKIs such as imatinib are actively excreted in breast milk in animal studies. Although several reports show no harm, generally TKIs should be avoided during lactation as they have been reported to cause arrhythmias and cardiac toxicity [24].

Ciprofloxacin is excreted in breast milk and it has been reported to cause pseudomembranous colitis, arthropathies and cartilage erosions so the drug should be used with extreme caution, while fluconazole, itraconazole, voriconazole and posaconazole should be avoided during lactation [24]. However, there are no published data on the use of caspofungin and liposomal amphotericin-B in breast feeding women so they should be avoided in lactating women [24].

15. Fertility in patients with leukemia

Cytotoxic drugs, administered to premenstrual females having leukemia, may have adverse effects on ovarian reserve even in the setting of regular menses [119]. Hemato-oncologists, infertility specialists and patients should be aware of the potential risks of chemotherapy on ovarian function and should consider the available options for fertility preservation [119]. Options for fertility preservation in cancer patients include: (1) ovarian suppression during chemotherapy by hormonal therapy, (2) embryo cryopreservation, (3) oocyte cryopreservation, (4) ovarian tissue cryopreservation or gonadal tissue banking, (5) recent developments of in vitro fertilization for cancer patients and development of gonadotropin releasing hormone antagonists, (6) ovarian transposition during radiotherapy, and (7) additional considerations such as third party reproduction and adoption of children [120-122].

16. Conclusions and future directions

Leukemia is a rare event in pregnancy. Acute leukemia represents 90% of leukemias coexisting with pregnancy with AML accounting for two thirds of acute leukemias in pregnant mothers.

Vertical transmission of leukemic cells from the mother to her offspring is possible but very rare. During the first trimester of pregnancy, standard chemotherapy has a teratogenicity rate of 10-20% depending on the specific agent employed. Exposure to cytotoxic agents during the second and third trimesters is not teratogenic but carries the following risks: fetal growth retardation, premature delivery, fetal myelosuppression in addition to fetal and maternal exposure to malignancy and therapy-related toxicities such as thromboembolism and sepsis. Only absolutely necessary radiologic work-up is justified during the first trimester of pregnancy. Exposure to radiation during the first 2 weeks of pregnancy is usually lethal. Thereafter, radiation predisposes to congenital malformations, growth retardation and malignancy in the newborn. Few studies have demonstrated the potential risk of adult cancer after intrauterine exposure to radiation. Cytotoxic chemotherapy and radiotherapy increase genetic defects in germ cells. Although most infants exposed to multi-agent chemotherapy seem to suffer no long-term detrimental consequences, cytotoxic chemotherapy can cross the placenta and cause teratogenic effects.

The management of each pregnant patient with leukemia has to be highly individualized and should have a multidisciplinary approach. In the first trimester, the termination of pregnancy should seriously be considered if the disease is aggressive and if intensive chemotherapy is needed. In the second and third trimesters, standard chemotherapy can safely be administered without resorting to pregnancy termination. The choice of specific regimens depends upon: the gestational age, the clinical status of the patient, the specific type of leukemia and the anticipated toxic effects of the cytotoxic agents employed. The decision is often difficult and confounded by heightened emotions, ethical concerns and religious beliefs. Vaginal delivery is preferable while caesarean section is reserved for certain obstetric complications. The timing of delivery is essential. It is preferable between 32 and 36 weeks of gestation to ensure optimal fetal maturation, and it is advisable to avoid maternal myelosuppression prior to delivery.

Leukemia diagnosed during pregnancy can be considered a poor clinical prognostic factor owing to the less than average long-term disease free survival due to high relapse rates and high incidence of refractoriness to chemotherapy, particularly in young patients. Countries should have registries for mothers and children exposed to chemotherapy and radiotherapy. Also, it is essential to have guidelines on the management of various types of leukemia during pregnancy.

Author details

Khalid Ahmed Al-Anazi*

Address all correspondence to: kaa_alanazi@yahoo.com

Department of Hematology and Hematopoietic Stem Cell Transplantation, Cancer Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia.

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