Article published online: 2023-05-17

Case Report with Review of Literature

Pregnancy and Acute Lymphoblastic Leukemia: A Case Series and Review of Literature

Sukrita Bhattacharjee[1] Shouriyo Ghosh[2] Siddhartha Sankar Ray[1] Sambit Samanta[1] Nilanjan Sinha[1] Sandeep Saha[3] Maitreyee Bhattacharyya[1]

[1] Institute of Haematology and Transfusion Medicine, Medical College Kolkata, West Bengal, India
[2] L/BMT Program, Vancouver General Hospital, Vancouver, Canada
[3] Department of Clinical Haematology, NRS Medical College, Kolkata, West Bengal, India

Address for correspondence Maitreyee Bhattacharyya, MBBS, MD, DM, Institute of Hematology and Transfusion Medicine, Medical College Hospital, 88, College Street, Kolkata 700073, West Bengal, India (e-mail: mbhattyacharyya@yahoo.co.in).

Ind J Med Paediatr Oncol

Abstract

Acute lymphoblastic leukemia (ALL) diagnosed during pregnancy is rare and causes ethical and therapeutic challenges. We performed a retrospective search of ALL patients ($n = 202$) treated at our institution from 2015 to 2020 and found five patients diagnosed during pregnancy. In this report, we discuss the individual patients in detail and the challenges faced during their treatment. The use of established lymphoblastic leukemia treatment protocols and the modifications made therein to prevent untoward chemotherapy-related toxicities to the fetus are discussed in this study. We report the second use of rasburicase during pregnancy in literature with favorable maternal and fetal outcomes. We also present an extensive literature review of 41 cases of ALL in pregnancy previously reported. It is important to note that there is a dearth of guidelines for the treatment of these complex situations, and although certain general principles can be established, an individualized approach is needed in most cases of leukemia diagnosed during pregnancy.

Keywords
- acute leukemia
- ethical considerations
- pregnancy
- maternal well-being
- fetal outcome
- chemotherapy

Introduction

Acute leukemia is uncommonly encountered during pregnancy, occurring in approximately 1 in 75,000 cases and its management is a challenging task.[1] It requires a multidisciplinary approach to treat this life-threatening condition, keeping in mind the health and well-being of the mother and fetus. Patient management entails a gamut of challenges from treatment decisions to ethical and social considerations. Moreover, there is a dearth of trials in this unique and rare cohort of patients. Data from case reports, case series, and retrospective studies are the only evidence available, thereby emphasizing the need for an individualized approach.

Herein we report five cases of acute lymphoblastic leukemia (ALL) diagnosed during pregnancy at our center and challenges faced in managing these patients. We also reviewed the available literature to summarize the data on the clinical presentation, treatment complications, maternal, and fetal outcomes of these patients.

This is a series of ALL patients presenting during pregnancy who were treated at our institute between January 2015 and July 2020 (5 years). Clinical and laboratory data and outcomes of these patients were retrieved from our archives and reviewed for the purpose of this report. Informed consent was taken from the patients and/or next of kin while reporting these cases. For each patient, an institutional medical board, comprising specialists from hematology, obstetrics, neonatology, anesthesiology, and transfusion medicine, was convened to formulate the management plan. For the management of ALL in the adolescent and young

DOI https://doi.org/10.1055/s-0043-1766129.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

adults age group, our institutional practice is to use pediatric inspired protocols, namely, the Berlin Frankfurt Munster-2002 regimen. Our institute has a state-of-the art neonatal intensive care unit that can manage preterm births as early as 25 weeks of gestational age.

A total of 202 ALL patients were treated during the period 2015 to 2020 at our institution of which five were ALL with pregnancy (B-ALL, $n = 4$; Philadelphia positive B-ALL, $n = 1$). All five cases were women aged between 20 and 29 years (median age: 26 years) of whom three were primigravidae. None of the patients were diagnosed in the first trimester ($n = 2$, third trimester, $n = 3$, second trimester). The first two patients involving late third trimester mothers with newly diagnosed ALL were relatively stable and therefore could be managed with transfusion support till delivery, after which standard chemotherapy was administered. In the other three patients, chemotherapy had to be started with the fetus in-utero as a life saving measure for the mother. Institutional protocol for ALL induction therapy comprised of prednisolone at 60 mg/m^2, vincristine at 1.4 mg/m^2, daunorubicin at 30mg/m^2, and L-asparaginase at 5000 IU/m^2 in accordance with the BFM-2002 protocol in phase IA and 6-mercaptopurine, cyclophosphamide, and cytarabine in phase IB, followed by consolidation, re-induction and maintenance treatment limbs.

Case Series

Patient 1: A 28-year-old third gravida (32 weeks gestation) who presented with anemia was diagnosed with intermediate-risk Philadelphia negative pre-B-ALL. Her pregnancy was supported till 37 weeks with transfusions after which she delivered a healthy male baby by normal vaginal delivery (NVD). Subsequently BFM-2002 protocol was started and the induction was complicated by recurrent episodes of maxillary sinusitis, sepsis (Klebsiella species), and central line associated blood stream infection, which were managed with appropriate antibiotics. Subsequent phases of chemotherapy were administered without any interruptions.

Patient 2: A 24-year-old primigravida at 35 weeks gestation, developed intermittent fever, and generalized weakness of 1 month duration and was diagnosed as intermediate risk pre-B-ALL. Similar to patient 1, she was also kept on supportive care with packed red blood cells and platelets till she delivered a healthy male child by NVD at 37 weeks gestation. Subsequently, she was initiated on BFM-2002 protocol and received chemotherapy without any modifications.

Patient 3: A 29-year-old primigravida at 28 weeks of gestation was diagnosed as Philadelphia negative pre-B-ALL with leucocytosis (50,000/cumm with 80% blasts) and retinal hemorrhage. She received BFM-2002 induction without any modifications. Fetal assessment during leukemia induction revealed no anomalies. At 35 weeks of gestation and at the end of induction IA when her counts had recovered, she underwent planned Cesarean Section (CS) and delivered a healthy baby boy, appropriate for gestational age. Subsequently she received phase IB of BFM-2002. She unfortunately relapsed post-induction, and therapy was switched to rituximab-hyper-CVAD (comprising of hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone). During the second cycle of hyper-CVAD, she developed febrile neutropenia, septic shock, and succumbed to it. The child was healthy at last known follow-up.

Patient 4: A 26-year-old third gravida (26 weeks) presented with fever, generalized lymphadenopathy, and multiple skin nodules and plaques. On evaluation, she had hyperleukocytosis (with 90% blasts), anemia, and thrombocytopenia and was diagnosed as Philadelphia positive (Ph+) B-ALL with leukemia cutis and central nervous system (CNS) involvement. She developed tumor lysis syndrome (TLS) and was given rasburicase during initial stabilization. She was then started on modified E-WALL protocol which included a tyrosine kinase inhibitor (TKI)—imatinib 600 mg daily along with weekly pulsed dexamethasone and vincristine injections. Intrathecal chemotherapy was given with cytarabine and hydrocortisone, while methotrexate was omitted. Her platelet counts recovered by 31st week of gestation. Her pregnancy was continued till 32 weeks of gestation after which she underwent an elective CS and gave birth to a healthy female child. Post-induction bone marrow on day 52 of E-WALL protocol was in morphological remission and BCR-ABL measurable residual disease (MRD) was negative. She received one cycle of E-WALL consolidation after which she was lost to follow-up.

Patient 5: The last case is that of a 20-year-old primigravida at 24 weeks gestation who presented with progressive weakness, exertional dyspnea, low-grade fever, and was found to have severe anemia and atypical cells in peripheral blood. A diagnosis of Ph negative pre-B-ALL was made. She developed hepatic encephalopathy, TLS, and septic shock that were managed effectively. In this background of deranged liver functions and an early pregnancy, she was started on a modified BFM-2002 protocol, consisting of steroids and vincristine only. Subsequently, she went on to receive a modified phase IB of BFM-2002 protocol where only the cytarabine blocks were administered intravenously and intrathecal cytarabine chemotherapy was given, while omitting methotrexate, 6-mercaptopurine, and cyclophosphamide from the protocol. Her phase IB of induction was completed at 32 weeks of gestation. Pregnancy continued till term and she delivered a healthy male child. Post-induction, bone marrow was in remission and MRD was negative. However, she had persistence of CNS disease and was given high-dose intravenous methotrexate consolidation @ 5gm/m^2 along with triple intrathecal chemotherapy. Her reinduction chemotherapy phase was interrupted by coronavirus disease 2019 pandemic. Subsequently on resumption of chemotherapy, she developed febrile neutropenia, macrophage activation syndrome, went into septic shock, and unfortunately succumbed to her illness.

A summary of the patients, course of treatment in hospital, and their outcome are mentioned in ►**Table 1**.

Table 1 Patient characteristics, disease and pregnancy details, protocol and modifications used, issues faced, and fetomaternal outcomes

Case no.	Patient details (age/obstetric history/POG)	Presenting counts (Hb [g/dl]/total leucocyte count (cumm)/platelets (cumm)/blast [%])	Diagnosis IPT/CNS status/ Ph status/CG/ risk group/ EM disease	Protocol	Indication for treatment; modification done	Significant Issues faced during treatment	Disease outcome	Pregnancy outcome	Last follow-up
1	28 y G3P2 32 weeks	9.1/41,500/20,000/ 50% blasts	Pre-B-ALL/CNS-1/ Ph- neg/46XX/IRG	BFM-2002	Protocol started post-delivery No dose adjustments	Induction: Maxillary sinusitis, CLABSI and sepsis	Remission	NVD, male baby@37 weeks gestation	4 years: mother and child doing well
2	24 y G1P0 35 weeks	9.4/10600/218,000/ 30% blasts	Pre-B-ALL/ CNS-1/ Ph- neg/ 46XX/ IRG	BFM-2002	Protocol started post-delivery Vinblastine given in view of peripheral neuropathy	Induction- CLABSI, genital herpes, pneumonia, vincristine induced PN	Remission	NVD, male baby@ 37 weeks gestation	3 years: mother and child doing well
3	29 y G1P0 28 weeks, 4 days	8.3/50000/20000/ 80% blasts	Pre B-ALL/CNS-1/ Ph- neg/NDC/IRG	BFM-2002	Protocol started in third trimester in view of bleeding. No dose modification. Phase IB given post-delivery	Induction- cytopenia Relapsed prior to consolidation. Switched to Hyper-CVAD.	Relapse post-induction 2# Hyper-CVAD: death due to septic shock	Elective CS Male baby @ 35 weeks	Child was healthy at last follow-up
4	26y G3P2 26 weeks	7/250,000/10,000/ 90% blasts	Philadelphia +ve B-ALL/CNS-3/ 46XX/HRG/ leukemia cutis	Modified E-WALL; Imatinib 600 mg OD	Induction started in late second trimester. Rasburicase given IT: ARA-C and hydrocortisone. MTX omitted	TLS	Remission	Elective CS, female baby@ 32 weeks	Lost to follow-up after first cycle of consolidation
5	20y G1P0 24 weeks	6/84,600/25,000/ 40% blasts	Pre-B-ALL/CNS-1/ BCR- ABL neg/ 46XX/IRG	BFM 2002 with changes	Induction: second trimester: VCR and steroid only IB: Only Ara-C; IT ARA-C Consolidation: MRC UK-ALL HD-MTX @ 5gm/m^2 and L-ASP 10000 IU/m^2 triple IT with MTX, ARA-C and hydrocortisone	Pre-treatment: Hepatic encephalopathy, septic shock, TLS Consolidation: CNS relapse Reinduction: therapy interruption due to COVID-19 pandemic	Remission post-induction Consolidation: Isolated CNS relapse Re-induction: Death due to septic shock and MAS	Elective CS, male baby@ 37 weeks	Child healthy at the time of her death

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin Frankfurt Munster; CLABSI, central line associated bloodstream infection; COVID-19, coronavirus disease 2019; CNS, central nervous system; CS, cesarean section; EM, extramedullary; IPT, immunophenotype, IRG, HRG, intermediate and high-risk groups respectively; MAS, Macrophage Activation Syndrome; NDC, nondividing cells in cytogenetics; NVD, normal vaginal delivery; POG, Period Of Gestation; RDP, random donor platelets; PN, peripheral neuropathy; TLS, tumor lysis syndrome; IT, Intrathecal Chemotherapy.

Discussion

Among leukemia cases encountered in pregnancy, around 28% cases of leukemia in pregnancy are ALL, the rest being acute myeloid leukemia (AML) and chronic myeloid leukemia, (CML).[1] The major concern in the management of these cases has been the optimal timing and dosing of chemotherapy so as to prevent harmful effects to the fetus. An extensive search of the literature revealed 41 cases of ALL in pregnancy (summarized in ►**Table 2**)[2–12] in addition to the 60 cases of ALL during pregnancy described by Cardonick and Iacobucci.[3] Pregnancy leads to physiological changes such as increased plasma volume as well as changes in drug pharmacokinetics due to altered hepatic and renal clearance of drugs. Pregnancy can also change drug metabolism by creation of a third space in the form of the amniotic sac.[13]

Table 2 Synopsis of cases of pregnancy with acute lymphoblastic leukemia reported in literature

Sl. no.	Reference (total cases; ALL cases)	Patient details (age/obstetric history/POG)	Diagnosis	Therapy used; modifications (if any)	Pregnancy and fetal outcome	Disease status	Maternal outcome
1	Krueger et al [1976] (4)	15/-/26	ALL	COAP regimen: cyclophosphamide, vincristine, cytarabine, prednisone	Induction of labor. Normal Infant at 38 weeks	PD	Relapse1-month post-partum
2	O' Donnell et al [1979] (4)	24/-/15	ALL	TAD regimen (thioguanine, cytarabine, daunorubicin)	Pre-eclampsia and intrauterine fetal death at 30 weeks	CR	Alive
3	Okun et al [1979] (5)	18/-/12	ALL	1st Induction: VCR, Pred, IT MTX. 2nd induction: CTX, L-Asp, DNR, 6-mercaptopurine; WBRT	CS at 31 weeks; baby with transient pancytopenia, CHF, normal development at 1 year	Relapse	CNS relapse 5 weeks post-partum
4	Dara et al [1981] (4)	26/-/21	ALL	6-MP, MTX, discontinued when pregnancy confirmed; relapse at 21 weeks, second line initiated with doxorubicin, VCR, Pred, Cyt, MTX	CS at 36 weeks. infant with polycythemia and hyperbilirubinemia Normal growth and development at 6 months	CR	Alive
5	Sigler et al [1988] (4)	26/-/32	ALL	Pre, DNR, Ctx, Cyt, L-asp	Induction at 35 weeks. Normal infant	CR	Remission followed by maintenance
6	Avasthi et al [1993] (4)	20/-/22	ALL	Two courses of VCR, Pred	Preterm delivery at 29 weeks to live infant	–	Sudden death 2 days after delivery
7	Camera et al [1996] (4)	21/-/17	ALL	VCR, Pred, DNR, L-asp	C-section at 29 weeks Normal male infant	Relapse	Death 9 months later from relapse
8	Tewari et al [1999] (4)	17/-/33	ALL	VCR, Pred for relapse ALL	Induction at 35 weeks Normal infant	CR	Consolidation s/p allo-SCT 22 months later
9	Hansen et al [2001] (4)	24/-/26	ALL	Induction CALGB 9111. At 26 weeks: DNR, VCR, Pred, L-asp At 30 & 34 weeks: IT-MTX, Ctx,6-MP, Cyt, VCR, L-asp	Spontaneous delivery at 36 weeks. Normal male infant	–	Unclear
10	Ali et al [2002] (10 cases: 2-ALL) (5)	24/G1/24 21/G2P0/8	B-ALL Relapsed B-ALL	Not documented Not documented	Therapeutic abortion Therapeutic abortion	Remission relapse	Alive Dead
11	Terek et al (2003] (4)	21/-/31	ALL	VCR, DNR, Pred, L-asp	C-section, newborn respiratory distress (required intubation)	–	Maternal death due to sepsis
12	Chelghoum et al [2005] ($n = 37$) (6) 6 ALL cases	1. 25/G1/27 2. 34/G2/9 3. 33/G4/26 4. 30/G1/10 5. 21/G1/28 6. 25/G1/9	T-ALL Pre B-ALL Pre B-ALL Ph+ B-ALL Pre B-ALL T-ALL	All cases received VCR + Dauno + CTX + Pred	NVD, premature Therapeutic abortion CS; premature Therapeutic abortion CS; premature Therapeutic abortion	PD CR CR CR CR CR	
13	Molkenboer et al [2005] 2 ALL cases (7)	1. 30/G3P2/6 2. 37/G1/15	Ph+ B-ALL Ph+ B-ALL	Pred + VCR + Dauno + Asp + ITMTx; High-dose cytarabine+ imatinib Same as above	Missed abortion at 11 weeks Spontaneous delivery at 22 weeks; stillborn	CR PD post-induction	Death post-HSCT Imatinib palliation. Death few weeks later
14	Dilek et al [2006] (1/21, ALL) (8)	25/G1/term	ALL	4 drug regimen induction	NVD; LBW	CR post-induction	Alive

Table 2 (*Continued*)

Sl. no.	Reference (total cases; ALL cases)	Patient details (age/obstetric history/POG)	Diagnosis	Therapy used; modifications (if any)	Pregnancy and fetal outcome	Disease status	Maternal outcome
15	Matsouka et al [2007] (9)	16/G1/26 + 3d	B-ALL	BFM-95; Recombinant G-CSF use during cytopenic phase. Delivered post-induction	Elective CS at 32.4 weeks; LBW	CR	Alive
16	Papantoniou et al [2008] (4)	16/-/26	ALL	DNR, VCR, L-asp, Pred, IT-Mtx, G-CSF	CS at 32 weeks. Infant normal at 18 months	CR	Remission at 18-months follow-up
17	Udink Ten Cate et al [2009] (4)	30/-/23	ALL	VCR, Pre, IT-MTX, Ctx, DNR. VCR, Ctx, DNR. Maintenance 6-MP	PROM at 33 weeks, NVD baby; pancytopenic, normal development at 2 years	CR	MUD—HSCT In CR 2 years after transplant
18	Aljurf et al [2009] 2 ALL cases (4)	37/-/29 27/-/13	ALL ALL	VCR, dexamethasone, idarubicin Unknown	Full-term infant; anemia Spontaneous abortion at 14 weeks during induction	CR CR	CR with induction Allo-SCT in CR 1 Alive 4 years later
19	Ticku et al [2013] (4)	22/G1/26	Ph+ B-ALL	Induction: Hyper-CVAD + dasatinib Ph+ mutation F317L; Ponatinib started 10 days post-partum	Elective CS at 30 weeks; LBW	CR	Alive
20	Nakajima et al [2013] (10) 3 ALL cases	1. 20/G1/37 2. 36/G1/29 3. 29/G1/5	ALL ALL/ t(9;22) ALL	Not available DNR + VCR +, CTX + Pred Not available	Emergency CS; live birth Elective CS; live birth Therapeutic abortion	PD CR CR	Dead Alive Alive
21	Saleh et al [2014] ($n = 32$; 6 ALL cases) (2)	1. 23/G2/38 2. 25/G1/12 3. 26/G3/28 4. 23/G3/13 5. 37/G7/29 6. 21/G1/31	Pre B-ALL Pre B ALL Pre B-ALL Pre B-ALL Pre B- ALL T-ALL	None None 5 drug regime None 5 drug regime VCR + Pred	Live birth at term Spontaneous abortion Spontaneous abortion Spontaneous abortion Live birth at term Preterm birth at 33+ weeks	PD PD CR PD LTFU PD	Death Death Alive, post-SCT Dead, post-SCT LTFU Death
22	Farhadfar et al [2016] ($n = 23$) 5 ALL cases (11)	1. 26/-/12 2. 23/-/6 3. 34/-/10 4. 19/-/16 5. 28/-/35	B-ALL B-ALL Ph+ ALL B-ALL B-ALL	Post-termination induction C10403 Post-termination induction C10403 CALGB9111; Reinduction: Imatinib with ara-C HSCT: MUD, TBI/VP-16 DNR/VCR/Pred; Consolidation: HiDAC Post-delivery - DNR/VCR/Pred Relapse: DNR/VCR/Pred, HiDAC, MTX/L-Asp	Therapeutic abortion Therapeutic abortion Fetal loss at 19 weeks Fetal loss 22 weeks NVD,38 weeks	- CR CR, f/b HSCT CR PD	Alive Alive Death on D21 of HSCT d/t septic shock Death Death
23	Vlijm-Kievit et al [2017] (12)	37/G2P1/36	T-ALL	Pred + VCR + Dauno + Peg-asparaginase (HOVON 100 protocol)-Asp and MTX delayed till post-delivery Therapeutic LMWH given upto 6 weeks post-partum	NVD 37 weeks	Remission	Alive

Abbreviations: ALL, ALL, acute lymphoblastic leukemia; CR, complete remission; CS, cesarean section; CTX, cyclophosphamide; Cyt, cytarabine; DNR, daunorubicin; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; HSCT, hematopoietic stem cell transplant; IT, intrathecal; L-asp, L-asparaginase; LBW, low birth weight; LMWH, low molecular weight heparin; LTFU, lost to follow-up; MTX, methotrexate; MUD, matched-unrelated donor; NVD, normal vaginal delivery; PD, progressive disease; Pred, prednisone; VP-16–Etoposide; WBRT, whole brain radiation therapy.

Estrogen receptors like HL-60 have been found in human myeloblastic leukemia cell lines[14] however, pregnancy alone is not thought to have an adverse effect on leukemia.[13]

Management of leukemia in first trimester: In our study, none of the patients presented with leukemia in the first trimester. As per recommendations, the pregnancy should be terminated prior to initiation of chemotherapy (many recommend 20 weeks and earlier).[3,15] Another approach in precious pregnancies is to give a short course of steroids to carry forward the pregnancy past the period of embryogenesis, after which cytotoxic chemotherapy can be administered.[15] The limited evidence suggests that almost all chemotherapeutic drugs used in ALL induction can be given during pregnancy, albeit, with risks to the fetus including still-births, intrauterine growth restrictions, spontaneous abortions, and congenital malformations, especially in the first trimester.[15–17] Beyond first trimester, however, almost all chemotherapeutic drugs can be used. Some modifications

have also been recommended with regard to L-asparaginase and intrathecal methotrexate in view of risk of thromboembolism and fetal aminopterin syndrome.[18] In our literature search, we found 11 pregnancies in the first trimester with ALL, 8 of whom underwent therapeutic abortion prior to starting chemotherapy and 2 had spontaneous abortion and only 1 pregnancy resulted in a live birth (premature) where induction was with only vincristine and prednisolone.[4–6,10,12]

Management of leukemia in second trimester: In our report, both patients with second-trimester pregnancies presented with complications for which several key modifications were made and the results were favorable. In the fourth patient, presence of a targetable lesion (BCR-ABL) prompted us to use a TKI along with steroids and vincristine as per the E-WALL protocol.[19,20] Data from CML patients with pregnancy proves that TKIs are teratogenic when used during organogenesis and may also lead to adverse pregnancy outcomes when used in later trimesters. However, other studies have advocated the use of Imatinib safely in second and third trimesters of pregnancy.[21–23] Data on other second-generation TKIs are scanty with isolated cases of fetal exposure to dasatinib and nilotinib.[24,25] We, therefore, used imatinib, instead of dasatinib (as per the E-WALL protocol) for our patient.[19] There are six cases of Ph+ ALL described in ►**Table 2**, mostly treated with imatinib as the TKI of choice.[4,6,7,10] In one case, both dasatinib and ponatinib were used due to tyrosine kinase domain mutation. However, as chemotherapy was started post-partum, the effects of these drugs on fetal outcome cannot be commented upon.

The fifth patient in our cohort was also a second-trimester pregnancy, but she had multiple complications at diagnosis itself, precluding the use of full-fledged BFM-2002 protocol.[26] L-asparaginase was added to the consolidation limb of chemotherapy, similar to the UKALL and E-WALL consolidation protocols for the treatment of Ph+ ALL.[19,27] Of note, there is in vivo antagonism of methotrexate and L-asparaginase due to opposing mechanisms of action. This can be overcome by administration of L-asparaginase *after* (but, *not before*) high dose methotrexate. This prompted us to use it 24 hours after completion of methotrexate infusion.[28,29] Although the patient succumbed to infectious complications later-on during the course of treatment, both maternal and fetal outcomes of pregnancy were favorable.

Management of leukemia in third trimester: Chemotherapy should ideally be withheld 3 weeks prior to childbirth to allow the counts to recover at the time of delivery and also to prevent neonatal myelosuppression.[30] A planned delivery is always essential in these scenarios. Another option for patients presenting near term is to initiate preinduction with steroids alone and then continue with the full chemotherapy once the child is delivered.[31] A conservative approach with transfusion support till delivery was safely adopted for first two relatively stable patients presenting in late third trimester, while in the third patient, we started chemotherapy ante-partum. In the cited literature, we found two cases of third-trimester pregnancies diagnosed near term, in whom chemotherapy was started post-partum (►**Table 2**).

Supportive care: TLS is a common complication in highly proliferative hematological malignancies and is an oncologic emergency. Rasburicase use has not been deemed safe in pregnancy, in view of teratogenicity reports in animal studies. However, it has been used in cases where the benefits outweigh the risk.[32] The Ph+ ALL patient in our cohort presented to us with life-threatening TLS and after due consideration, we gave her rasburicase during induction and did not see any adverse fetal outcomes. To the best of our knowledge, only one earlier case of antepartum use of rasburicase has been published in literature at 35+ weeks of gestation in a case of ALL.[33]

Chemotherapy-induced neutropenia increases the chance of infections in the mother and poses numerous risks during pregnancy, both to the mother and the fetus. This is compounded by the fact that not all antibiotics can be used safely during this period.[13] Recombinant granulocyte colony-stimulating factor has been reported to be safe and can be used to shorten the period of neutropenia.[9,34] Leukemic patients may also present with thrombocytopenia that can be deleterious at the time of delivery, especially when the required platelet thresholds for vaginal (30,000/cumm) and cesarean delivery (50,000/cumm) are not met.[35,36]

In all our patients, fetal outcomes were favorable in terms of four babies being born at term either by NVD or elective CS. Only one baby was born prematurely at 32 weeks but is currently doing well. There is an association of intrauterine growth restriction and low birth weight (LBW) babies with exposure to chemotherapeutic agents in the second and third trimester. Preterm deliveries are also common. Prolonged durations of myelosuppression with their inherent complications such as infections have been observed in neonates born to mothers undergoing chemotherapy.[13] Long-term effects on growth and development of these children are also of concern and require follow-up of this rare and unique cohort. Among the 41 cases we reviewed in literature, there were 15 abortions (4 spontaneous, 11 therapeutic), 11 preterm/LBW babies, 1 still born, and 14 normal live births. In 23 cases, the fetuses were exposed to chemotherapy in utero and this resulted in four spontaneous abortions, sixteen LBW/preterm deliveries and fetal deaths. Some of these babies had complications at birth (►**Table 2**). Only three live healthy newborns were reported post-chemotherapy exposure in utero.

Post-delivery, due consideration should be given to breast feeding, future fertility, and reproductive health of the patient.[13] In most situations, breastfeeding is not recommended while the mother is on chemotherapy, as these agents can be secreted in breast milk. If at all breastfeeding is essential, it is recommended to commence at least 2 weeks after the last administration of chemotherapy.[15] Complications such as mastalgia and breast abscesses may arise and it is therefore recommended for lactating mothers on chemotherapy to express and discard the milk to prevent such issues. Fertility issues in surviving patients may also arise, and similar to any woman in the reproductive age-group undergoing chemotherapy, it is recommended to give a hiatus of at-least 2 to 3 years after completion of chemotherapy to try to conceive once again.[16]

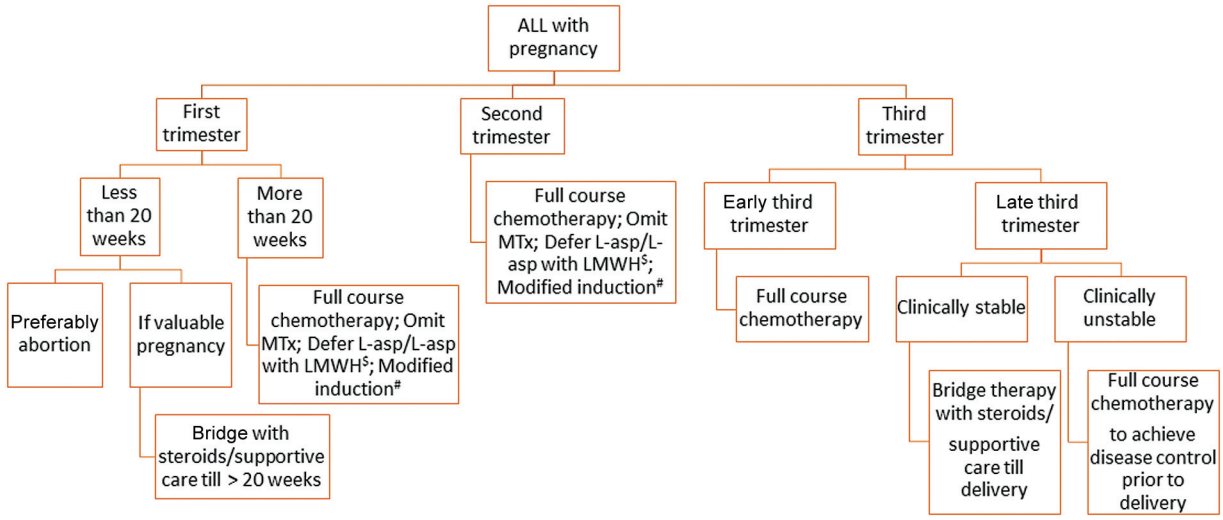

Fig. 1 Flowchart of management of acute lymphoblastic leukemia in pregnancy. $: L-asparaginase is associated with increased risk of thrombosis during pregnancy and should be combined with low molecular weight heparin (LMWH) prophylaxis or deferred till after delivery. #: Modification of protocol on a case-to-case basis; modification based on co-morbidities/intolerance to specific chemotherapeutics.

Saleh et al in their follow-up of 32 patients opined that acute leukemia patients had poorer long-term outcome compared to nonpregnant patients. Given the small number of patients in our cohort, we are unable to comment on this aspect.[2] Our experience shows that those patients who received full dose chemotherapy post-delivery were able to maintain remission and probably reflect the requirement of more aggressive therapy post-delivery to prevent relapse.

The cases described here were unique with respect to several factors including the time of presentation, clinical and leukemia risk profile, and complications. Hence, an individualized approach was undertaken. A proposed algorithm for the management of ALL in pregnancy is described in ►**Fig. 1**.

Conclusion

Management of leukemia in pregnancy is a challenging task and relies heavily on effort of a multidisciplinary team, from treating hematologists to obstetricians. Individualized approach to manage these patients is essential, considering the gestational timing of presentation of ALL, cytogenetics, clinical profile, and active medical issues at diagnosis. Novel approaches used in our patients such as the use of modified BFM and E-WALL protocols, modifications with regard to timing of L-asparaginase administration, and antepartum use of rasburicase were met with favorable pregnancy outcomes.

Authors' Contributions

S.B. was involved in conceptualization, data collection, and manuscript drafting. S.G. helped in conceptualization, clinical data curation, and manuscript editing and analysis. S.S.R., S. Samanta, N.S. and S. Saha were involved in Institutional Medical Boards convened for patient management strategies. M.B. was involved in conceptualization, manuscript editing, analysis, and overall supervision.

Ethics Approval

Retrospective study

Consent for Publication

Yes.

Availability of Data and Material

Available for publication/review.

Funding

None.

Conflict of interest

None declared.

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