Case Report

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A Rare Case of Acute Lymphoblastic Leukaemia in Pregnancy- Unique Maternal-Fetal Challenges

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ABSTRACT

Leukaemia in pregnancy is rare and lethal. Its incidence is estimated to be 1 in 75,000 pregnancies. Use of chemotherapeutic agents during pregnancy can give rise to maternal and fetal adversity; resulting in dilemma regarding proper management plan.

A 25-year-old pregnant lady was presented at 24 wk of gestational age with cervical and inguinal lymphadenopathy and bicytopenia in complete blood counts. Diagnosis of acute lymphoblastic leukaemia was confirmed by bone marrow biopsy. Treated with appropriate chemotherapeutic regimen with some modification in the standard protocol due to pregnancy and delivered successfully by lower segment caesarean section at 34 wk of gestational age.

Diagnosis of acute leukaemia during pregnancy need high index of suspicion and need prompt management with the proper chemotherapeutic regimen. Clinical judgement regarding the risk benefit ratio of using chemotherapeutic drugs ensures better mother and fetal outcome.

Keywords: Acute leukaemia, Chemotherapy, Delivery

CASE REPORT

A case of 25-year-old female, married for four years was reported to antenatal clinic at 24 wk of gestation with acute onset swelling of neck and groin area. Her current pregnancy was uneventful till 24 wk of pregnancy. This was her third pregnancy with two previous as Caesarean section. She had no history of fever, petechiae, bleeding gum or nose. She was a booked case and she was referred to our institute. She had a history of weight loss in past one month (from 50 to 49kg).

On examination, she had mild pallor. She had one (2×2 cm) lymph node in submandibular region; few small lymph node in supraclavicular region; also one lymph node in both right (2x2 cm) and left femoral region (1x1 cm) each. Rest of the examination was unremarkable.

Her initial blood reports showed bicytopenia and normal total WBC count with differential count of lymphocyte 47% and neutrophil 44% [Table/Fig-1].

Ultrasonography of whole abdomen showed moderate spleno-megaly (16.7 cm) with normal echotexture; liver normal size (13.7 cm) with coarse echotexture and there was no intrahepatic biliary dilatation (portal vein diameter 8 mm and CBD diameter 2 cm). Her fetus was 24 wk gestational age with normal liquor and estimated fetal weight was 850 gm.

Lymph node biopsy was performed from left upper cervical region and histopathology report had come as high grade non-Hodgkin lymphoma. Immune-histochemical markers for confirmation showed CALLA positive lymphoblastic lymphoma/leukemia probable of B cell origin. {BCL – 2 Diffuse positivity, CD – 10 Diffuse strong +, Mib (Ki67) >90%positive, Tdt Diffuse strong positivity in tumour cells}

Bone marrow biopsy had confirmed the diagnosis of acute lymphoblastic leukemia (70% blasts) along with erythropoiesis and myelopoiesis suppressed; megakaryocyte slightly decreased.

She had reached 26 wk of gestation at the time of the diagnosis. As her pregnancy was in 2nd trimester and had crossed the age of viability; it was decided to continue the pregnancy and to start chemotherapy. Following chemotherapeutic regimen (Induction) was started:

- Inj. Dexamethasone (8 mg) intravenously form day1 to day7
- T. Prednisolone (60 mg/day) from day 8 to day 29
- Intrathecal Methotrexate (12 mg) weekly (day 1, day 8, day 15, day 22)
- Inj. Vincristine (2 mg) weekly intravenously
- Inj. L-asparaginase – 10000 U intramuscularly alternate day from day8 for 8 doses

Follow-up of serial complete blood count every 2-3 days showed improved blood counts after one month of therapy [Table/Fig-2].

After completion of induction chemotherapy; repeat bone marrow biopsy showed marrow in remission.

Fetus was monitored with serial USG and colour Doppler to detect any evidence of intrauterine growth restriction [Table/Fig-3]. Prophylactically inj. betamethasone for fetal lung maturation was given to her at 32 wk of gestation.

During the course of chemotherapy despite mild nausea and vomiting; her appetite and general well-being was improved and she had gained 4 kg of weight. She had complained of diffuse abdominal pain due to gastritis. She had developed puffiness of face due to prednisolone and numbness of fingers due to vincristine. She had also developed post dural puncture headache after intrathecal methotrexate which was managed symptomatically.

Interim maintenance regime was then started with:

- Inj. Vincristine (2 mg) intravenously single dose
- Intrathecal methotrexate (12 mg) for 3 consecutive weeks
- T. Mercaptopurine (100 mg) orally for 1 month

She was delivered at completed 34 wk of gestation by elective LSCS. A live male of 2.08 kg was delivered with APGAR of 8/9/9. Her postoperative period was unremarkable and the patient recovered well. After delivery she was given remission consolidation therapy with her primary medical oncologist and at her last contact she was in remission.

DISCUSSION

Leukaemias are malignancies of the haematopoietic system, derived from transformed haematopoietic stem cells within the bone marrow. Leukaemia during pregnancy is acute in 90% cases and chronic in 10% cases. Among acute leukaemia in pregnancy

Investigation	Baseline (Mid September	29.9.2010	01.10.2010	12.10.2010
Haemoglobin (gm%)	10.6	7.6		7.4
WBC (/cu mm)		9500 N44 L47		7900 N69 L22
Platelet(/cu mm)		74000	73000	87000
Peripheral smear		Normochromic normocytic		Normochromic normocytic
Billirubin			Total 1.3mg%, Direct 0.5 mg%	Total 1.4 mg%' direct 0.5mg%
Uric acid(mg/dl)			7.8	
Creatinine(mg/dl)	0.8		0.8	
TSH(mU/L)		2.63		
Serum Feritin			252.4ng/ml	
Vitamin B12			1922pg/ml	

[Table/Fig-1]: Initial blood reports,

	29.10.10	02.11.10	06.11.10	10.11.10	15.11.10	22.11.10	25.11.10
Hb(gm%)	7.9	8.1	7.8	8.4	8.9	9.9	9.6
WBC(/ cumm)	5800	5100	2300	2100	3400	6300	9000
Platelet(/ cumm)	81000	91000	89000	98000	198000	334000	302000

[Table/Fig-2]: Improvement in blood counts following treatments

04.11.2010	17.11.2010	01.12.2010	13.12.2010
28 wks	30 wks	32 wks	33+4 wks
EFW 1.127 kg	EFW 1.427 kg	EFW 1.7 kg	EFW 2.0 kg
AFI 12	AFI 11	AFI 9.4	AFI 12
AGA	AGA	AGA	AGA
Umbilical artery Doppler- Normal		Umbilical artery Doppler- Normal	

[Table/Fig-3]: Serial Ultrasonography of fetus
AGA= average for gestational age, EFW= estimated fetal weight, AFI=amniotic fluid index

with low birth weight, intrauterine growth retardation, spontaneous abortion, premature birth, microcephaly and mental retardation [2].

Before the initiation of treatment with chemotherapy in a pregnant woman, the potential benefits to the mother should be weighed against the potential risks to the mother and fetus. The major prognostic factors for survival in this case was age, cytogenetic abnormalities, immunologic subtype, white blood cell (WBC) count, and time to achieve complete remission (CR) [3]. In case of acute leukaemia where cure is the realistic goal appropriate treatment should be started immediately irrespective of gestational age. Pregnancy does not alter the course of leukaemia; but the outcome is far worse when treatment is delayed [4].

Treatment of ALL outside pregnancy is dependent on +/- of BCR-ABL mutation. Approximately 25% of ALL have this mutation and these have significantly improved outcomes if a Tyrosine Kinase Inhibitor is used with chemotherapy. But in our case we need not identify the mutation as this will not change the chemotherapeutic regimen; because limited information is available about the use of tyrosine kinase inhibitor before conception and during and after pregnancy [5]. In this case, induction-remission phase is started with prednisolone, vincristine, L-asparagenase and intrathecal methotrexate [6]. Although incorporation of the anthracycline daunorubicin during the first three days of induction therapy into a chemotherapy program that included vincristine, prednisone, and L-asparaginase demonstrated superior CR rates (83 versus 47 percent) and median remission duration (18 versus 5 months) [7]; daunorubicin is not included because it can cause myelosupression. In our case, WBC count was in the range of 2500/µl to 3500/ µl for about three weeks after initiation of induction-remission phase. Daunorubicin would cause further fall in WBC count which can potentially cause maternal sepsis and adversely affect fetal wellbeing.

After the induction phase instead of consolidation phase, interim maintenance regime is started. Because consolidation phase regime has cyclophosphamide which myelosupressive is also with potentially can cause maternal sepsis. So, in interim maintenance, non myelosuppressive chemotherapy (e.g., vincristine and intravenous MTX) are administered to maintain remission and allow the bone marrow to recover.

	Age	Gravida	Type	Diagnosed	Regime	Fetal outcome	Maternal outcome
Chelghoum Y et al., [10]	21	G1	ALL pre B	28wks	DNR, VCR, CPM, L-Asp, Pred	LSCS PTB	CR
Chelghoum Y et al., [10]	33	G4	ALL pre B	26 wks	DNR, VCR, L-Asp,Pred	LSCS PTB	CR
Matsouka et al., [11]	16	G1	ALL pre B	26wks	DNR, VCR, L-Asp, Pred, IT-MTX	LSCS PTB	CR
Justin Bottsford-Miller et al., [9]	27	G4	ALL pre B	24wks	DNR,VCR, L-Asp, Pred, IT-Mtx & Cytarabine	LSCS PTB	CR
Jonathan Ticku et al., [12]	22	G1	ALL pre B	26wks	Doxorubicin, VCR,CPM, Dexamethasone	LSCS PTB	CR

[Table/Fig-4]: Comparison with earlier reported cases
DNR: Daunorubicin, VCR: Vincristine, CPM: cyclophosphamide, L-Asp: L-asparaginase, Pred: Prednisolone, IT: intrathecal, CR: complete remission

2/3rd are myeloid and 1/3rd are lymphoblastic. Among chronic leukaemia most common are myeloid [1]. Diagnosis in pregnancy is most frequently done in 2nd and 3rd trimester; although disease may have been present earlier. This is because early symptoms are nonspecific. This emphasises the importance of early bone marrow examination in unexplained anaemia in pregnancy.

Effect of leukaemia on pregnancy can be due to leukaemia itself or due to chemotherapy induced. The timing of fetal exposure to the chemotherapeutic agents is one of the most important determinants of pregnancy outcome. In the first trimester, exposure to chemotherapy can result in congenital malformations or abortion. The risk of congenital malformations has been reported to be as high as 17%. Syndromes of congenital anomalies include cranial anomalies, cleft palate, anencephaly, and micrognathia. Second- and third-trimester exposure to chemotherapy has been associated

Obstetric management in first trimester is termination with proper counselling; in 2nd and 3rd trimester continuation of pregnancy can be done with proper fetal surveillance [8]. Anomaly scan and serial growth scan is to be done to detect malformation or growth restriction.

Delivery can be done at haematological remission after the 1st treatment course [8,9]. Goal is to deliver after 34 wk pregnancy. Caesarean section is done in obstetric indications only. If the diagnosis made in 3rd trimester; delivery may be indicated before beginning of chemotherapy [7]. A brief comparison of case reports of acute lymphoblastic leukemia treated during pregnancy is shown in [Table/Fig-4].

Epidural anaesthesia is given for caesarean section. Appropriate antibiotic is administered to prevent post operative sepsis and ensure wound healing. Postpartum thromboprophylaxis is given in postoperative period and baby is advised formula feeding.

CONCLUSION

In acute lymphoblastic leukaemia during pregnancy, maternal and fetal outcome can be favourable if promptly managed and delivered in appropriate time.

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