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ORIGINAL ARTICLE

Obstetric Complications and Management in Chronic Myeloid Leukemia

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Abstract Chronic myeloid leukaemia (CML) is amongst the most common haematological malignancies encountered in adults. The younger age of onset and increased incidence of CML in Indians leads to higher chances of encountering it in pregnancy. Pregnancy in CML is a complex situation as first line therapy with tyrosine kinase inhibitors (TKI), is fraught with multiple fetal safety issues. The fetal aspects have been elucidated in literature, but there is scarcity of information on the obstetric outcome per se in presence of CML, excluding the influence of TKI. Obstetric outcomes of 5 pregnancies in four patients with CML are being reported. Literature on interplay of CML and bleeding or thrombotic manifestations is reviewed. The major complications encountered were antepartum (APH) and postpartum haemorrhage (PPH), preterm labour, intrauterine growth retardation and intrauterine fetal death. Patients in the reproductive age group with diagnosis of CML should be carefully counseled regarding the effect of disease and TKI on the maternal-fetal health. Bleeding complications, particularly APH and PPH may be encountered in CML patients. Close coordination of the obstetrician, haematologist, and neonatologist is required in managing these cases successfully. The need for absolute contraception till the remission of disease needs to be emphasized for further pregnancies.

Keywords Chronic myeloid leukaemia · Pregnancy · Haemorrhagic obstetric complications · Tyrosine kinase inhibitors

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Introduction

Leukaemia is rare in pregnancy as it mostly affects the older age. The annual incidence is one per 75,000–100,000 pregnancies [1–3]. Leukaemias during pregnancy are primarily acute, two third being acute myeloid leukaemia (AML) and remaining one third acute lymphoblastic leukaemia (ALL). Annual incidence of CML in females ranges from 0.6 to 1.6 per 100,000 population [4]. The median age of CML in India is reported variably as 32–42 years, a decade younger than in Europe (55 years) and America (66 years) [1, 5]. CML constitutes 30–60 % of all adult leukaemias in India [1]. CML constitutes less than 10 % of all leukaemias in pregnancy.

Chronic myeloid leukaemia (CML), a clonal myeloproliferative neoplasm (MPN) has a higher chance of being encountered in pregnancy in India due to its occurrence at younger age as compared to West [1]. It has a variable clinical course with an accelerated blast phase and a chronic remitting phase of variable durations. In accelerated phase (AP), blood or marrow blasts constitute 10–19 % while in chronic phase (CP) blast cells are less than 10 %. Some patients may get into rare crisis called blast phase, characterized by more than or equal to 20 % blood or marrow blasts and hyposegmented neutrophils.

Pregnancy usually does not affect the course of CML, however CML in pregnancy may lead to increased risk of leukostasis and placental insufficiency resulting in intrauterine fetal growth restriction (IUGR), prematurity and increased fetal mortality.

Therapeutic options for CML include cytotoxic drugs like imatinib, hydroxyurea, busulfan and interferons, leukapheresis and stem cell transplantation. Imatinib, a newer category D drug is a tyrosine kinase inhibitor (TKI) which can prolong CP of CML thereby improving the quality of life, short of curative option of stem cell transplantation. TKI in pregnancy have shown fetal abnormalities recently despite contradicting anecdotal reports of favourable outcomes in the past [6–8]. Though there is enough information on the use of TKI in pregnant females with CML, surprisingly there is little information on the effects of CML per se on the pregnancy and on the complications encountered both in baby/mother secondary to CML. We present four cases (five pregnancies) with obstetric complications in patients with CML (Tables 1, 2). Antepartum (APH) and postpartum haemorrhages (PPH) have rarely been reported in CML.

Case 1

A 22 years old unsupervised second gravida with one previous abortion, presented with premature rupture of membranes (PROM) with *abruptio placentae* in early labour at 33 + 3 weeks period of gestation (POG). Examination was consistent with obstetric history but splenomegaly (10 cm below left subcostal margin) was incidentally revealed. Complete blood count revealed hemoglobin—11 g/dl, leucocytosis with shift to left (leukocyte count—354,000/μL differential: Myelocyte 30 %, Metamyelocyte 20 % and blast cells 4 %) and platelet count of 440,000/μL. She was taken for emergency caesarean section in view of abruption and a live born neonate weighing 2.1 kg with an apgar score of 8, 9 was delivered. Retroplacental clots of 200 g were removed. On second postoperative day a swelling and blood stained discharge from the stitched incision was observed, confirmed on ultrasound examination to be *bilateral rectus sheath hematoma.*

Treatment for CML in the form of hydroxyurea 500 mg and allopurinol 100 mg thrice daily was started. A bone marrow aspiration and trephine biopsy revealed hypercellularity with 3 % blasts and granulocytic and megakaryocytic hyperplasia suggestive of MPN. RT-PCR from peripheral blood was positive for *BCR-ABL gene*. By day 11 of hydroxyurea, her WBC count dropped to 12,000/μL and abdominal wound healed well with secondary intention. She was discharged on imatinib 400 mg once daily with instructions to avoid breast feeding, however, was lost to follow up.

After 14 months, she again, presented as unsupervised twin pregnancy of 27 weeks POG and a similar *abruptio placentae*. She confessed to have taken imatinib only for a week after discharge from the last hospitalization. However, she continued taking hydroxyurea on pretext of high leucocyte count thus presently being in CP of CML. She conceived while taking hydroxyurea and discontinued it only after 8 weeks POG. She had *preterm vaginal delivery* at 27 weeks and delivered two live born male babies with apgar scores 8, 9 who died due to prematurity at 12 and 14 days of age respectively despite intensive care. She was restarted on imatinib 400 mg once a day after 10 days and was counseled regarding the need for treatment compliance and strict contraception. She achieved complete haematological remission (CHR) on imatinib at 8 weeks and 1 year follow up.

Table 1 Obstetric details of the patients with CML

Characteristic	Case 1 1st pregnancy	Case 1 2nd pregnancy	Case 2	Case 3	Case 4
Gestation at admission Weeks (POG)	33 + 3	27	37	34	14 + 5
Presenting complaint	PROM with abruptio	Abruptio placenta	IUGR, oligohydramnios	IUGR (Intrauterine growth retardation)	Threatened abortion
Parity	G2P0010	G3P0111	Primigravida	Primigravida	Primigravida
Antenatal or postpartum complications	Abruptio placenta, rectus sheath hematoma	Abruptio placenta	Postpartum haemorrhage	Preterm labour	Threatened abortion with intra uterine foetal death
POG at delivery/ abortion (weeks)	Preterm delivery: (33 + 3)	Preterm delivery: (27)	Delivery: (37)	Preterm delivery: (34)	MTP: (15 + 2) (Medical termination of pregnancy)
Baby outcome	Discharged	Both babies died (prematurity)	Discharged	Discharged	Abortus

Table 2 Haematological details of the patients with CML

Characteristic	Case 1 1st pregnancy	Case 1 2nd pregnancy	Case 2	Case 3	Case 4
Time of diagnosis	At time of delivery	Previous pregnancy	At time of delivery	At time of delivery	Pre-pregnancy 7 months back
Haemoglobin (gm/dL)	11	10.2	8	9.2	7.5
TLC (/μL)	354,000	169,000	140,000	64,000	147,000
Platelets (/μL)	440,000	382,000	400,000	540,000	630,000
Drugs for CML at time of conception	None	Hydroxyurea till 8 weeks	None	None	Imatinib since 6 weeks pregnancy
Phase of CML	CP (chronic phase)	AP (accelerated phase)	CP	CP	CP
Splenomegaly	10 cm	8 cm	12	+	13
Drugs for CML Postpartum/postabortal	Hydroxyurea	Imatinib	Hydroxyurea then imatinib	Hydroxyurea	Imatinib

Case 2

A 25 years old unsupervised primigravida presented in spontaneous labour at 37 + 1 weeks POG, with *IUGR and oligohydroamnios*. Examination was consistent with obstetric history with a moderate splenomegaly. Her hemoglobin was 8 g/dl, TLC of 140,000/μL with shift to left and platelet count of 400,000/μL. She delivered live born, 2.25 kg neonate with good apgar scores and no malformations. She had PPH with diffuse multiple bleeding points in vagina. Multiple haemostatic sutures were applied despite which the bleeding persisted. Haemostatic vaginal packing was done and 4 units of packed red blood cells were transfused. Bone marrow aspiration and biopsy was morphologically suggestive of CML. Hydroxyurea 500 mg thrice daily was started. BCR-ABL positivity was revealed by RT-PCR and she was shifted to imatinib 400 mg/day therapy with advice to stop breast feeding. She is under regular follow up and presently in CHR at 10 months of follow up.

Case 3

A 24 years old primigravida presented with *preterm labour* at 34 weeks POG. She had bilateral cervical lymphadenopathy and massive hepatosplenomegaly. Complete blood count revealed leukocyte count of 64,000/μL with 20 % myelocytes and 4 % peripheral blasts. Keeping in view, a non-reassuring cardiotocography of the fetus an artificial rupture of membranes was done. Liquor was meconium stained and a live male baby weighing 2.24 kg with Apgar score of 8, 9 was delivered vaginally. Cervical lymph node biopsy revealed infiltration by CML without any blasts infiltration. Bone marrow examination revealed features suggestive of CML in CP which was confirmed by bone marrow cytogenetics (Philadelphia positivity). She was started on imatinib 400 mg OD and is presently in CHR at 1 year of follow up.

Case 4

A 20 years old primigravida with unsupervised twin pregnancy, presented with threatened abortion at 14 + 5 weeks POG. She was diagnosed 7 months back with CML and was given imatinib which she discontinued after 1 month. She restarted imatinib at 6 weeks POG. On admission, her leucocyte count was 147,200/μL with 13 % myelocytes, 5 % metamyelocytes and 2 % blast cells. On ultrasonography, one fetus had intra uterine death (IUD) and other was alive with approximate 14 weeks POG.

As the risk of fetal malformations with imatinib intake was explained to the patient, she decided to undergo medical termination of pregnancy. She received mifepristone 200 mg followed 36 h later by 400 μg misoprostol vaginally and expelled two fetuses weighing 100 and 200 g each within 6 h. Her post-abortal period was uneventful and continued on imatinib 400 mg daily. She is currently in CHR and on imatinib therapy at 1 year of follow up.

Discussion

CML during pregnancy poses a unique clinical challenge for short and long-term concerns of maternal and fetal health. Diagnosis during pregnancy is usually delayed as early symptoms of CML are nonspecific [3]. Choice of treatment is influenced by the time of diagnosis, clinical stage of the

disease and the toxic effects of chemotherapeutic agents on mother and child [4].

The present patients showed occurrence of hemorrhagic complications, with the first patient presenting with APH in both pregnancies and second patient with postpartum hemorrhage. Harita et al. reported a case of abruptio placentae with hepatosplenomegaly when she was incidentally diagnosed to have CML [9]. In a study by Wang DP, two of seven patients who reached third trimester had postpartum haemorrhage [10]. Bleeding manifestations de novo in CML are not infrequent. Patients presenting with hemorrhagic manifestations (cerebellar hemorrhages, minor hemorrhages in right lower frontal area/anterior thalamus) as primary complaints were reported in literature [11]. This manifestation is more common during blast crisis, though none of our cases with hemorrhagic complications were in blast crisis phase [11]. Vignal et al. demonstrated higher incidence of bleeding and thrombosis in patients with CML secondary to prolonged BT, but no associated abnormality in platelet aggregation abnormalities [12]. In a study on etiology of death in CML patients, amongst 109 patients the commonest cause in the accelerated phase were due to infection or hemorrhage, whereas in patients with blast crisis they were mainly due to infection (54 of the 94 cases), followed by hemorrhage and leukostasis. This study emphasizes the relevance of hemorrhage in CML cases [13]. The pathophysiology of bleeding manifestations in CML patients though debated, have been variably reported to be secondary to thrombocytopenia, impaired platelet function and low intraplatelet concentrations of beta TG and PF4 [14, 15]. Though not extensively evaluated, any of the above mentioned patho-physiologies can explain the APH/PPH in these patients.

IUGR was also observed in present case series. CML leads to increased risk of leukostasis and placental insufficiency resulting in intrauterine growth retardation, prematurity and hence increased fetal morbidity and mortality [16, 17]. IUGR amongst our cases can be secondary to materno-placental insufficiency due to thrombotic complications. Thrombotic complications in CML can be secondary to increase of whole blood viscosity, plasma viscosity, ESR, fibrinogen elevation [18].

Oligohydroamnios is commonly reported in leukaemia secondary to multi-agent therapy [19]. Oligohydroamnios is also classically described with paclitaxel or ranstuzumab therapy. Placental causes in CML may be due to placental thrombosis or infarction due to leukostasis. Fetal causes may be chromosomal and congenital abnormalities. Oligohydroamnios in one of our patients was multifactorial possibly due to uteroplacental insufficiency, leukostasis, thrombotic complications and fetal factors.

The role of TKI in pregnancy has been riddled with controversies due to potential fetal malformations [6–8]. Apperly suggested interruption of TKI 7–10 days after ovulation and absolutely no TKI therapy between 5–13 weeks, or 31–71 days after last menstrual cycle during period of organogenesis. He also suggested strict monitoring of molecular status and to restart therapy in case of loss of remission status. During the post-partum period breast feeding can be considered during the first 2–5 days to give the child colostrum; if in CHR to consider continuing breast feeding depending on PCR results and finally to restart treatment with the TKI used before [20, 21].

A close interaction between hematologist, obstetrician and the neonatologist is essential to successfully manage CML in pregnancy. The patient should be informed of the available therapeutic options to treat CML in pregnancy and the potential maternal and fetal risks involved as imatinib is potentially teratogenic in pregnancy. Although termination may be considered in early pregnancy, there is not much evidence that it improves maternal prognosis. CML itself appears to have an antecedent risk of low birth weight, preterm labour, and ante and postpartum hemorrhage in pregnancy. CML may be a rare cause for APH and PPH whenever other known etiology is not obvious, as observed in these patients. Preconceptional counseling about conception in remission phase of CML, and effect of disease on pregnancy needs to be emphasized for planning further pregnancies.

Conflict of Interest We declare that there is no conflict of interest.

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