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CASE REPORT

Leukemia in pregnancy

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Abstract: Pregnancy complicated with leukemia is rare. Validated data, out of which conclusions may be drawn regarding the management of pregnancy with leukemia are sparse. We report 5 cases of leukemia diagnosed during pregnancy with an overview of published literature *(Ref. 19).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: leukemia, pregnancy, chemotherapy.

The incidence of leukemia in pregnancy is low. The relatively small number of women in this situation makes it difficult to produce absolutely reliable statistics. Although the short-term risks for children exposed in utero to cytotoxic agents are predictable, there is little information on long-term complications. We report herein our experience in the treatment of five cases of acute leukemia diagnosed during pregnancy.

Case reports

A 36-year-old woman, gravida 2, para 1, presented at 28 weeks of gestation with a 2-month history of palpitation, breathlessness, vertigo, and headache. On examination: marked pallor, mild hepatosplenomegaly. On investigation: WBC 10.39x10^9/l, Hb 46 g/l, platelets 12x10^9/l, blasts 39 %. Bone marrow (BM) cytology, cytogenetic and immunophenotyping study confirmed the diagnosis of AML FAB M2 (intermediate risk). Ultrasonography revealed a single live fetus; liquor was adequate. The patient received blood and platelets transfusion. After two weeks, due to progression of the disease, caesarian section was performed at 30 weeks with viable healthy male baby (wt. 1700 g). Cord blood examination was without malignant cells. On the 4th postpartum day, induction chemotherapy (CHT) was delivered. Post induction CHT was complicated by prolonged vaginal bleeding (treated with platelets transfusion), febrile neutropenia (treated with antimicrobial drugs). Breast feeding was withheld during chemotherapy. Result of induction CHT was complete remission (CR) with full hematological recovery. To maintain remission consolidation, CHT was given. Planned allogeneic stem cell transplantation (SCT) from HLA-matched sibling was not performed due to relapse of AML 2 months after the start of consolidation (16 % blasts in BM). Re-induction CHT was given without the achievement of remission, she died shortly due to sepsis. The baby was followed up with no features of malignancy.

A 26-year-old female, gravida 2, para 0, abortion 1, presented at 8 weeks of pregnancy with features of anaemia (shortness of breath on exertion, palpitation, pre-collapse state), bone pain (hip & thoracic spine), cough. On examination mild splenomegaly. On investigation: WBC 98.40x10^9/I, Hb 133 g/l, platelets 75x10^9/l, blasts 80 %. BM examination (cytology, cytogenetic and immunophenotyping) confirmed the diagnosis of T-ALL. Treated with prednisolon 60 mg/m^2/day (within 3 days decrease in WBC to 8x10^9/l). She wished to terminate the pregnancy. After the stabilization of her condition, abortion was done without complications. Induction CHT was given with the achievement of CR. To maintain remission further consolidation CHT was given, followed by HLA-matched unrelated donor allogeneic SCT. 76 days after SCT she presented with focal epilepsy, CT brain was negative; immunophenotyping examination of cerebrospinal fluid (CSF) confirmed central nervous system (CNS) relapse, BM was in CR, chimerism was of donor type. She was treated with intrathecal CHT, systemic CHT and CNS radiotherapy. CSF became without malignant cells but with high protein contents. Therefore MRI of brain was done with a feature of multiple metastases. She died 129 days after SCT due to sepsis and multiorgan failure.

A 20-year-old female, gravida 1, para 0, at 4.5 months of pregnancy accidentally during routine visit found to have leukocytosis and hepatosplenomegaly. WBC 132.1x10^9/I, Hb 10.8 g/l, platelets 623x10^9/I, MCV 76.8 fl., neutrophils 42 %, metamyelocyte 12 %, myelocyte 18 %, lymphocyte 2 %, blast 0 %. BM examination revealed hypercelullar BM with increased granulopoiesis, 1.3 % blasts. Cytogenetic study (46,XY, t(9;22)(q34;q11), bcr/abl positive), confirmed the diagnosis of chronic phase CML. Treated initially with leukapheresis (only once), later alpha Interferon was given for 4 months without complications, repeated fetal monitoring revealed a single live fetus with mild

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growth retardation. Liquor was adequate. She delivered vaginally a normal full term female infant weighing 2.05 kg. No congenital anomaly was identified. Allogeneic SCT from HLA-matched sibling was performed, but she died 18 days after SCT because of veno-occlusive disease of liver and sepsis. Long-term follow up of the baby did not show any significant disease.

A 24-year-old healthy asymptomatic woman, gravida 1, para 0, was seen in her 4th month of pregnancy for routine laboratory evaluation and was noted to have leukocytosis (WBC $110x10^9/l$). Her physical examination showed an enlarged and palpable spleen measuring 5 cm under the left costal margin. Bone marrow aspiration showed hypercelullar BM with increased granulopoiesis, with only 0.9 % blast cells. Cytogenetic (46, XY,t(9;22) (q34;q11)), FISH and molecular study (bcr/abl positive) confirmed the diagnosis of chronic CML. The patient wished to continue with her pregnancy, she was treated with leukapheresis (a total of 15 leukapheresis), until her delivery at 36 weeks of gestation. The procedure was without significant adverse effects on the patient or fetus. She had a normal vaginal delivery of a healthy female infant. After delivery she received Interferon alpha for 15 months with no remission so treated with Hydroxyurea for 8 months followed by autologus SCT with the achievement of complete hematological recovery. Molecular relapse treated with Imatinib (Glivec) for 61 months, with initial successful molecular response (decrease in bcr/abl), and complete hematological response. Imatinib resistance necessitated an increased dose of Imatinib, and later a treatment with Dasatinib. Long-term follow up of the child revealed normal life.

A 44-year-old healthy female, gravida 3, para 2, presented at 33 weeks of pregnancy with gradually increasing weakness and breathlessness. On examination, marked pallor was noted with pulse 100/min. No leg edema was noted. A soft systolic murmur was present over the precordium. On abdominal examination, the fundal height corresponded to 33 weeks of gestation with fetus in cephalic presentation. No hepatosplenomegaly was present. On investigation WBC $1.09x10^9/l$, Hb 88 g/l, platelets $60x10^9/l$, MCV96.3 fl., neutrophils 26 %, blast 0 %. Bone marrow examination revealed 17 % blast cells. Cytogenetic and immunophenotyping were normal. The diagnosis was settled as MDS/RAEBt. She was treated with supportive therapy until the delivery of a full term healthy male baby. Due to progression of the disease to AML (after 6 months BM blast 33 %), induction CHT was given followed by HLA-matched related allogeneic SCT in first remission. 180 days after SCT she developed relapse in BM and she died shortly. The baby's growth was normal, with nomalignant disease.

Discussion

The occurrence of leukemia during pregnancy is very rare, with an estimated incidence of one in 75,000 to 100,000 pregnancies annually (1). It has been estimated that during pregnancy most leukemias are acute: two thirds are acute myeloid leukemia (AML) and one third are acute lymphoblastic leukemia (ALL). Chronic myeloid leukemia (CML) is found in less than 10 % of leukemias during pregnancy and chronic lymphocytic leukemia (CLL) is extremely rare (1).

Diagnosis during pregnancy is made most frequently in the second and third trimester although the disease may have been present earlier. This is because the early symptoms are nonspecific. This emphasizes the importance of carrying out proper investigations including bone marrow examination for unexplained anemia in pregnancy.

Leukemia in pregnancy offers a unique management dilemma and should be managed jointly between the haematologist and the obstetrician with full involvement of the mother. Pregnancy itself does not seem to affect the prognosis of the disease (2, 3). Acute leukemia (AL) is invariably fatal and without aggressive treatment with cytotoxic drugs, the disease is characterized by rapid deterioration and death within weeks of diagnosis. AL can affect pregnancy and the fetus, clinical problems result from the disease process itself and its treatment. Intrauterine growth retardation, pre-term labor, and spontaneous abortions, as well as, stillbirths are common in AL without treatment. Fetal loss occurs in approximately 33 % of women with AL (3). With supportive therapy alone, 20 to 30 % of women did not survive the gestation period and fetal mortality was 50 % (4). With combination CHT, most mothers survive through the delivery with concomitant improvement in fetal survival. Thus pregnant leukemic women should be treated as non-pregnant women with aggressive CHT until the remission is achieved. The risk of malformation in first trimester is as high as 17 % especially with folate antagonists (5). Therapeutic abortion should be considered in early gestation, but if the woman decides to continue her pregnancy, CHT should be started and certain drugs, like methotrexate, should be replaced. Delay in maternal treatment is associated with an adverse outcome (Kawamura et al, 1994, Greenlund et al, 6). However, Patients who are well, with stable disease may choose to defer CHT and be supported with growth factors and blood products up to the delivery of a viable infant that can be safely induced at about 30 weeks (19). Standard antileukemic treatment can be safely administered during the second and third trimesters (3, 5, 6, 7) if appropriate monitoring and obstetric care are available. Delivery should be accomplished when fetal survival can be ensured and the mother is in complete remission. CHT given close to delivery may result in significant fetal pancytopenia requiring intensive haematological support (Murray et al, 1994; Reynoso et al, 1997). The termination of pregnancy when therapy is started in the second or third trimester has to be carried out on moral and medico-social grounds, as the fetus is likely to develop normally (7). Toronto Leukemia Study Group showed an increased risk of premature delivery as well as small for date babies in series of 53 women who received CHT during their pregnancies, long-term follow-up of these babies has shown normal growth and development and no further malignancies (8). Hansen et al observed transient oligohydraminos during the treatment with multiagent CHT (7); no other side effects were noted. They conclude that fetal concerns should not delay therapy.

Chronic myeloid leukemia during pregnancy is usually managed conservatively because the disease has an initial chronic phase that may not require immediate therapy, and pregnancy does not appear to affect the course of CML, however there is still a risk of leukostasis and placental insufficiency with consequent low birth weight, fetal prematurity, and increased mortality if CML is left untreated for the duration of pregnancy (9–15). A more aggressive approach, such as bone marrow transplantation, may be considered after delivery. There is limited information regarding the successful management of CML during pregnancy; most of this information is derived from case reports using leukapheresis (9, 10) hydroxyurea (11–13) and interferon (13–15). Leukapheresis can be considered for treatment of CML as early as in the first trimester of pregnancy and then it can be successfully continued throughout the pregnancy. Because of the lack of teratogenic and other adverse effects, it may be the optimal treatment for pregnant patients with CML who tolerate and respond to the procedure. Hydroxyurea inhibits DNA synthesis and therefore can potentially cause abortion, intrauterine growth retardation and congenital malformations. However, neither teratogenic effects nor hematological consequences to the fetus have been reported with hydroxyurea treatment (11–13). Alpha Interferon has been used for the treatment of CML with variable success (13–15). Laboratory evidence suggests that it crosses the placental barrier and increases the incidence of abortion in rhesus monkeys (14). There are no reports about its adverse effects on pregnancy and the developing fetus in humans, but there are reports of normal infants delivered following treatment with alpha-interferon during pregnancy (13). However, alpha-interferon therapy may decrease fertility due to decreases in serum estradiol and progesterone levels (14). Imatinib mesylate (STI571, Gleevec, Glivec; Novartis, Basel, Switzerland), a bcr-abl tyrosine kinase inhibitor, is now a standard therapy for patients with CML, with dramatic hematological and cytogenetic responses. Imatinib has a teratogenic potential in animals, but the effect of exposure to imatinib during conception and pregnancy in humans is not known. There is no data concerned with continued imatinib therapy during pregnancy (16), however, a record of 18 patients who conceived while receiving imatinib for the treatment of CML in the university of Texas showed that there is no evidence that a brief exposure to imatinib during conception and pregnancy adversely affects the developing fetus, most patients lose their response after treatment interruption. Patients receiving imatinib should be advised to practice adequate contraception (17).

Pregnancy complicated by hairy cell leukemia is extremely rare (18). Treatment is usually conservative. Spleenectomy is a safe and effective treatment option during the second trimester for this rare condition (18). Single cases have been treated with interferon during pregnancy (15).

Conclusion

Acute leukemia during pregnancy should be treated as in non pregnant women as soon as possible. Chronic leukemia can be treated conservatively until the normal delivery of the fetus. Leukapheresis is safe in CML if well tolerated. There is no evidence that pregnancy can accelerate the progression of the disease or affect the outcome.

Reference

1. Lichtman M, Liesveld J. Acute myelogenous leukemia. 1047—1084. In: Beutler E, Lichtman M, Coller B et al (Eds). Williams Hematology (ed 6). New York, NY, McGraw-Hill 2001.

2. Zuazu J, Julia A, Sierra J et al. Pregnancy outcome in hematologic malignancies. Cancer 1991; 67: 703—709.

3. Mclain CR. Leukemia in pregnancy. Clin Obstet Gynec 1974; 17: 185—94.

4. Dhubashini, Raghuram G. Pregnancy complicated by malignancy. 255—259. In: Krishna U, Daftary S (Eds). Pregnancy at risk: Current concepts. New Delhi, FOGSI Publication. Jaypee Brothers 1997. 5. Brell J, Kalajcio M. Leukemia in Pregnancy. Semin Oncol 2000; 27: 667—77.

6. Greenland LJ, Letendre L, Tefeeri A. Acute leukemia during pregnancy: a single institutional experience with 17 cases. Leuk Lymphoma 2001; 41: 571—576.

7. Hansen WF, Fritz P, Hunter SK et al. Leukemia in pregnancy and fetal response to multiagent chemotharapy. Obstet Gynecol 2001; 97: 809—812.

8. Reynoso, FA Shepherd, HA Messner et al, the Toronto Leukemia Study Group experience with long-term follow-up of children exposed in utero to chemotherapeutic agents Acute leukemia during pregnancy. J Clin Oncol 1987; 51: 1098—1106.

9. Bazarbashi MS, Smith MR, Karanes C et al. Successful management of Ph chromosome chronic myelogenous leukemia with leukapheresis during pregnancy. Amer J Hematol 1991; 38: 235—237. 10. Strobl FJ, Voelkerding KV, Smith EP. Management of chronic myeloid leukemia during pregnancy with leukapheresis. J Clin Apher 1999; 14: 42—44.

11. Celiloglu M, Altunyurt S, Undar B. Hydroxyurea treatment for chronic myeloid leukemia during pregnancy. Acta Obstet Gynecol Scand 2000; 79: 803—804.

12. Patel M, Dukes IA, Hull JC. Use of hydroxyurea in chronic myeloid leukemia during pregnancy: A case report. Amer J Obstet Gynecol 1991; 165: 565—566.

13. Baykal C, Zengin N, Coskun F et al. Use of hydroxyurea and alpha-interferon in chronic myeloid leukemia during pregnancy: A case report. Europ J Gynaecol Oncol 2000; 21: 89—90.

14. Reichel RP, Linkesch W, Schetitska D. Therapy with recombinant interferon alpha-2c during unexpected pregnancy in a patient with chronic myeloid leukaemia. Brit J Haematol 1992; 82: 472—478.

15. Baer MR, Ozer H, Foon KA. Interferon-alpha therapy during pregnancy in chronic myelogenous leukaemia and hairy cell leukaemia. Brit J Haematol 1992; 81: 167—169.

16. Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility and pregnancy. Semin Hematol 2003; 40: 21—25.

17. Ault P, Kantarjian H, O'Brien S et al. Pregnancy Among Patients With Chronic Myeloid Leukemia Treated With Imatinib. J Clin Oncol 2006; 24: 1204—1208.

18. Managing hairy cell leukemia in pregnancy. Ann Intern Med 1994; 120 (12): 1048—1049. 19. Milligan DW, Grimwade D, Cullis JO et al. Guidelines on the management of acute myeloid leukaemia in adults. British Committee for Standards in Haematology (BCSH) April 2005.

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