Normal pregnancy outcome in a woman with chronic myeloid leukemia and epilepsy: a case report and review of the literature

Abstract

**Introduction:** The management of chronic myeloid leukemia (CML) during pregnancy is a matter of continued debate. Imatinib therapy for CML might be associated with fetal anomalies and discontinuation of the drug with disease progression. We present the achievement and management of a pregnancy in a woman with both CML and epilepsy. We describe the first uneventful pregnancy and successful delivery of a healthy, normal baby in a patient with CML and epilepsy.

**Case report:** A 25-year-old woman with both CML and epilepsy presented with infertility to our in vitro fertilization unit. She has CML diagnosed 5 years ago and epilepsy 9 years ago. She was on imatinib therapy for CML and valproic acid therapy for epilepsy. She became pregnant with ovulation monitoring in a spontaneous cycle. Because the patient was asymptomatic and stable, she stopped imatinib therapy and was observed with only a single antiepileptic drug, valproic acid, during the entire pregnancy. No problem occurred during the pregnancy, and she delivered a healthy baby by cesarean section at 38 weeks' gestation.

**Conclusion:** The management of CML during pregnancy might be individualized on the basis of clinical manifestations, and close observation without any intervention may be an option after proper counseling of the patient. A healthy birth is possible in a well-controlled pregnancy in a woman with both CML and epilepsy.

**Keywords:** Chronic myeloid leukemia; epilepsy; pregnancy.

Introduction

The management of malignant diseases during pregnancy remains a considerable clinical challenge. Chronic myeloid leukemia (CML) constitutes 90% of chronic leukemias and 10% of all leukemias identified during pregnancy, with an incidence of 1 in 750,000 pregnancies [3]. Although CML might be left untreated during the pregnancy, as pregnancy does not appear to affect the course of CML, there are risks of leukostasis and placental insufficiency [16].

Imatinib, a tyrosine kinase inhibitor, is the first example of a molecularly targeted therapy and the first-line treatment for CML [14]. It is well tolerated by patients, with few side effects and could prolong the chronic phase of CML to 12–15 years [14]. However, imatinib is teratogenic in rats and the data for the human fetus are limited [16]. Therefore, some authors recommend discontinuation of imatinib therapy when the patient becomes pregnant [9, 16]. However, whether imatinib therapy may be discontinued safely in patients with complete remission remains an important question. Discontinuation of imatinib therapy in CML patients with remission >2 years resulted with 50% relapse [15].

Epilepsy is the most common serious neurological disorder, and many women with epilepsy are in their active reproductive years. Women with epilepsy who are planning to have a baby should be counseled about the worsening of seizures, feto-maternal complications, abnormal delivery, and fetal malformations. There is a 2- to 3-fold increase in the major congenital malformation rate in babies of women with epilepsy treated with antiepileptic drugs (AEDs) during pregnancy [12, 17]. However, most women with epilepsy will have a normal pregnancy and a favorable outcome. Effective control of maternal seizures with the least risk to the fetus is the goal during pregnancy.

We described the first successful pregnancy and healthy birth of a normal baby in a woman with CML and epilepsy. We further summarized the related literature.
Case

A 25-year-old woman presented with secondary infertility of 1-year duration to our in vitro fertilization unit. She had three biochemical abortions in the previous 4 years with no dilatation and curettage. In her medical history, she had epilepsy diagnosed at 16 years of age. She was on AED therapy and used valproic acid (VPA). She had CML diagnosed 5 years ago and was on therapy with imatinib.

She was evaluated for secondary infertility, and no pathology was found. Ovulation monitoring in a spontaneous cycle was initiated, and she achieved pregnancy at the second cycle. Upon the positive pregnancy test result, imatinib was stopped by her hematology doctor as she was asymptomatic. The patient’s white blood cell count was $6.5 \times 10^3/\mu L$ (neutrophil 52%, lymphocyte 36%, monocyte 10%, basocyte 0.7%), hemoglobin 11.8 g/dL, and platelet count $225 \times 10^3/\mu L$ at the beginning of the pregnancy. Her hematological controls were normal, and she required no therapy for the rest of her pregnancy. Her neurology doctor advised her to continue VPA monotherapy at a 250 mg daily dose during her pregnancy. She had an uneventful pregnancy and delivered by cesarean section at 38 weeks’ gestation without any complication. A 2900 g, healthy baby boy with Apgar scores of 9 and 10 at 1 and 5 min, respectively, was delivered. No anomaly was observed and the infant’s complete blood count was also normal. Imatinib was resumed 12 weeks after delivery. Four and a half months after the delivery, both the mother and the baby are in good health.

Discussion

The present case illustrates an epileptic CML patient who successfully gave birth to a healthy, normal baby without any obstetric complications. This case is unique in that a woman with both CML and epilepsy, who used imatinib initially and AED during the entire pregnancy, had an uneventful pregnancy and eventually gave birth to a healthy, normal baby.

The management of CML in pregnant women is a challenging problem for both the physician and the patient. Treatment options mentioned in the literature are imatinib, interferon-α, hydroxyurea, and leukopheresis [5, 14]. Imatinib is the most commonly used drug for CML. However, its safety during pregnancy has not been clearly ascertained, as there are animal studies that suggested an embryotoxic effect [14]. The major concern is whether to use this drug, which carries the risk of serious fetal abnormalities or spontaneous abortion, or to stop the medication and have a risk of relapse [14]. There are several case reports of successful pregnancies and deliveries without any complication or congenital anomaly (Table 1). In some of those cases, imatinib was stopped upon a positive

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Jiang et al., 2012 [10]</td>
<td>Imatinib use throughout pregnancy</td>
<td>Healthy neonates, no congenital defects</td>
<td>2</td>
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<tr>
<td>Martin et al., 2011 [11]</td>
<td>Imatinib use stopped by the 10th week of pregnancy</td>
<td>Healthy newborn</td>
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<td>Ali et al., 2009 [2]</td>
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<td>1</td>
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<td>Tsuzuki et al., 2009 [16]</td>
<td>Imatinib use during the first 5 weeks of pregnancy</td>
<td>No maternal or fetal adverse outcome</td>
<td>1</td>
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<tr>
<td>Pye et al., 2008 [14]</td>
<td>Imatinib use during the first and second trimesters</td>
<td>Mostly live birth without congenital anomaly, but bony abnormalities, meningocele, exomphalos, hypospadias, pyloric stenosis in some newborns</td>
<td>125</td>
</tr>
<tr>
<td>Garderet et al., 2007 [7]</td>
<td>Imatinib use during the first 4 weeks of pregnancy</td>
<td>No fetal abnormality</td>
<td>1</td>
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<tr>
<td>Ault et al., 2006 [4]</td>
<td>Imatinib use stopped on recognition of pregnancy</td>
<td>No fetal anomaly but disease relapse occurred</td>
<td>10</td>
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<tr>
<td>Choudhary et al., 2006 [6]</td>
<td>Imatinib use during the first 6 weeks of pregnancy</td>
<td>Hydroxyurea administered during the rest of pregnancy, fetal meningocele</td>
<td>1</td>
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<tr>
<td>Ali et al., 2005 [1]</td>
<td>Imatinib use during the first 8 weeks of pregnancy</td>
<td>Disease relapse at the 7th month of pregnancy, healthy infant delivery</td>
<td>1</td>
</tr>
<tr>
<td>Prabhash et al., 2005 [13]</td>
<td>Imatinib use continued throughout the pregnancy</td>
<td>Healthy newborn</td>
<td>2</td>
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</table>

Table 1  Pregnancy and neonatal outcome in women with CML who conceived while on imatinib treatment.
pregnancy test; however, in some others, imatinib therapy was continued throughout the pregnancy (Table 1) [1, 2, 4, 6–8, 10, 11, 13]. However, it was reported that pyloric stenosis, hypoplasias, or meningocele were detected in children born to mothers with CML who even stopped imatinib after the recognition of pregnancy [6, 14]. Pye et al. [14] reported one of the biggest series of 180 women who were exposed to imatinib during pregnancy. Outcome data were available in 125 of them and in those women, 50% of pregnancies resulted in a normal outcome and a healthy infant. Fetal abnormalities were observed in 12 infants (9.6%), such as deformities of skull bones, exomphalos, renal agenesis, meningocele, cardiac defects, hypoplastic lungs, hypoplasia, pyloric stenosis, and scoliosis. Our patient used imatinib for the previous 5 years until the positive pregnancy test result. After patient counseling, imatinib was stopped upon the diagnosis of pregnancy and no medication was required during the rest of her pregnancy. No fetal congenital malformation was noted.

The management of epilepsy during pregnancy aims to balance the maternal and fetal risks associated with uncontrolled seizures against the potential teratogenic effects of AEDs. Exposure to AEDs in utero has been associated with an increased risk of major congenital malformations, fetal growth retardation, and impaired postnatal cognitive development [12, 17]. In contrast, epilepsy history without AED use did not seem to increase the risk [17]. Monotherapy with the most commonly used AEDs is associated with an increase in the risk of major congenital anomalies by two to three times, and the risk further increases in offspring exposed to polytherapy [12]. The most notable drug-specific increased risks were observed for VPA in relation to NTD, oral clefts, heart defects, and hypoplasias [17]. Almost all studies have suggested that exposure to VPA is associated with a greater incidence of anomalies than with other AEDs [12]. However, the increase in risk is dose dependent and especially evident at doses above 800–1000 mg/day. Individualization of the drug therapy, optimization of the dose, and periconceptional folic acid supplementation are important measures to reduce the potential risk to the fetus. In the present case, the neurologist recommended to continue VPA monotherapy at the least therapeutic dose, 250 mg daily. She had an uneventful pregnancy and delivered a healthy, normal baby by cesarean section at 38 weeks’ gestation without any obstetric or fetal complications.

To our knowledge, this is the first report of a pregnant woman who had both CML and epilepsy. The presence of both of those two significant diseases in a pregnant woman is associated with a higher probability of congenital anomaly. However, management of epilepsy with monotherapy at the least possible dose and no exacerbation of CML during pregnancy would most probably result in a healthy birth. Although risk and benefit evaluation must be carried out on an individual basis as regards the management of chronic diseases during pregnancy, healthy births are likely with a meticulous follow-up.

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References


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