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# The Effect of Imatinib on the Fetus Growth and Development of a Pregnant Woman Involved with CML, a Case Report and a Literature Review

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## Abstract

Chronic Myeloid leukemia (CML) is a chronic myeloproliferative leukemia which may involve the women during their fertile period of life. Despite the standard therapy for CML is targeted therapy with tyrosine kinase inhibitor, most authorities recommend to withdraw the treatment with the maternal pregnancy. In this case report, we present a known case of CML who was under standard treatment with Imatinib and Hydroxyurea for 5 years and continued her therapy despite her unplanned pregnancy till 2 weeks before her baby's delivery. She delivered a full term low birth weight male after 40 weeks and 3.5 days of her last menstrual period. His physical examination has shown that he was a healthy male without any congenital anomaly.

**Keywords:** Pregnancy; Imatinib; Chronic Myeloid Leukemia; Thyrosine kinase Inhibitor

## Introduction

Chronic myeloid leukemia (CML) is an uncommon type of cancer of the bone marrow characterized by Philadelphia chromosome which is a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11).

Because this translocation results in the BCR-ABL fusion gene that encodes a protein with tyrosine kinase activity, the standard therapy for CML is targeted therapy with a Thyrosine kinase inhibitor (TKI) such as Imatinib. Lots of studies have shown that this group of drugs including Imatinib is potentially teratogenic in animal models [1-9]; Moreover, some reports have shown that consuming TKI during pregnancy of the mothers involved with CML resulted in emergence of congenital anomalies in the fetus [10,11]; therefore, it is currently recommended that these agents should be avoided during the pregnancy of the mothers with CML [11,12]. In this case report, we present a mother involved with CML for 5 years and she consumed Imatinib throughout her pregnancy.

## Case Presentation

A 28-year-old mother presented to the obstetric ward in labor for normal vaginal delivery. She was a known case of Chronic Myeloid leukemia (CML) since five years ago. She has consumed Imatinib 400 mg plus Hydroxyurea 500 mg daily since her CML diagnosis regularly and her disease was

under control and in chronic phase. She had an unplanned pregnancy under consuming Imatinib and Hydroxyurea; it was her second pregnancy. After the first trimester of the recent pregnancy, despite experiencing severe vomiting following taking Imatinib she continued the drug plus Hydroxyurea regularly for controlling her disease. Both of the drugs have withdrawn 2 weeks before her delivery by her physician order. Moreover, her drug history in the recent pregnancy included consuming Ferrus sulfate (60 mg elemental Iron), Vitamin D (1000 IU) and Multivitamin once daily of each one as supplemental drugs since 12 weeks of her gestation irregularly. Furthermore, she had a regular prenatal care, without any positive history of gestational hypertension, diabetes, and preeclampsia as well as any history of abortion, stillbirth or any chronic diseases.

In her past history, she had a 5.5-year-old healthy live boy who delivered full term with the birth weight 3100 gram. Her last laboratory tests before the delivery included: CBC: WBC: 231000/ml, PMN: 50%, Band: 9%, Lymphocyte: 2%, Promyelocyte: 11%, Myelocyte: 12%, Metamyelocyte: 13%, Blast cell: 3%, RBC: 3.030,000 /mm, Hb: 7.7 g/dl, Hct: 22.5%, platelet: 267000/ml; MCV, MCH, MCHC, BUN, Cr, and uric acid: all in normal ranges. She has attended in labor after 40 weeks and 3.5 days of her last menstrual period. Her baby was a full term male with first minute Apgar score 9/10. His growth rate findings at birth included: birth weight: 2300 gram, length: 47 cm, head circumference: 32.5 cm, and chest circumference: 32 cm. In fact with regard to his gestational age, he was a low birth weight healthy newborn. In his physical examination, everything was normal and there was no congenital anomaly. The mother involved with bleeding following uterine atony after vaginal delivery and received 2 units of packed cell. Besides, the mother started Imatinib 400 mg and Hydroxyurea 500 mg daily 2 weeks after her baby delivery again for controlling the chronic phase of her CML. According to the manufacturer recommendations as the maternal breast milk was not advisable for the babies of the mothers with CML, breastfeeding of the infant discontinued and low birth weight specific formula has initiated for him after his birth.

The baby visited again at 1 month of age. His physical growth findings included: weight: 3400 gram, length: 50 cm, head circumference: 35 cm, chest circumference: 37 cm. In his physical examination, everything was normal. His physical growth findings at 2 months of age included: weight: 3800 gram, length: 52 cm, head circumference: 37 cm, chest circumference: 37.5 cm. In his physical examination, everything was normal. Besides, all his developmental milestones were normal.

## Discussion

This article introduces a mother involved with CML and consumed Imatinib regularly for 5 years before an unplanned pregnancy; she continued Imatinib during the pregnancy and delivered a full- term low birth weight healthy male baby without any congenital anomaly. A few points are worthwhile in this case. First of all, the mother has consumed Imatinib regularly for five years before her pregnancy. Moreover, she continued Imatinib regularly throughout her pregnancy until 2 weeks before her baby's delivery. She could deliver a full term low birth weight healthy male baby without any congenital anomaly. To our knowledge just 2 articles reported consuming Imatinib by a pregnant mother with CML throughout the pregnancy (Table 1): one of them mentioned delivery of a preterm (gestational age: 32 weeks) healthy baby without any congenital anomaly; in this case the mother has consumed Imatinib for 8 months before her pregnancy Mashhadi MA [13]; the other one mentioned delivery of a preterm (gestational age about 28 weeks) healthy baby without any congenital anomaly; in this case the mother has consumed Imatinib for about 5.5 years before her pregnancy Webb MJ, et al. [14] It sounds that our case is the third healthy one that the mother with CML had consumed Imatinib throughout the pregnancy. The previous 2 babies delivered preterm and low birth weight; however, our case was full term and low birth weight (Table 1).

| Author(year) | Preterm | Outcome Low Birth Weight | Full Term |
|---|---|---|---|
| Mashhadi [13] | * | * | |
| Webb [14] | * | * | |
| Present case | | * | * |

**Table 1:** The different outcomes of the pregnant mothers with CML consuming Imatinib throughout pregnancy by literature review.

Despite, there are a number of case series in the literature which reported some of their CML cases consumed Imatinib throughout their pregnancies and resulted in delivery of healthy babies, the data about the history of consuming Imatinib by the mother, the time of initiating and ending of Imatinib during their pregnancy, the gestational age and birth weight of the babies were not available in the articles [15-24], therefore, we didn't able to use these data separately in our report. It is interesting

that the baby in this case report didn't have any congenital anomaly and after two months of his delivery has had a normal growth, development and physical examination, with regard to 5 years of regularly consuming Imatinib by the mother before her unplanned pregnancy and continuing Imatinib throughout the pregnancy until 2 weeks before her baby delivery. Reviewing the literature has revealed that some adverse reactions have occurred as the outcomes of the pregnancy following consuming Imatinib during the pregnancy of the mothers with CML which include spontaneous abortion, elective abortion, stillbirth [12], congenital anomalies, prematurity or low birth weight (Table 2).

| Author (Year) | Article Type | Imatinib Exposure During Pregnancy by Trimester | | | | Neonatal Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 1st & 2nd | 2nd & 3rd | 1st & 2nd & 3rd | Spontaneous Abortion | Congenital Anomaly | Preterm | Full Term and Healthy Baby |
| Ridvan [25] | #1 | * | | | | | | | * |
| Ault [15] | ##2 | * | | | | * | * | | * |
| Choudhary [12] | # | * | | | | | * | * | |
| Garderet [26] | # | * | | | | | | | * |
| Pye [16] | ## | * | * | | * | * | * | * | * |
| Skaumaloval (2008) | # | | * | | | | | | * |
| Buyukbayrak [27] | # | | | * | | | | | * |
| Skoumalova [28] | # | | * | | | | | | * |
| Mashhadi [13] | ## | | | | * | | | * | * |
| Tsuzuki [29] | # | * | | | | | | * | |
| Martin [30] | # | * | | | | | | * | |
| Webb [14] | # | | | | * | | * | * | |
| Jiang [22] | ## | | | | * | | * | * | |
| Sahin [31] | # | * | | | | | | | * |
| Shankar [32] | ## | * | | | | * | | | |
| Li [17] | ## | | | | * | * | | | * |
| Yadav [33] | # | | | | * | | | * | |
| Iqbal [19] | ## | * | | | | | * | | * |
| Jain [11] | # | | | | * | | * | * | |
| Mukhopadhyay [18] | ## | * | | | | * | * | | |
| Alizadeh [34] | # | | | | * | | | | * |
| Sheng [35] | # | | * | | | | | | * |
| Singhal [36] | # | | * | | | | | | * |
| Modi [23] | ## | * | | | * | * | * | * | * |
| Dou [37] | ## | * | | | | * | | | * |
| Madabhavi [20] | ## | | | | * | * | * | * | * |
| Moura [38] | ## | * | | | | | | * | |
| Kartanjian (2021) | ## | * | | | | * | * | * | * |
| Abruzzese [2] | # | * | | | | | | | * |
| Bhattacharjee [24] | ## | * | | | * | * | | * | * |
| Chethan (2023) | ## | * | | | | * | * | | * |
| This case | # | | | | * | | | | * |

**Table 2:** Distribution of the neonatal outcomes in the pregnant mothers with CML who exposed to Imatinib by trimester in the literature review.
#: Case Report, ##: Case Series

Moreover, lots of different kinds of congenital anomalies reported so far at the result of consuming Imatinib by the pregnant mother with CML such as meningocele, craniosynostosis, hypoplastic lungs, exomphalos, duplex left kidney, absent right kidney, a right shoulder anomaly, right renal agenesis, overriding aorta, ascites, pericardial effusion, communicating hydrocephalus, cerebellar hypoplasia, atrial septal defect, pyloric stenosis, microtia of the right ear, preauricular tag on the left side, absence of right depressor angular oris muscle, imperforate anus, rotation of small intestine, mild hydrocephalus, omphalocele, complex malformations, micro-ophthalmia, minor cardiac malformation, dextrocardia, hemivertebrae in the thoracic region, cervical spina bifida occulta, clinodactyly and low-set ears [11-15,17,20-22,25,26] (Table 2). Despite emergence of different types of congenital anomalies in the babies of the mothers with CML, they might not be just the direct result of consuming Imatinib by the mother, because of a few reasons as follow: First of all, some of the pregnant mothers might lose their complete remission following interruption of Imatinib before their planned pregnancy or with pregnancy diagnosis [15,23,24,27-29]; therefore, the adverse outcomes of the pregnancies could be the result of the CML itself, not consuming Imatinib. Furthermore, it is noteworthy that all the babies of the pregnant mothers who consumed Imatinib haven't shown the same outcome; moreover, all the pregnant mothers with the same outcome have not consumed Imatinib for the same time or duration during their pregnancy; besides, some pregnant mothers who consumed Imatinib at least before the maternal pregnancy's diagnosis, had uneventful pregnancies with healthy full-term babies [15-24]. Although teratogenicity of the Imatinib has approved in animal models and consuming of the drug by some pregnant mothers resulted in emergence of different kinds of congenital anomalies, some the colleagues reported that consuming of the drug by the pregnant mother for limited duration or until the diagnosis of the pregnancy could result in healthy full term [26-35] or low birth weight [12,13,37,38] baby without any congenital anomalies. All of the above remarkable points make inferring or generalizing the etiology of the adverse outcomes in the babies following consuming Imatinib by the pregnant mothers more complicated.

## Conclusion

Therefore, it seems that the pregnancy outcomes in the babies of the mothers with CML who consumed Imatinib during their pregnancies, are very controversial and needs to be studied more in-detail not only in animal models, but also in human's babies as prospective cohorts or randomized clinical trials for obtaining reliable results with regard to Imatinib effects on the growth and development of the fetuses or the babies of these mothers. Besides, filing the data of the mothers before her planned or unplanned pregnancy including the details of consuming Imatinib, its doses and duration as well as her disease trend and its response to treatment during their productivity period of life is very important for obtaining ultimate conclusions with regard to Imatinib effects.

## Patient Consent for Publication

Written informed consent for publication of the case report and any accompanying images, without any potential identifying information, was provided by the parents of the patient.

## Conflicts of Interest

The author declares no conflict of interest.

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