

Chemotherapy Can Interfere in Implantation in *In-vitro* Fertilization

Manish Banker, Parul Arora, Jwal Banker¹, Sandeep Shah

Department of Reproductive Medicine, Nova IVF Fertility, Ahmedabad, Gujarat, India,
¹Department of Reproductive Medicine, IVI RMA, Madrid, Spain

ABSTRACT

Improvement in cancer treatments has allowed more women to plan a pregnancy once the disease is cured. The effects of chemotherapy on ovaries are well proven but those on the uterus, especially the endometrium and embryo implantation are still unknown. Usage of newer tyrosine kinase inhibitors such as nilotinib has revolutionized the management of leukemias. Although nilotinib has been reported to be safe in pregnancy, further studies are needed to evaluate its effect on the process of embryo implantation, especially in women undergoing *in-vitro* fertilization. We report a case where successful pregnancy outcome was achieved after stoppage of nilotinib before embryo transfer in a woman who had previous four failed attempts while on nilotinib and no other obvious cause of implantation failure. Despite optimal endometrial thickness and receptivity, the pale appearance of endometrium on hysteroscopy was attributed to be a possible effect of nilotinib and prompted us to withhold it.

KEYWORDS: Chemotherapy, implantation, *in-vitro* fertilization, nilotinib, receptivity

INTRODUCTION

With advancements in oncological therapy, more women in the reproductive age group desire pregnancy after remission. Tyrosine kinase inhibitors (TKIs) like Imatinib have been successfully used in the control of leukocytic leukemias for the past two decades.^[1] Second-generation drugs such as nilotinib have recently and safely been used in pregnancy.^[2,3] With more patients being successfully cured with these “safer” TKIs, there is a need to study their effects on the endometrium and their safety on the embryo, and their usage during *in vitro* fertilization (IVF).

We present here a case report of a woman with acute lymphoblastic leukemia who underwent IVF with donor oocytes after chemotherapy. After four failed embryo transfers while on nilotinib, she underwent a transfer after the stoppage of the drug which successfully led to live birth.

CASE REPORT

Mrs. S was diagnosed with ALL in 2011 with Philadelphia chromosome-positive status. She received

Phase-1 induction-chemotherapy as per the BFM-95 protocol for standard-risk ALL. This was followed by Phase-2 induction-chemotherapy consisting of cyclophosphamide, cytarabine, methotrexate, and mercaptopurine and Consolidation phase chemotherapy with high-dose methotrexate and mercaptopurine. Thereafter, she received ten cycles of the central nervous system irradiation and twenty-seven cycles of vincristine and weekly methotrexate. She was then put on tablet nilotinib 600 mg which was tapered to 450 mg for maintenance therapy.

After her disease remission, her menstrual cycles remained regular. She got married in 2017 at 30 years of age and underwent two unsuccessful IUI cycles for infertility. In view of the history of her disease, chemo-radiation, and the associated poor ovarian reserve (AMH 0.5 ng/ml and Antral Follicular Count of 6), she opted for ovum donation. In the first cycle, she underwent two frozen embryo transfers (FET) of two

Address for correspondence: Dr. Parul Arora,
NOVA IVF Fertility, 108, Swastik Society, Navarangpura,
Ahmedabad - 380 006, Gujarat, India.
E-mail: drparul20arora@gmail.com

Received: 18-04-2020

Revised: 03-07-2020

Accepted: 30-12-2020

Published: 30-03-2021

Access this article online

Quick Response Code:



Website:
www.jhrsonline.org

DOI:
10.4103/jhrs.JHRS_69_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Banker M, Arora P, Banker J, Shah S. Chemotherapy can interfere in implantation in *in-vitro* fertilization. J Hum Reprod Sci 2021;14:94-6.

blastocysts each and both the transfers were negative. The endometrium preparation was done with 4 mg of estradiol valerate for 4 days and 8 mg thereafter. In each cycle, the endometrium was about 8 mm with a trilaminar appearance.

She was advised Endometrial Receptivity Analysis (ERA) as two embryo-transfers with good grade blastocysts failed to result in pregnancy. ERA was suggestive of a receptive endometrium at 5 days of progesterone supplementation. She underwent another IVF cycle with embryos created out of a different ovum donor and the third transfer (as per ERA) was also negative. Since she still had four blastocysts cryopreserved from this attempt, she was advised hysteroscopy to rule out undiagnosed endometrial factor before planning a FET. Hysteroscopy revealed her endometrium to be pale and yellowish, but the cavity was normal with no adhesions. Following this, she underwent one more FET using 8 mg estradiol valerate from the start and two blastocysts were transferred, again failing to result in pregnancy. After the failure of four embryo-transfers (two blastocysts each time), a receptive ERA with a pale endometrium on hysteroscopy, the patient was advised to stop her chemotherapy (Nilotinib) for 3 months after appropriate counseling and in consultation with her treating oncologist. She underwent a FET of the past two cryopreserved embryos using the same protocol after stopping nilotinib and this time she had a beta-human chorionic gonadotropin value of 2113 IU/ml. Nilotinib was restarted at 14 weeks of pregnancy as per the oncologist's advice. She carried a singleton pregnancy and developed mild preeclampsia at 36 weeks and was delivered by cesarean-section at 37 weeks of gestation giving birth to a healthy child weighing 2.4 kg. The neonatal and postpartum period was uneventful and both the mother and the child are doing well at 6 months of life.

DISCUSSION

Fertility can be impaired in women with leukemias due to the disease itself and as a consequence of chemotherapy. While the gonadotoxicity of chemotherapeutic drugs is proven; their effect on the endometrium and on the embryo-implantation still needs further exploration. This assumes importance in IVF practice where the majority of the women with controlled disease are planning an embryo transfer while still continuing the maintenance chemotherapy. The key question always remains: whether to stay on these medications, which have possible pregnancy risks or stop the medications for the purpose of pregnancy and risk disease-relapse. The lack of well-controlled studies of TKIs for such

women makes it difficult to counsel patients regarding the correct approach.

Studies have revealed contradictory evidences on the continuation of TKIs in the periconceptional period; some reporting that they can be safely stopped in those with major molecular remission^[4,5] while others have observed no significant effects on pregnancy even on continuation.^[6,7] Although numbers are small, there have been few congenital malformations linked with imatinib for it to be safely recommended.^[6,8] Current recommendations advise women who wish to conceive to discontinue imatinib during conception and pregnancy.^[5,9] However, in cases where alternative therapy or stopping therapy are not acceptable alternatives, second-generation TKIs such as nilotinib have been safely used during pregnancy.^[2,3,5]

The area which is still unexplored is the effect of these drugs on the endometrium and the implantation process. Studies in pregnant rats and rabbits showed maternal and embryo-fetal toxicity and lethality at exposures to nilotinib comparable to human exposure.^[8] Increased postimplantation loss and embryo toxicity were observed in other animal studies, but the extrapolation of such results in humans needs to be validated. Recent studies have also reported potential long-term effects on placentation and embryo survival by studying changes in placental epigenetic markers in the mouse model.^[10]

This case report assumes importance in view of the possible undocumented effect of nilotinib on the endometrium. In this index case, after the failure of three transfers with six good-grade blastocysts from different fertile oocyte donors in a receptive endometrium having trilaminar echogenicity and optimal thickness, we started to identify the cause of recurrent implantation failure. We performed a hysteroscopy, which revealed a pale endometrium [Figure 1]. The next embryo-transfer planned with a higher dose of estradiol valerate for endometrial preparation still ended being negative. As a last resort, we decided to stop the chemotherapy (Nilotinib) after oncologist's consultation. The last embryo-transfer was planned after 3 months of the stoppage of chemotherapy and resulted in a pregnancy. Nilotinib was restarted at 14 weeks, considering the little passage in the fetal compartment

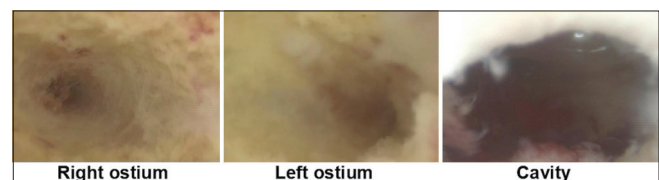


Figure 1: Hysteroscopy images depicting the pale endometrial cavity

after the blood-placental barrier is established and the completion of organogenesis.^[11]

This case report suggests a possible effect of nilotinib on the endometrium which hinders implantation of good grade blastocysts in a receptive endometrium or a postimplantation embryo-toxic effect. The stoppage of nilotinib for a brief period after disease-control and success after four failed previous attempts might indicate the negative effects of the drug on endometrium, embryos, or their interaction. However, this needs to be validated by controlled studies before safely advocating it to all patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, *et al.* Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996;2:561-6.
2. Santorsola D, Abruzzese E. Successful management of pregnancy and hepatic toxicity in a CML female patient treated with nilotinib: a case report and a review. *Mediterranean journal of hematology and infectious diseases*. 2015;7(1); DOI: <http://dx.doi.org/10.4084/MJHID.2015.020>
3. Conchon M, Sanabani SS, Bendit I, Santos FM, Serpa M, Dorliac-Llacer PE. Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy: Case study. *J Hematol Oncol* 2009;2:42.
4. Mahon FX, Rea D, Guilhot F, Guilhot J, Huguot F, Nicolini F, *et al.* Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: The prospective, multicenter Stop Imatinib (STIM) trial. *Lancet Oncol* 2010;11:1029-35.
5. Lasica M, Willcox A, Burbury K, Ross DM, Branford S, Butler J, *et al.* The effect of tyrosine kinase inhibitor interruption and interferon use on pregnancy outcomes and long-term disease control in chronic myeloid leukemia. *Leuk Lymphoma* 2019;60:1796-802.
6. Pye SM, Cortes J, Ault P, Hatfield A, Hagop K, Pilot R, *et al.* The effects of imatinib on pregnancy outcome. *Blood* 2008;111:5505-8.
7. Cole S, Kantarjian H, Ault P, Cortés JE. Successful completion of pregnancy in a patient with chronic myeloid leukemia without active intervention: A case report and review of the literature. *Clin Lymphoma Myeloma* 2009;9:324-7.
8. Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. *Mediterranean Journal of Hematology and Infectious Diseases*. 2014;6(1)., DOI: <http://dx.doi.org/10.4084/MJHID.2014.028>
9. Abruzzese E, Trawinska MM, de Fabritiis P, Baccarani M. Management of pregnant chronic myeloid leukemia patients. *Expert Rev Hematol* 2016;9:781-91.
10. Salem W, Li K, Krapp C, Ingles SA, Bartolomei MS, Chung K, *et al.* Imatinib treatments have long-term impact on placentation and embryo survival. *Sci Rep* 2019;9:2535.
11. Webb MJ, Jafta D. Imatinib use in pregnancy. *Turk J Haematol* 2012;29:405-8.