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Case Report

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Pregnancy a short time after multimodal therapy for bilateral breast cancer: A case report and review of literature

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Abstract
Pregnancy occurring after multimodal therapy in a woman with breast cancer with a 1-year follow-up period is a relatively rare condition and has been defined as pregnancy-associated breast cancer. A patient can become pregnant after chemotherapy for breast cancer while she is on tamoxifen. However, the effects of tamoxifen on fetus and on the course of the pregnancy are still unknown. Here, we present a 39-year-old woman treated with chemotherapy and radiotherapy for bilateral breast cancer, and who became pregnant while taking tamoxifen.

Keywords
Bilateral breast cancer, adjuvant therapy, pregnancy, tamoxifen

Case

In January 2003, a 33-year-old woman with synchronous bilateral breast carcinoma was referred to our Radiation Oncology Clinic for adjuvant treatment. The patient had three children before the breast cancer diagnosis. Her age at the first pregnancy was 26. No family history was detected for breast cancer. A bilateral modified radical mastectomy was performed. A tumor of the left breast was at upper medial quadrant and a tumor of the right breast was at the lower medial quadrant. Tumor dimensions on macroscopic examination were $5 \times 3 \times 2\,cm^3$ for the left breast and $4 \times 3 \times 1.5\,cm^3$ for the right breast. Histopathological findings for the left breast specimen revealed the following features: invasive ductal carcinoma, histologic grade II (modified Scarf Bloom Richardson), nuclear grade II (modified Black), no necrosis, minimal elastosis, positive lymphatic and positive vascular invasion, peritumoral lymphocytic invasion positive, extensive intraductal component positive, and focal microcalcification. Axillary nodal sampling dissection showed seven positive lymph node invasions and none of them had an extracapsular invasion.

Histopathological findings for the right breast specimen were as follows: invasive ductal carcinoma with

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lobular focuses, histological grade II, nuclear grade I, necrosis positive, minimal elastosis. Axillary nodal sampling dissection showed four lymph node invasions with no capsular invasions.

Estrogen and progesterone receptors were three and four positive for the left breast, at levels two and three positive for right breast, respectively. The C-erb-B2 status was evaluated by fluorescence *in situ* hybridization (FISH) and immunohistochemistry and was determined to be negative for both breast specimens. Genetic testing for BRCA-1 and -2 was negative. The patient received six cycles of FEC chemotherapy (fluorouracil 500 mg/m^2; day 1, epirubicin 75 mg/m^2; day 1, cyclophosphamide 500 mg/m^2; day 1, every 21 days for six cycles). After the last cycle of chemotherapy, she was given 50 Gy radiotherapy to each chest wall with conventional fractionation from tangential fields. Each of the supraclavicular, axillary, and internal mammary lymph nodes was given 50 Gy radiotherapy from both sites. After the radiotherapy, the patient started to use 20 mg daily tamoxifen therapy and luteinizing hormone-releasing hormone (LHRH) agonist goserelin. Four weeks after the last radiotherapy course, she was referred to our clinic because of pregnancy while the daily tamoxifen treatment was still continuing. The patient was from a rural area and the pregnancy was newly diagnosed by a local obstetrician.

According to the date of the last menstrual period, the patient was at the fourth gestational week. She was informed of the possible risks for the embryo induced by the chemotherapy, radiation therapy, and hormonal therapy. The patient refused a therapeutic abortion, but the administration of tamoxifen was interrupted. The time interval between the start of pregnancy and the last radiotherapy course was 1 month and, the time interval between the start of pregnancy and the last chemotherapy course was 2 months. Clinical and laboratory evaluations and ultrasonographic examinations (USG) were normal during monthly follow-ups for 8 months, from gestational 4th week to the 39th week and delivery. The photograph taken at the 27th of gestation is shown in Figure 1. USG findings at the gestational age of 27th week were as follows: polyhydramniosis, amniotic liquid index 240 cm, biparietal dimension 68 mm, femur length 49 mm, anteroposterior abdominal diameter 60 mm, lateral abdominal diameter 71 mm. The placenta was in an anterior location with grade 1 maturation. The patient was only suffering from mild abdominal distention and mild emesis. No congenital anomaly was detected with USG in any trimester.

The patient delivered a healthy female baby with Caesarean section in 39th gestational week. The birth weight of the newborn girl was 3.150 kg, and her clinical and laboratory evaluations were normal. No minor or major congenital malformations were detected in the physical examination at the pediatric clinic. We used newborn formulas for feeding. Both baby and mother were referred for psychiatric counseling. The baby is now healthy in her 66th month.



Figure 1. Figure of the pregnant woman with bilateral breast cancer.

The menopausal hormonal status of the patient was checked and because she was still premenopausal, tamoxifen and LHRH agonist (goserelin) therapy were prescribed 3 months after delivery. She used LHRH agonist therapy for 2 years and interrupted tamoxifen after 5 years. There is no recurrence or metastasis in the 7th year after the diagnosis.

Discussion

Breast cancer is the most common malignancy affecting women in reproductive age.[1] Due to the trend to delay childbirth for different reasons (educational, professional, and personal) and the rising incidence of breast cancer with age, increasing numbers of women find themselves with the dilemma to deal with a potentially fatal condition and the desire to have children. Pregnancy occurring after breast cancer is an important problem in young and especially nulliparous patients. Review of the literature shows that patients with breast cancer who subsequently become pregnant have good survival rates, which are the same or sometimes better than those of patients with no subsequent pregnancy.[2,3]

Both chemotherapy and tamoxifen can affect ovarian function. Specific chemotherapy regimens for treating breast cancer may cause predictable rates of ovarian failure. Because of inhibition of gonadal

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function by chemotherapy, pregnancy is a relatively rare condition in breast cancer patients treated with curative intent. However, the frequency of amenorrhea related to a given agent or regimen depends on the age of the patient and the cumulative exposure to the agent(s).[4,5]

Tamoxifen was originally developed as a contraceptive agent that prevents the implantation of the blastocyst into the uterus.[6] Contrary to its expected contraceptive properties, tamoxifen has also been found to induce ovulation.[7] Tamoxifen is contraindicated during pregnancy and the use of nonhormonal contraception is recommended during tamoxifen treatment and for 2 months thereafter, due to the extended half-life of tamoxifen and one of its metabolites.[8–10] Pregnancy is possible in patients on tamoxifen. There are few data available on the effects of tamoxifen on human fetal development or pregnancy outcomes. However, in rodent laboratory models, neonatal tamoxifen exposure has shown an increase in the incidence of abnormalities of the genital tract.[11] Tamoxifen produces similar teratogenic properties to diethylstilbestrol.[12]

It is difficult to predict the individual risk for the development of abnormalities in the newborn when the mother has been treated with cytotoxic drugs before or during pregnancy. There are few reports for children whose mothers received cytotoxic drugs and radiation therapy for breast cancer during their fetal periods. In these reports, congenital malformations and low birth weight were major problems. But minor congenital abnormalities can also be detected in newborns considered as a normal delivery.[13] There have been six case reports with detailed information about tamoxifen use during the pregnancy.[14–18] Of these six cases, where tamoxifen had been used at conception and during the first trimester of pregnancy or longer, four women delivered healthy babies. One child was born with abnormalities of the genital tract suggestive of a tamoxifen effect on the fetus.[14] In another case, the fetus was exposed to a number of other potentially toxic agents as well as tamoxifen (cocaine and marijuana use and a bone scan) and was born with a congenital craniofacial defect.[15] In summary, there is only one case report confirming animal studies which show genital tract abnormalities in female fetuses exposed to tamoxifen.[14]

Von Schoultz et al. have suggested that women taking tamoxifen who wish to become pregnant should stop tamoxifen at least 2 months prior to conception because of the drug's long half-life. Better survival rates were reported in cancers with positive estrogen receptors. However, this finding is probably related to the mere fact that women with positive receptors have better survival rates overall.[19]

The appropriate time for pregnancy in patients who have received cancer therapy is still not known. But it has been recommended that, pregnancy must be delayed for 2 years in patients who have received cytotoxic therapy for breast cancer.[20] There are some important reasons for delaying pregnancy after breast cancer therapy: first, recurrences are seen most commonly in the 2-year follow-up period; second, second-line therapies for recurrences during the pregnancy can complicate the pregnancy; third, Survivors of an initial breast cancer are at significantly increased risk of developing a second breast primary.[21] Further, pregnancy can complicate detection of contralateral breast cancers. However, in bilateral breast cancer patients these problems are duplicated. Because of the worse prognosis, recurrences and metastasis can develop earlier and more rapidly in simultaneous bilateral breast cancer. The prognosis may be worse in patients with bilateral simultaneous breast carcinoma than those who have nonsimultaneous cancers.[22] Also, feeding of the newborn is a major problem in patients with bilateral mastectomies. Psychosocial effects on baby and mother must also be considered.

Because the animal studies and case reports have shown congenital abnormalities after tamoxifen exposure during pregnancy and because of the lack of long-term data on outcomes, it is prudent to stop tamoxifen before attempting pregnancy. Women who became pregnant unexpectedly while taking tamoxifen should be informed of the case reports of babies who were born with congenital abnormalities suggestive of tamoxifen effect on the fetus. They should also be made aware that no long-term data of children who were exposed to tamoxifen *in utero* are currently available. However, the majority of babies exposed to tamoxifen *in utero* have been normal and the pregnancy could continue if the parents are willing to accept these risks. In conclusion, here we would like to first highlight that the risk of getting pregnant after the first injection of LHRH analogs is still present, if the couple do not continue another safe contraceptive method at least 1 month after the LHRH injection. Additionally, although there are some potential side effects of *in utero* tamoxifen exposure, our case suggest that continuing pregnancy may be allowed in case of the parent's insistence.

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References

1. Adami HO, Malker B, Holmberg L, Persson I and Stone B. The relation between survival and age at diagnosis in breast cancer. *N Engl J Med* 1986; 315: 559–563.
2. Danforth Jr DN. How subsequent pregnancy affects outcome in women with a prior breast cancer. *Oncology* 1991; 11: 23–30.

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3. Petrek JA. Pregnancy safety after breast cancer. *Cancer* 1994; 74: 528–531.
4. Reichman BS and Gren KB. Breast cancer in young women: effect of chemotherapy on ovarian function, fertility, and birth defects. *J Natl Cancer Inst Monogr* 1994; 16: 125–129.
5. Hensley ML and Reichman BS. Fertility and pregnancy after adjuvant chemotherapy for breast cancer. *Crit Rev Oncol Hematol* 1998; 28: 121–128.
6. Harper MJK and Walpole AL. Contrasting endocrine activities of cis and trans isomers in a series of substituted triphenylethylenes. *Nature* 1966; 212(5057): 87.
7. Klopper A and Hall M. New synthetic agent for the induction of ovulation: preliminary trial in women. *BMJ* 1971; 2: 152–154.
8. *Physicians' Desk Reference Health*; Nolvadex, http://www.pdrhealth.com/drug_info (2003, accessed July 2004).
9. Mehta DK (ed.) *Pregnancy*. British National Formulary No. 45. London: British Medical Association and Royal Pharmaceutical Society, 2004, p.726 [Appendix 4].
10. Briggs GG, Freeman RK and Yaffe SJ. *Drugs in pregnancy and lactation*, 6th ed. Philadelphia: Williams & Wilkins, 2002, p.1307–1313.
11. Diwan BA, Anderson LM and Ward JM. Proliferative lesions of oviduct and uterus in CD-1 mice exposed prenatally to tamoxifen. *Carcinogenesis* 1997; 18(10): 2009–2014.
12. Cunha GR, Taguchi O, Namikawa R, Nishizuka Y and Robboy SJ. Teratogenic effects of tamoxifen on the developing human female genital tract. *Hum Pathol* 1987; 18: 1132–1143.
13. Ebert U, Löffler H and Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther* 1997; 74: 207–220.
14. Tewari K, Bonebrake RG, Asrat T and Shanberg AM. Ambiguous genitalia in infant exposed to tamoxifen in utero. *Lancet* 1997; 350(9072): 183.
15. Cullins SL, Pridjian G and Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994; 271(24): 1905–1906.
16. Öksüzoglu B and Güler N. An infertile patient with breast cancer who delivered a healthy child under adjuvant tamoxifen therapy. *Eur J Obstet Gynecol Reprod Biol* 2002; 104(1): 79.
17. Koizumi K and Aono T. Pregnancy after combined treatment with bromocriptine and tamoxifen in two patients with pituitary prolactinomas. *Fertil Steril* 1986; 46(2): 312–314.
18. Isaacs RJ, Hunter W and Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy-case report and literature review. *Gynecol Oncol* 2001; 80(3): 405–408.
19. Von Schoultz E, Johansson H, Wilking N and Rutqvist LE. Influence of prior and subsequent pregnancy on breast cancer prognosis. *J Clin Oncol* 1995; 13: 430–434.
20. Moore HC and Foster Jr RS. Breast cancer and pregnancy. *Semin Oncol* 2000; 27: 646–653.
21. Rutgers E, van Slooten E and Kluck H. Follow-up after treatment of primary breast cancer. *Br J Surg* 1989; 76: 187–190.
22. Gülay H, Hamaloglu E, Bulut O and Göksel HA. Bilateral breast carcinoma: 28 Years' Experience. *World J Surg* 1990; 14: 529–534.

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