Introduction
Breast cancer is the most common cancer type among women worldwide. It is treated by surgery, chemotherapy, radiation therapy or in combination of these modalities. For the adjuvant treatment, tamoxifen is used widely. Pregnancy can occur during tamoxifen treatment in the premenopausal patients. But, there is not sufficient data on the safety of tamoxifen during pregnancy. Here, we presented a case with usage of tamoxifen until the 16th week of pregnancy. The patient was followed and delivered at the 38th week of pregnancy. No fetal anomalies were observed in this case in the following three years. In the review of the literature addressing tamoxifen exposure during pregnancy, many studies are laboratory based and there are only a few reports about human pregnancy. Tamoxifen may be potentially teratogenic, but this effect has not been often observed in humans. So, exposure to tamoxifen during pregnancy may not have a serious effect on the fetus.

Keywords: tamoxifen, pregnancy, breast cancer

CASE REPORT

Exposure to Tamoxifen During Pregnancy

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Abstract
Breast cancer is the most frequent cancer type in women worldwide. It is treated by surgery, chemotherapy, radiation therapy or in combination of these modalities. For the adjuvant treatment, tamoxifen is used widely. Pregnancy can occur during tamoxifen treatment in the premenopausal patients. But, there is not sufficient data on the safety of tamoxifen during pregnancy. Here, we presented a case with usage of tamoxifen until the 16th week of pregnancy. The patient was followed and delivered at the 38th week of pregnancy. No fetal anomalies were observed in this case in the following three years. In the review of the literature addressing tamoxifen exposure during pregnancy, many studies are laboratory based and there are only a few reports about human pregnancy. Tamoxifen may be potentially teratogenic, but this effect has not been often observed in humans. So, exposure to tamoxifen during pregnancy may not have a serious effect on the fetus.

Keywords: tamoxifen, pregnancy, breast cancer

Özet
Gebelik Esnasında Tamoksifene Maruz Kalma

Anahtar sözcükler: tamoksifen, gebelik, meme kanseri

Introduction
Breast cancer is the most common cancer type among women worldwide. Approximately, 85% of breast cancer cases are seen after the age of 40, and 75% after 50, respectively. It is treated by surgery, radiation therapy, chemotherapy or in combination of these modalities. Afterwards, tamoxifen is used widely to reduce risk of recurrences and the incidence of contralateral breast cancer.

Tamoxifen is a non-steroidal drug and partly an estrogen receptor antagonist. It has antiestrogenic activity on the breast though expressing partial estrogenic activity on the endometrium. Also tamoxifen may stimulate ovulation and pregnancy can occur during the use of tamoxifen. But, there is no sufficient data about the safety of tamoxifen during pregnancy. In addition, long-term prognosis of the children exposed to tamoxifen during pregnancy is not known. So here, we present a case on the use of tamoxifen during pregnancy.

Case
A 41 year-old woman, gravida 4, parity 2, attended to Obstetrics and Gynecology Clinic due to 6 months of amenorrhea. During the vaginal and abdominal examination the uterus was detected to be in the 16th week of pregnancy. Fetal hard rate was revealed with Doppler foetoscope. In the past history, she was diagnosed with and treated for breast cancer (clear cell carcinomas, histological grade 2, nuclear grade 2, node negative) before 2 years. She had a modified radical mastectomy, axillary lymph node dissection and four

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courses of chemotherapy. Afterwards, tamoxifen was started. In the 15th months of tamoxifen usage, pregnancy was diagnosed and tamoxifen was stopped. A normal healthy baby was detected at the 17th week of pregnancy by ultrasound. After discussion with the patient, pregnancy was maintained by her decision. Amniocentesis was performed due to maternal age and anxiety. There were no structural and numerical abnormalities in the chromosomal analysis. The case was followed in the antenatal period without any problems and cesarean section was performed because of repeat cesarean section and maternal anxiety for uterine dehiscence at the 38th weeks of pregnancy according to grayscale ultrasound (Figure 1). A 3205 g healthy male baby was born without any anomalies. Placenta was sent to histopathological analysis and no metastases were found. The case and baby have been followed for 3 years without any recurrences or problems related to tamoxifen exposure. Tamoxifen was not used during lactation.

**Figure 1.** Fetal view at 29-30 weeks of gestation (Presentation: head, Placenta: posterior, Amniotic fluid: normal, BPD: 30w+2d, FL:29w+6d, FAC: 29w+4d).

**Discussion**

Breast cancer is a frequent cancer type in women in reproductive ages. The incidence of the disease increases with age. Today, active participation of women in business life leads to delay of pregnancies to the 4 and 5th decades of life. In addition, due to recent developments in obstetrics, pregnancy is possible in older ages with in vitro fertilization techniques. As a result, presenting with breast cancer before completing family planning, and/or becoming pregnant during cancer therapy is now more often than before.

Tamoxifen is a non-steroidal drug having estrogen receptor antagonist effect. At first, it was found as a contraceptive agent (5). The contraceptive effect of tamoxifen occurs with prevention of implantation of blastocyst in the endometrium (6). In spite of this contraceptive effect, it is known that tamoxifen can be used for ovulation induction (7). In the UK, tamoxifen has been licensed for infertility treatment. Also, it is stressed that tamoxifen induces endometrial hyperplasia and carcinoma (8). This effect is thought to arise from its resemblance of diethylstilbestrol (DES). For women who have used DES during pregnancy, it was found that there was a delay in the differentiation of the uterus into endometrial stroma and myometrial layers in their female fetuses (6). In these pregnant women, it was found that there were congenital anomalies of fallopian tubes (e.g. hyperplastic tube, disorganized tube) (6). Tamoxifen shows similar teratogenic effects as mentioned above for DES (9). But in this case, the fetus was male. There are six cases in the literature (10-14) concerning the use of tamoxifen during pregnancy. While four of these women gave birth with healthy babies, one baby had an anomaly of the genital path (10) and another baby had craniofascial defects which might also be attributable to other reasons such as use of potentially toxic agents (cocaine, marihuana and bone visualization) (10). Barthelmes and Gateley (5) reported that, considering the potential risks of tamoxifen, it was prudent to stop the use of the drug if there was a will for pregnancy. But, if there is engorgement (1). So, tamoxifen should not be used during lactation. Tamoxifen was not used during lactation in our case.

There is not sufficient data reported in the literature regarding the effects of tamoxifen during pregnancy. Many studies addressing tamoxifen exposure consist of laboratory experiments and have different results than in humans. Low birth weight was reported by Ketani and colleagues involving pregnant rats treated with tamoxifen (2). In another study reported by Yamasaki and colleagues, pregnant rats were treated with 0.12, 0.6 and 3 µg/kg/day tamoxifen (3). During the whole period of pregnancy, weight gain in pregnant rats was normal. In the rats given 0.12 and 0.6 µg/kg/day tamoxifen, anomalies and health problems were not observed. At the same time the reproductive functions of the young rats were also seen to be normal. On the other hand, for rats given 3 µg/kg/day tamoxifen, three of the pregnant rats died because of reasons considered to be arising from toxic effects of tamoxifen. Also, some young rats showed an increased incidence in low birth weights. In a study by Leena Hilakivi-Clarke et al. (4), it was reported that there were no anomalies in weight gain of the mother and young rats treated with tamoxifen, but a delay in the opening of the eyelids of the young, and also, less increase in the uterine weight with respect to the control group. In addition, the beginning of puberty of the litter was delayed in comparison with the litter of the control group.

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tamoxifen exposure during pregnancy, pregnancy can be allowed after all aspects of drug has been explained to the mother. Parents must be informed about all possible congenital defects related to tamoxifen, the mother must be told that the long term fetal effects of the drug is unknown.

Tamoxifen may act as a carcinogenic agent on the breast tissue. Hilakivi-Clarke et al. (4) reported that exposure to tamoxifen during pregnancy induced mammary tumorogenesis including less differentiated breast cancer in the female offspring. Tamoxifen acts as an estrogenic agent on the fetus contrary to the effects on adults. This may be responsible for the development of breast cancer. Yet, for the human, there is not enough data addressing the long term effect of tamoxifen on breast tumorogenesis.

In conclusion, pregnancy can be allowed during tamoxifen usage, but all possible effects of tamoxifen should be explained to the mother and pregnancy should be followed with respect to the data in the literature.

References