CASE REPORT

Exposure to Tamoxifen During Pregnancy

Tayup **ŞİMŞEK**, Barış **SEVER**

Department of Obstetrics and Gynecology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

Received 08 March 2008; received in revised form 11 August 2008; accepted 12 August 2008; published online 01 September 2008

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 premenoposal patients. But, there is not sufficient data on the safety of tamoxifen during pregnancy. So, 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 areonly a few reports about human pregnancy. Tamoxifen may be potentionally 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

Meme kanseri, kadınlarda en sık görülen kanser tipidir. Meme kanseri cerrahi, radyoterapi, kemoterapi veya bunların kombinasyonları ile tedavi edilir. Adjuvan tedavi için tamoksifen yaygın olarak kullanılır. Premenopozal dönemde tamoksifen kullanımı esnasında gebelik oluşabilir. Fakat gebelik esnasında tamoksifen kullanımının güvenilirliği ile ilgili yeterli bilgi yoktur. Biz burada gebeliğin 16. haftasına kadar tamoksifen kullanan olguyu sunduk. Hasta takip edildi ve 38. haftada doğurtuldu. Üç yıllık takip sonucunda fetal anomali izlenmedi. Gebelik esnasında tamoksifene maruz kalan hastalar ile ilgili literatür gözden geçirildiğinde birçok çalışma deneysel olup, insanlarda gebelik ile ilgili çok az yayın vardır. Tamoksifen potansiyel olarak teratojeniktir, fakat bu etki insanlarda sıklıkla gözlenmemektedir. Sonuç olarak gebelikte tamoksifene maruz kalınması fetüs üzerine ciddi etki yapmayabilir.

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

Corresponding Author: Dr. Tayup Şimşek
Gürsu Mah. 356 Sokak, 7 Likya Evleri, Antalya, Türkiye
Phone : +90 242 249 65 75
GSM : +90 542 432 75 13
E-mail : tsimsek@akdeniz.edu.tr

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.

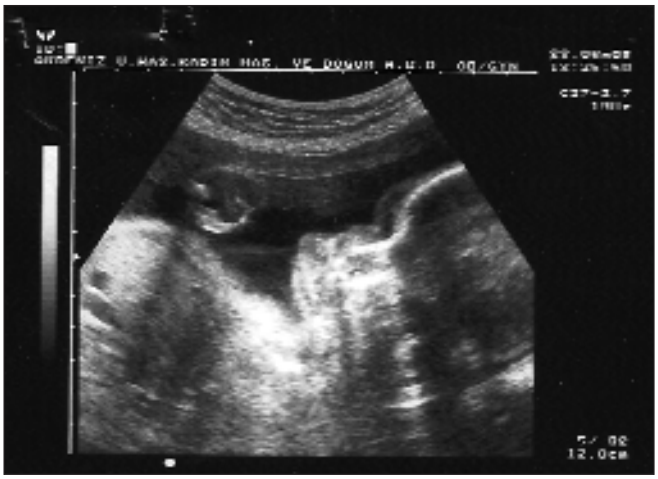

Figure 1. Fetal view at 29-30 weeks of gestation (Presentation: head, Placenta: posterior, Amniotic fluid: normal, BPD: 30w+2d, FL:29w+6d, FAC: 29w+4d).

Diccussion

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 estrogen receptor agonist-antagonist drug. It shows different effects on different tissues. While estrogenic (partial agonist) effect of tamoxifen is observed on the endometrium and bone, it is anti-estrogenic on the breast. This antiestrogenic effect of tamoxifen on the breast prevents milk secretion and breast 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.

Tamoxifen is a non-steroidal drug having estrogen receptor antagonistic 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

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

1. Shaaban MM. Supression of lactation by an antiestrogen, tamoxifen. Eur J Obstet Gynecol Reprod Biol 1975;4:167-9.
2. Ketani MA, Ketani S, Kaloğlu C, Güney B. Effects of tamoxifen administration in rat vaginas: an ultrastructural and light microscopy study. Eur J Gynaecol Oncol 2002;23(6):557-60.
3. Yamasaki K, Noda S, Muroi T et al. Effects of in utero and lactational exposure to tamoxifen in Sprague Dawley rats. Toxicology Letters 2005:156;289-96.
4. Hilakivi-Clarke L, Cho E, Onojafe I et al. Maternal exposure to tamoxifen during pregnancy increases carcinogen-induced mammary tumorigenesis among female rat offspring. Clinic Cancer Research 2000;6;305-8.
5. Barthelmes L, Gateley CA. Tamoxifen And Pregnancy. The Breast 2004:13;446-51.
6. Pugh DM, Sumano HS. The anti-implantation action of tamoxifen in mice; Arch Toxicol Suppl 1982;5(suppl.):209-13.
7. Klopper A, Hall M. New synthetic agent for the induction of ovulation. Preliminary trial in women. Br Med J 1971;2:152-4.
8. Jaiyesimi IA, Buzdar AU, Decker DA. Use of tamoxifen for breast cancer. J Clin Oncol 1995;13:513-29.
9. Cunha GR, Taguchi O, Namikawa R et al. Teratogenic effects of clomiphene tamoxifen and diethylstilbesterol on the developing human female genital tract. Hum Pathol 1987;18:1132-43.
10. Tewari K, Bonebrake RG, Asrat T, Shanberg AM. Ambiguous genitalia in infant exposed to tamoxifen inutero. Lancet 1997;350(9072):183.
11. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. J Am Med Assoc 1994;271(24):1905-6.
12. Öksüzoğlu B, 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.
13. Koizumi K, Aono T. Pregnancy after combined treatment with bromocriptine and tamoxifen in two patients with pituitary prolactinomas. Fertil Steril 1986;46(2):312-4.
14. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy–Case report and literature review. Gynecol Oncol 2001;80(3):405.