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BREAST CANCER TREATMENT AND LATER FERTILITY

LIJEČENJE RAKA DOJKE I KASNIJA PLODNOST

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Review

Key words: breast cancer, treatment, fertility, pregnancy

Summary. The article presents an overview regarding the influence of breast cancer treatment on later fertility. Although breast-conserving surgery is desirable in nulliparous women regarding later fertility, however because of a greater risk of local recurrence it is often accompanied by adjuvant therapy including chemotherapy, ovarian ablation, anti-estrogen therapy and combination of these. Although chemotherapy and radiotherapy have increased long-term survival of premenopausal women with breast cancer, sometimes the price paid is ovarian failure with subsequent amenorrhea and infertility. However, currently several fertility-sparing options including the use of endocrine therapy and assisted reproductive technologies, cryopreservation and ovarian tissue transplantation, are showing a very promising role. The offspring of patients who became pregnant after completion of chemotherapy have shown no adverse effects and congenital anomalies from the treatment, but sometimes high abortion (29%) and premature deliveries with low birth weight (40%) rates have been demonstrated. Therefore, the issue of recent cytotoxic treatment remains controversial and further researches are required to define a »safety period« between cessation of treatment and pregnancy.

Pregled

Ključne riječi: rak dojke, liječenje, plodnost, trudnoća

Sažetak. Rak dojke kao najčešći maligni tumor u žena nalazimo uglavnom u starijoj životnoj dobi, nakon menopauze, ali je u oko četvrtine svih slučajeva u žena mlađih od 50. godine. U razvijenim zemljama suvremenog svijeta zbog brojnih razloga opća je pojava kasnijeg sklapanja braka i rađanja, što je pridonijelo snižavanju nataliteta i relativno većem broju nulipara kasnije reprodukcijske dobi. S druge strane, viši životni standard i razvoj znanosti poboljšali su kvalitetu življenja koja uključuje i kvalitetniju zdravstvenu uslugu. Premda bi suvremena medicina trebala dovesti do zdravije populacije, ipak bolja dijagnostika i liječenje na sve brojnijoj populaciji žena poodmakle životne dobi koje još nisu rodile, omogućuje sve češće i ranije otkrivanje raka dojke žena kojima još predstoji rađanje. Stoga je za očekivati da ćemo se sve češće susretati s problemom kako će se liječenje novootkrivenog raka dojke u populaciji žena koje su odgodile rađanje, odraziti na kasniju fertilnost. Premda bi konzervativni kirurški zahvat kod ranog stadija raka dojke bio poželjan što se tiče rizičnosti i utjecaja na kasniju plodnost, nažalost zbog češće kasnije pojave lokalnih recidiva bolesti to nije konačno liječenje i zato je potrebna adjuvantna terapija. Nakon liječenja raka dojke zračenjem nisu opaženi nepovoljni učinci na kasniju plodnost, osim reducirane laktacije, a kod djece ni nakon nekoliko godina nisu uočene nikakve malformacije. Nakon primjene kemoterapije raka postiže se relativno povoljan terapijski učinak, no nažalost često se dugoročno javljaju nepoželjne ili toksične nuspojave te zbog oštećenja jajnika pojava amenoreje od 40% do 68%, uz druge simtome prijevremene menopauze. Oštećenje tkiva jajnika ovisno je od starosti bolesnice i veće je kod manje ovarijske pričuve, a ovisi još i o trajanju, dozi, vrsti liječenja te o drugim čimbenicima. Mehanizam nepovoljnog djelovanja na tkivo jajnika je uglavnom izazivanje apoptoze zrnatih stanica primordijalnih folikula, uz nepovratni gubitak svih folikula i jajnih stanica s posljedičnom fibrozom i atrofijom. Preporučeno prosječno vrijeme nezanošenja nakon kemoterapije je između dvije i pet godina; u to se vrijeme preporuča uporaba barijernih metoda kontracepcije. Da bi se izbjegli dugoročni nepovoljni učinci toksičnosti kemoterapije na plodnost u premenopauzalnih žena s rakom jajnika, koje bi htjele kasnije rađati, alternativno je indicirana primjena endokrinološke terapije (gonadotropni otpuštajući hormon i tamoksifen). Kako učinkovitost citostatične terapije povoljno djeluje na izlječenje, zbog čega preživljava sve više žena u premenopauzi s rakom dojke, sve je veća kasnije zainteresiranost tih bolesnica za trudnoćom. Kod takvih bolesnica suočenih s prijetećom prijevremenom menopauzom i željom za potomstvom, zahvaljujući znanstvenom i tehnološkom napretku, danas se primjenjuje više tehnološki asistiranih postupaka. U izboru je mogućnost liječenja kasnije plodnosti postupkom izvantjelesne oplodnje u prirodnom ili induciranom ciklusu (tamoksifen, letrozol, polovične doze folikularnog stimulirajućeg hormona), krioprezervacijom embrija ili ovarijskog tkiva s reimplantacijom.

Introduction

The appearance of breast cancer is in a constant increase as the most common female malignancy in many countries. In the United States there were 178 700 new cases of breast cancer in 1998 which increased to the number of 205 000 newly diagnosed cases in 2002; since 40 000 patients died in the same year, breast cancer was the second most common cause of cancer death in women.[1,2] The incidence of breast cancer increases progressively with the older age with a maximum in postmenopausal women. However, its occurrence in premenopausal women is relatively rare, because about 21.8% of all breast cancers are diagnosed in women under 50 years: 6.5% by the age of 40, 2.7% under 35 years, and only less than 1% of all breast cancers cases occur before the age of 30 years.[3,4] Similarly, in Croatia in women 25 to 44 years of the age the incidence of breast cancer in pre-

menopausal women is only 0.57/100 000, what means that it could be expected yearly about 4 cases of breast cancer during pregnancy and 4 cases of pregnacies after completed treatment of breast cancer.[5]

In modern countries of developed world an increasing trend toward delay in childbearing from 30 to 40 years of age for different reasons (educational, professional, personal, socioeconomic, and fertility problems) is concordant with the increasing incidence of breast cancer in women who have not yet completed their family.[2,6] An increased breast cancer risk with advancing maternal age at first childbirth is supported by 3.7 relative risk in women with an estimated first median age of 41 years, compared with those with an estimated first birth age of 23 years.[6] The USA National Center for Health Statistics notes that childbirth among women older than 30 years more than doubled between 1970 and 1986. Furthermore, the American women have postponed their first childbearing experience from the median age of 26.2 years in 1972 to the age of 29.1 in 2000.[6–8]

Because the incidence of premenopausal women with breast carcinoma delaying childbearing is increasing, they may have concerns regarding preservation of ovarian function due to advanced reproductive age and whether breast cancer treatment would interfere with the outcome of later fertility and pregnancy after breast carcinoma. The risk of infertility and of foregoing motherhood is a potential hardship to be faced by the patients following treatment of breast cancer.[4,9] Although the principles of managing breast carcinoma in young women are the same as that for older women, breast-conserving surgery is obviously desirable in young women. However, these patients have biologically more agressive disease with increase in the risk of local recurrence associated with conservative surgery.[10]

Current choice for premenopausal women is adjuvant therapy, that includes cytotoxic chemotherapy, ovarian ablation (by surgery, irradiation or chemical ovarian supression), anti-oestrogen therapy or any combination of these. Although, the use of adjuvant therapies with cytotoxic drugs can significantly reduce the mortality in the majority of young women with breast cancer, it raises issues of the long-term toxicity, such as induction of an early menopause and fertility impairment.[11–16]

This paper reviews the literature regarding the influence of breast carcinoma treatment on subsequent fertility, as well as current options available for fertility preservation.

Surgery and radiotherapy

The two principle considerations when deciding between breast-conserving surgery versus mastectomy are the cosmetic results and the risk of local recurrence. Although breast-conserving surgery is regarded desirable in young women, Arrigada et al.[10] have found that patients less than 40 years at the time of surgery had a 5-fold greater risk of local recurrence compared with older patients, but the effect of young age on the risk of local recurrence was not seen with mastectomy. Similarly, in an analysis of two large trials of mastectomy versus conservative surgery and radiotherapy, Voogd et al.[17] found that patients aged less than 35 years had a 9 times higher risk of local recurrence after conservative surgery than patients older than 60 years. The most important risk factors for local recurrence after breast conserving surgery are younger age (<35 years), infiltrating tumour with an extensive intraductal component, vascular invasion and microscopic involvement of excision margins.[10,17,18] Therefore, Consensus panels of the National Institutes of Health and St. Galen conference have recommended adjuvant therapy for all patients aged under 35 years, based on the evidence that they have poor prognosis.[19] However, the use of adjuvant therapies in young women raises issues of the long-term side effects, such as induction of an early menopause and fertility impairment.[4]

The effect of radiotherapy analysed in a study by Malamos et al.[11] showed no consequence of radiotherapy on the rate and clinical outcome of pregnancy, and at a mean follow-up of 18 months no anatomical defects were observed in the offspring. In one of the largest studies by Dow et al.[20] of 1624 patients providing information about the influence of radiotherapy on later fertility, there were 23 women who had subsequent pregnancies after the mean time of 30 months (range 6–84 months). Out of 23 women 22 deliveried normal full-term babies, and the remaining patient a low birth-weight infant, with no adverse clinical outcome on pregnancy subsequent to treatment. They reported only diminished lactation from the irradiated breast in those women who had had undergone radiotherapy following breast-conserving surgery, which had been presumbly due to atrophy of the breast lobules. Similar problem with lactation were noticed in a series of 13 patients by Higgins et al.[21] who reported that one patient successfully breast fed following surgery and radiotherapy and three further patients lactated from the treated breast, but were unable to breast feed.

Chemotherapy

With improved education and increased screening, it is likely that more women will be diagnosed with early-stage breast cancer at younger ages than ever before. Most national guidelines of early-stage invasive breast cancer with negative estrogen receptor recommend treatment with adjuvant cytotoxic therapy, and hormone therapy in those with estrogen positive receptor tumours. The exception to these guidelines refers to cases in which the tumours are small. Thus, the majority of young women diagnosed at early-stage breast cancer will undergo adjuvant chemotherapy. Long-term survival is likely when breast cancer is diagnosed at an early stage, especially after adjuvant cytotoxic therapy.[12]

However, another important aspect of therapy decisions in the young premenopausal women undergoing chemotherapy is the preservation of fertility. Although many of these women benefit from chemotherapy, they are afraid to risk the opportunity to bear children, because of ovarian damage and failure that is an important and unfortunately common long-term side effect of cura-

tive chemotherapy.[13] Indeed, after such treatments, the incidence of amenorrhea has been reported to vary from 40% to 68%. Also, the patients who recover menses after chemotherapy face the likelyhood of a premature menopause as a result of depleted follicular store. These facts represent a serious problem for these cured patients because many of them are relatively young and have expectations of a normal reproductive life. The prospect of ovarian failure and impaired fertilty after anti-neoplastic therapy is a difficult topic for patients and clinicians to deal with, because the lack of good prognostic information. The incidence of ovarian failure varies with factors such as the type, duration, the total cummulative dose of a drug, age of the patient, and possibly on factors yet to be determined.[14] The proportion of women developing ovarian failure rises dramatically after age 40 years, and is irreversible in most cases. The higher grade of ovarian failure in older women might be explained by the lower number of remaining follicles.[15] Although breast cancer per se does not cause changes in ovarian function, after treatment with cytotoxic agents the ovaries appear identical to postmenopausal, and the clinical consequences of drug-induced ovarian damage include oligomenorrhea, amenorrhea, and the sequelae of menopause.[16]

The exact mechanism of chemotherapy induced ovarian failure is poorly understood. An in vitro model has demonstrated that in the human ovary chemotherapy acts primarly on primordial follicles, through induction of apoptotic changes in pregranulosa cells, which lead to irreversible loss of follicles and oocytes, along with evidence of fibrosis.[22] The category of the drugs most likely to induce ovarian failure is that of alkylating agents, such as cyclophosphamide and melphalan, whereas antimetabolites have a lesser effect. Combination chemotherapy is used more often than single agents, and it is therefore difficult to evaluate the contribution of each individual drug. The largest body of data on ovarian failure in breast carcinoma patients is derived from the experience with cyclophosphamide, methotrexate, and 5-fluouracil (CMF) regimen.[4,8,15,16]

In a retrospective review by Sutton et al.[23] of 227 consecutive breast cancer patients who were 35 years of age and younger in 25 women after chemotherapy, there were 33 pregnancies: 10 pregnancies were terminated, 2 patients had spontaneous abortions, and 19 patients gave birth to full-term offspring without fetal malformation. Two patients were still pregnant at time of that report. The median interval between the completion of treatment and pregnancy was 12 months, and several patients became pregnant a few months after treatment. Of the 25 patients who became pregnant, recurrent disease subsequently developed in 7 and 3 died. It was concluded that in a sizeable fraction of patients 35 years of age or younger treated with adjuvant chemotherapy, ovarian function remained intact, and subsequent pregnancy did not affect disease-free interval or survival of the patients. The offspring of patients who became pregnant soon after completion of chemotherapy showed no adverse effect.

With regard on teratogenicity of adjuvant systemic therapy Doll et al.[24] have shown that if chemotherapy is administred during pregnancy, there is 16% incidence of fetal malformations in the first trimester, but without increase in the incidence of teratogenesis if treatment started in the second or third trimester. The incidence was lowered to 6% if folate antagonists were used in combination with chemotherapy. In a study by Mulvihill et al.[25] has been found that the children born to women who conceived after cytotoxic therapy did not appear to be at higher risk for congenital anomalies. However, the study reported a 40% rate of abnormal pregnancies, mainly of premature birth and low birth weight, both of which were attributed to dysfunction of the uterine hormonal gestational milieu. In a recent study by Blakely et al.[26] the high rate of miscarriage (29%) has been explained by the older age of the women, and changes to ovarian function that can occur after chemotherapy. Unfortunately, the delayed effects on offspring remains to be determined in those who conceive either whilst the mother is undergoing chemotherapy or subsequently.

Although following completion of chemotherapy it was shown that there was no evidence of a teratogenic effect and increased incidence of fetal abnormalities, Sutton et al.[23] included the use of barrier contraceptives during cytotoxic treatment and for 4 to 8 weeks later in order to prevent an undesired pregnancy. The use of barrier contraceptives following chemotherapy of breast cancer has been also used by Mignot et al.[27] and Petrek[28] during the period of 2–3 years. Because the risks of recurrence are more frequent during these several years following chemotherapy Valle et al.[29] recommended the use of barrier contraceptives for a longer period, while Delač et al.[30] used the same contraception for 2–5 years depending of a stage of disease.

Endocrine therapy

Adjuvant chemotherapy is frequently incorporated as the only useful adjuvant treatment into the management of premenopausal women with *estrogen receptor negative* breast cancer. As noted previosuly,[7,8,15,16] issues of long-term toxicity from chemotherapy for breast cancer, frequently including the induction of premature ovarian failure, appear to be of increasing importance for the survivors, becoming infertile due to ageing and diminished ovarian reserve. Therefore, avoidance of chemotherapy-related ovarian toxicity may provide best prospects for fertility after treatment.[4,31]

For young women with *receptor-positive* breast cancer endocrine therapy, including ovarian suppression-ablation with gonadotrophin releasing hormone (GnRh) analogues and tamoxifen, was considered at least as a legitimate alternative or complement to conventional or to chemotherapy.[19] Although several clinical trials have not found a definitive benefit for combined medical suppression and chemotherapy, it has been suggested that the subgroup of premenopausal patients with receptor-positive tumors who do not become amenorrheic with chemotherapy, may benefit from the adition of reversible ovarian suppression.[32,33] It is regarded that ovarian medical suppression combined with tamoxifen is currently ac-

cepted as adjuvant endocrine treatment for premenopausal receptor-positive breast cancer. This treatment represents a reasonable alternative for women with good risk early-stage breast cancer (receptor-positive, lymph node-negative disease), particulary those wishing to preserve fertility.[34] From recently it is strongly suggested that the associaton of GnRh agonist and tamoxifen offers excellent protection against the endometrial side effects induced by tamoxifen. Moreover, tamoxifen appears to be able to reduce the significant bone loss induced by GnRh agonist in young women.[35]

Current options for fertility preservation

In recent decades there has been progress in the fields of breast cancer cytotoxic treatment, which has led to increasing numbers of survivors, but often with significant reproductive impairment. It is reasonable to assume that the preservation of future fertility is likely to be a priority for women desiring pregnancy under the age of 40. Therefore, currently there are several potential options for women facing premature ovarian failure and desiring preservation of fertility, including all available assisted technologies, such as in-vitro fertilization and embryo transfer (IVF-ET), oocyte and embryo cryopreservation, and cryopreservation of ovarian tissue.[15,36–38]

The first reported case of successfully achieved pregnancy using ovarian stimulation with human menopausal gonadotrophins and IVF-ET and delivery of a healthy baby was in 1992 in a patient who had primary infertility of six years after radical mastectomy for invasive carcinoma of the breast.[36] Unfortunately, because breast cancer cell proliferation and dissemination can be induced by higher concentrations of estrogen, conventional ovarian stimulation regimens are currently considered by many oncologists to be contraindicated in these patients.[39] Because increased estrogen levels are thought to be potentially risky in breast cancer patients, natural cycle IVF in combination with embryo cryopreservation has been used to treat infertility and preserve fertility. In addition it is known that tamoxifen, a drug of choice in breast cancer treatment and prophylaxis worldwide, has been used for the treatment of annovulatory patients for many years, but it has never been used as an ovarian stimulant in IVF cycles.[40] In order do develop a safe ovarian stimulation protocol of IVF and fertility preservation in breast cancer patients Oktay et al.[37] in their study compared tamoxifen stimulation with natural cycles during IVF. In the group of 12 women on tamoxifen stimulation, who had IVF with either fresh embryo transfer or cryopreservation, there were a higher number of embryos in comparison with 5 patients in natural cycles. Although in the group of patients on tamoxifen stimulation there were increased estradiol levels comparing with the patients in natural cycles, yet it was regarded that tamoxifen could reduce breast cancer incidence with its suppressive effects in these patients. In a more recent study the same authors[38] tried to develop another safe ovarian stimulation methods to perform IVF in breast cancer patients. Of 60 women with breast cancer 29 patients underwent ovarian stimulation with either tamoxifen alone or in combination with low doses of follicle stimulation hormone (FSH) or aromatase inhibitor letrozole in combination with FSH. It was found that tamoxifen or letrozole in combination with low doses of FSH showed similar superiority regarding on the number of embryos, in comparison with tamoxifen alone, but the letrozole protocol may be prefered because it results in a lower peak of estradiol. Although previous studies[23–25] have not shown any increase of congenital malformations in pregnancies occurring long after administration of chemotherapy, the safety of using IVF and embryo cryopreservation in breast cancer patients who have recently undergone chemotherapy is questionnable.[8] Therefore, further research is needed to define a »safety period« between cessation of treatment and oocyte retrieval for IVF. Until definitive data are achieved, it would be useful to monitor the pregnancy outcome of all cancer patients who undergo oocyte retrieval and IVF, and possibly screen fetuses and babies cytogenetically for analyses. In a recent study by Donnez et al.[41] has been reported a livebirth after orthotopic autotransplantation of cryopreserved ovarian tissue. Before chemotherapy was initiated in a woman with stage IV Hodgkin's lymphoma, biopsy samples of ovarian cortex were taken and cryopreserved. After her cancer treatment, the patient had premature ovarian failure and three years later following freeze-thawing the orthotopic autotransplantation of cortical tissue was done by laparoscopy. The patient conceived spontaneously 11 months after reimplantation with a single pregnancy which resulted in the livebirth of a healthy girl weighing 3.72 kg. It was suggested that in clinical situations for which chemotherapy needs to be started for young patients facing premature ovarian failure, ovarian tissue preservation looks to be a promissing option to restore fertility, in conjuction with other options, like immature oocyte retrieval, in-vitro maturation of oocytes, oocyte vitrification, or embryo cryopreservation. However, the risk of cryopreserving and transferring malignant cells with reimplantation remains and screening methods with immunohistochemical markers should be developed to detect minimal residual disease.[39]

Conclusions

It is known that in the past many women with breast cancer thought that the information about later fertility they have received, was either insufficient or unavailable. This information might not be actual at the time of diagnosis, but it became very important after diagnosis of breast cancer. Currently several fertility-sparing options with the use of assisted reproductive technology have developed, and they are available before, during, and after treatment of breast cancer. Therefore, many women would consider that the information about fertility should be given prior or after breast cancer treatment. Because fertility after breast cancer is a major for young women desiring pregnancy, the patient's future chance of pregnancy should be maximized by organizing an appropriate assisted reproduction center with a multidisciplinary team, as soon as the diagnosis is made rather

than after treatment, to enable patients do discuss their options for fertility preservation.

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