Editorial Article

Breast cancer treatment - later pregnancy and survival

M. Kasum, *Asso. Prof.*

Clinic of Gynaecology and Obstetrics, School of Medicine, University of Zagreb, Zagreb (Croatia)

Summary

Although breast cancer (BC) affects patients at older age, it occurs more frequently in premenopausal women due to better diagnostic methods and an increasing trend towards delay in childbearing. The increasing population of women with BC delaying childbearing may be of concern regarding the effect of treatment on later pregnancy, as well as the influence of pregnancy on the prognosis of disease and survival. Radiotherapy has shown no adverse effects on the clinical outcome in the offspring except diminished lactation. The offspring of patients who became pregnant after chemotherapy have shown no congenital anomalies, although sometimes a high abortion rate (10-29%) has been demonstrated. Currently, several fertility-sparing options, including the use of endocrine therapy and assisted reproductive technologies, cryopreservation and ovarian tissue transplantation, are very promising. The survival of BC patients is not decreased by a subsequent pregnancy; compared with the non-pregnant group their survival rates are often the same or better, with favourable relative risks and lower recurrence of metastases.

Key words: Breast cancer; Treatment; Pregnancy; Survival.

Introduction

The appearance of breast cancer (BC), the most common female malignancy in many Western countries, is in constant increase. In the USA there were 178,700 new cases of BC in 1998. The number increased to 205,000 newly diagnosed cases in 2002, being the cause of death for 40,000 patients and the second most common cause of cancer death in women [1]. The incidence of BC increases progressively with age, reaching the maximum in postmenopausal women. Its occurrence in premenopausal women is still relatively rare: about 21.8% of all BC have been diagnosed in women under 50 years, 6.5% by the age of 40, 2.7% under 35, and only less than 1% of all BC cases occur before the age of 30 [2]. Between 1970 and 1986 childbirth among women older than 30 more than doubled, and the first childbearing experience was postponed from the median age of 26.2 years in 1972 to the age of 29.1 in 2000 [3]. The increasing trend towards postponing childbearing in many developed countries, in addition to improved diagnostic and therapeutic methods, is concordant with the increasing incidence of BC in women who have not yet completed their family [4]. Many of those women may have more negative motivations toward childbirth as well as concerns regarding preservation of ovarian function due to the advanced reproductive age, whether BC treatment would interfere with the outcome of a later pregnancy, possible risks of future childbearing on the prognosis of BC and their overall survival [5, 6]. This paper reviews the literature regarding the influence of BC treatment on subsequent pregnancy and current options available for fertility preservation, as well as the effects of pregnancy on survival of the patients.

Surgery and radiotherapy

Although young women with BC regard breast-conserving surgery as desirable, several authors [7,8] have found a 5 to 9-times higher risk of local recurrence when compared to older patients. However, the effect of young age on the risk of local recurrence has not been seen with mastectomy. The most important risk factors for local recurrence after breast conserving surgery are: younger age (< 35 years), infiltrating tumour with an extensive intraductal component and vascular invasion, and microscopic involvement of excision margins [9]. Therefore, the Consensus panels of the National Institutes of Health and St. Galen conference have recommended adjuvant therapy for all patients under 35, based on the evidence that they have poor prognoses [10]. Radiotherapy has shown no consequence on the rate and clinical outcome of pregnancy subsequent to the treatment [11]. However, diminished lactation from the irradiated breast in those women who had had undergone radiotherapy following breast-conserving surgery, presumably due to atrophy of the breast lobules, has been noticed [12].

Revised manuscript accepted for publication January 9, 2006

Chemotherapy

With improved education and increased screening, it is likely that more women will be diagnosed with early-stage BC at a younger age. Most national guidelines on early-stage invasive BC with negative estrogen receptors, recommend treatment with adjuvant cytotoxic therapy because of long-term survival [13]. Although BC per se does not cause changes in ovarian function, these women are afraid of risking childbearing because of ovarian damage and failure, which is an important and unfortunately common long-term side-effect of curative chemotherapy [14]. The risk of chemotherapy-induced ovarian failure is directly related to the age of the patient and varies with factors such as the type, duration, and total cummulative dose of drug [2, 5, 15]. In the human ovary chemotherapy primarily acts on primordial follicles, through induction of apoptotic changes in pregranulosa cells, which leads to irreversible loss of follicles and oocytes, along with fibrosis [16]. The incidence of ovarian failure after BC occurs at rates of 10-33%, 33-81%, and 61-95% after one, six and 12 cycles of chemotherapy, respectively [17]. It has been found that the offspring of patients who became pregnant soon after the completion of chemotherapy suffered no adverse effect from the treatment [18]. Moreover, several studies [19, 20] reported that in terms of perinatal complications, chemotherapy can be safely administered to women during the second and third trimester of pregnancy. However, some authors have reported a spontaneous abortion rate as high as 24% [21] and 29% [22], whereas others have found a rate as low as 10% [23]. The high rates of miscarriage may have resulted from the older age and altered hormonal profile due to BC treatment, which is less able to support a pregnancy [22]. Although during and following the completion of chemotherapy there was no evidence of a teratogenic effect, the use of barrier contraceptives following chemotherapy of BC has been recommended for a period of two to three years in order to prevent an undesired pregnancy and because the risks of recurrence are more frequent [24].

Endocrine therapy

For young women with estrogen receptor-positive BC adjuvant endocrine therapy, including ovarian suppression/ablation with gonatrophin releasing hormone (GnRh) analogues and tamoxifen, is currently accepted as at least equal to conventional chemotherapy [10]. This treatment represents a reasonable alternative for women with good risk with early-stage BC (receptor-positive, lymph node-negative disease), particularly those wishing to preserve fertility. However, currently the available data do not definitively support the addition of ovarian suppression to adjuvant chemotherapy followed by tamoxifen [25]. Recently it has been strongly suggested that the combination 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 [26]. Although GnRh analogues are popular as the only available medical protection for gonadotoxic chemotherapy they have not been confirmed by randomized clinical trials [27, 28].

Current options for fertility preservation

In recent decades there has been progress in the fields of BC cytotoxic treatment, which has led to an increasing number 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 [29-31]. The first reported case of delivery of a healthy baby using ovarian stimulation with human menopausal gonadotrophins and IVF-ET was in 1992 in a patient who had had primary infertility after radical mastectomy for invasive BC [29]. Unfortunately, because BC 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 [32]. Therefore, natural cycle and tamoxifen stimalation protocol of IVF in combination with embryo cryopreservation have been used to preserve fertility [30]. Subsequently, tamoxifen or aromatase inhibitor letrozole stimulation in combination with low doses of FSH resulted in a higher number of embryos, but the letrozole protocol may be preferred because it results in a lower peak of estradiol [31]. Although an experimental procedure of ovarian tissue cryopreservation is not accepted in most countries, it is introduced prior to chemotherapy to preserve fertility in BC patients facing premature ovarian failure [28]. In a recent trial by Oktay *et al.* [33] after heterotopic transplantation of frozen-banked ovarian tissue and oocyte aspiration the generation of an embryo resulted but no pregnancy occurred. Similarly, Donnnez *et. al.* [34] reported the first reported case of a livebirth using orthotopic autotransplantation of cryopreserved ovarian tissue after chemotherapy in a woman with Stage IV Hodgkin's lymphoma. It has been concluded that in clinical situations where chemotherapy needs to be started for young patients with threatened reproductive potential, ovarian tissue preservation seems 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 main limitations of ovarian tissue cryopreservation and transplantation may be the loss of a large fraction of follicles during the initial ischemia after transplantation and the

induction of anti-ovarian antibodies [35, 36]. Unfortunately, the risk of cryopreserving and transferring malignant cells with reimplantation remains and therefore screening methods with immunohistochemical markers to detect minimal residual disease should be developed [32].

Survival of patients with later pregnancies

BC is for the most part hormone dependent, and pregnancy is a condition in which hormone levels are at an all-time high [22]. The main concern regarding the possible adverse effect of a subsequent pregnancy on BC prognosis is that hormonal changes might stimulate growth of the remaining BC cells or dormant micrometastases, increasing thereby the risk of recurrence [21, 37, 38]. The influence of a subsequent pregnancy on the prognosis of BC is usually regarded through its impact on patient survival, observing survival rates or relative risk and appearance of recurrence or distant metastases [5]. The literature in any earlier or recently published series indicates that the subsequent pregnancy of women with BC does not decrease their survival. Moreover, survival rates in BC patients who subsequently became pregnant are good, often the same and sometimes even better than in patients without subsequent pregnancy [38-46]. The limited data on the outcome after subsequent pregnancy in BC patients are derived from retrospective studies, some of which employ case-matching methodology, in an attempt to eliminate the obvious bias of pregnancy occurring in those women with better prognoses. In this case case control studies cases are defined as women treated for BC who subsequently became pregnant, and controls are women treated for BC without a subsequent pregnancy [5]. In non-population based studies employing case-matching methodology, which provided more data to allow analysis of 5 and 10-year survival rates, there appears to be a survival advantage in the group of cases in comparison with the controls. This survival superiority presented in survival rates is also observed in those patients with negative lymph nodes, and is compared favourably with the patients with positive lymph nodes in both case control studies and case series (Table 1). Population-based studies tried to avoid the recollection bias prevalent in retrospective studies, but perhaps they added bias in the choice of control subjects for the matching. These studies in addition to the retrospective studies have shown that a subsequent pregnancy results in improvement in survival with favourable relative risks between 0.2 (0.1-0.5) [38] and 0.8 (0.3-2.3) [21] (Table 2).

Table 1. — *Non-population based studies reporting survival rates in breast cancer survivors after pregnancy.*

Author (Ref.)	Year	No. of cases	5-year survival				10-year survival			
			node negative		node positive		node negative		node positive	
			cases	controls	cases	controls	cases	controls	cases	controls
Cooper and Butterfield [43]	1970	32	94%	71%	45%	45%				
Cheek [41]	1973	10	50%							
Harvey *et al.* [44]	1981	41					80%		79%	
Mignot *et al.* [39]	1986	68	97%	92%	90%	53%				
Clark and Chua [42]	1989	136	76%	63%						
Lethaby *et al.* [45]	1996	14	100%	80%	50%	50%				
Gelber *et al.* [46]	2001	94	92%	85%			86%	74%		

Table 2. — *Population-based studies reporting relative risks of survival in breast cancer after pregnancy.*

Author (Ref.)	Year	No. of cases	Relative risk of survival 95% confidence interval (CI)
Sankila *et al.* [38]	1994	91	0.2 (0.1-0.5)
Von Schoulz *et al.* [47]	1995	50	0.48 (0.18-1.29)
Kroman *et al.* [23]	1997	173	0.55 (0.28-1.06)
Velentgas *et al.* [21]	1999	53	0.8 (0.3- 2.3)
Mueller *et al.* [40]	2003	438	0.54 (0.41-0.71)
Blakely *et al.* [22]	2004	47	0.70 (0.25-1.95)

Excluding the effects of pregnancy after BC on survival rates and relative risks, other outcome measures include recurrence and incidence of distant metastases. Several authors [11, 18, 22, 47] have reported that the incidence of local recurrence in the pregnant and non-pregnant groups occurs at rates 8-28%, and 24-54%, respectively. Therefore, it is evident that pregnancy may not have an adverse effect on the incidence of recurrence or distant metastases in patients previously treated for BC. When looking at the mean interval from diagnosis of BC to pregnancy, Mignot [24] has recommended that it would be reasonable to wait for two or three years before pregnancy, when the risk of relapse is high (patients with positive nodes or negative nodes grade 3). However, when the risk of recurrence is quite low (microinvasive or low grade with negative node tumour), it is not necessary to delay the pregnancy after BC treatment in order to preserve the good prognosis.

Hypothesis regarding survival

The consistent observation in reviews on the survival superiority of patients who become pregnant subsequent to the diagnosis of BC may be in part due to the bias of retrospective studies. Women who do become pregnant may be healthier and younger than women who did not have subsequent pregnancies [22]. Unfortunately, the biologic effect, if any, on improvement in survival is not clearly understood. Whether the disproportional high rise of oestriol, a relatively weak oestrogen, and possibly the antagonistic effect of oestrone and oestradiol during pregnancy confers protection remains to be determined [48]. A foetal antigen hypothesis postulated that BC and foetal cells share common antigens which can elicit a memory response through the immune system, possibly preventing the development of disease

through an immunologic response to subclinical metastases [49]. This hypothesis has been confirmed by the presence of MUC1 - specific tumour antigen, on both foetal and BC tissue [50]. However, recently Rosenberg *et al.* [51] found a successively worse prognosis for parous than nulliparous women with a shorter delay between their last birth and BC diagnosis. This adverse effect on prognosis of childbirth persisted beyond ten years among women with a first pregnancy before the age of 20 years. Similarly, Largent *et al.* [52] confirmed the observations that the pregnancies, particularly recent, had an adverse effect on the progression of BC that was already developing. However, if a woman has a full-term pregnancy and has not already had a prior event then the pregnancy would be expected to leave the breast tissue more differentiated and less susceptible to carcinogenic influences. In a recent study Culliname et al. [53] found in parous women at high risk of BC that among BRCA1 carriers, parity per se was not associated with the risk of BC, because they had a 38% decrease in BC risk compared to nulliparous women. However, among women with BRCA2 carriers, increasing parity was associated with an increased risk of BC.

Conclusion

The overall survival of patients with BC has improved dramatically, but it is associated with diminished reproductive potential. In the past, information about later fertility was insufficient. However, several fertility-sparing options with the use of assisted reproductive technology have been developed recently and they are available before, during, and after the treatment of BC. Evidence from the literature has shown that the overall survival in patients treated for BC who become pregnant following an interval of two to five years is not decreased and moreover it is characterised by good survival rates. However, the issue of pregnancy with regard to subclinical recurrences remains questionable, and therefore more clinical trials and further research are needed to clarify this uncertainty.

References

[1] Jemal A., Thomas A., Murray R., Thun M.: "Cancer statistics 2002 CA". *Cancer J. Clin.,* 2002, *52,* 23.
[2] Shannon C., Smith I.E.: "Breast cancer in adolescents and young women". *Eur. J. Cancer,* 2003, *39,* 2632.
[3] Lee S.H., Akuete K., Fulton J., Chelmow D., Chung M.A., Cady B.: "An increased risk of breast disease after delayed parity". *Am. J. Surg.,* 2003, *185,* 409.
[4] Strowitzki T.: "Schwangerschaft nach Mammakarcinom". *Zentralbl. Gynakol.,* 2004, *126,* 14.
[5] Upponi S.S., Ahmad F., Whitaker I.S., Purushotham A.D.: "Pregnancy after breast cancer". *Eur. J. Cancer*, 2003, *39,* 736.
[6] Braun M., Hasson-Ohayon I., Perry S., Kaufman B., Uziely B.: "Motivation for giving birth after cancer". *Psychooncology,* 2005, *14,* 282.
[7] Arriagada R., Le M.G., Contesso G., Guinebretiere J.M., Rochard F., Spielmann M.: "Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer". *Ann. Oncol.,* 2002, *13*, 1404.
[8] Voogd A.C., Nielsen M., Peterse J.L.: "Difference on risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials". *J. Clin. Oncol.,* 2001, *19*, 1688.
[9] Macmillan R.D., Purushotham A.D., Mallon E.., Love J.G., George W.D.: "Tumour bed positivity predicts outcome after breast-conserving surgery". *Br. J. Surg.,* 1997, *84,* 1559.
[10] Goldhirsch A., Glick J.H., Gelber R.D., Coates A.S., Senn H.J.: "Meeting highlights: International consensus panel on the treatment of primary breast cancer. Seventh international conference on adjuvant therapy of primary breast cancer". *J. Clin. Oncol.,* 2001, *19,* 3817.
[11] Malamos N.A., Stathopoulos G.P., Keramopoulos A., Papadiamantis J., Vassilaros S.: "Pregnancy and offspring after the appearance of breast cancer". *Oncology,* 1996, *53*, 471.
[12] Higgins S., Hafty B.G.: "Pregnancy and lactation after breast conserving therapy for early stage breast cancer". *Cancer,* 1994, *73,* 2175.
[13] Kalantaridou S.N., Davis S.R., Nelson L.M.: "Premature ovarian failure". *Endocrinol. Metab. Clin. North. Am.*, 1998, *27,* 989.
[14] Minton S.E., Munster P.N.: "Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer". *Cancer Control.,* 2002, *9,* 466.
[15] Chiarelli A.M., Marett L.D., Darlington G.: "Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario". *Can. Am. J. Epid.,* 1999, *150*, 245.
[16] Blumenfeld Z.: "Ovarian rescue/protection from chemotherapeutic agents". *J. Soc. Gynecol Investig.*, 2001, *8,* 560.
[17] Stone E.R., Slack R.S., Novielli A., Ellis M., Baidas S., Gelmann E. *et al.*: "Rate of chemotherapy-related amenorrhea (CRA) associated with adjuvant Adriamycin and cytoxan (AC) and Adriamycin and cytoxan followed by Taxol (AC + T) in early stage breast cancer". *Breast. Cancer. Res. Treat.,* 2000, *64*, 61.
[18] Sutton R., Buzdar A.U., Hortobagyi G.N.: "Pregnancy and offspring after adjuvant chemotherapy in breast cancer patients". *Cancer,* 1990, *65*, 847.
[19] Berry D.L., Theriault R.L., Holmes F.A., Parisi V.M., Booser D.J., Singletary E. *et al.*: "Management of breast cancer during pregnancy using a standardized protocol". *J. Clin. Oncol.,* 1999, *17,* 855.
[20] Ring A.E., Smith I.E, Jones A., Shannon C., Galani E., Ellis P.A.: "Chemotherapy for breast cancer during pregnanvy: an 18-year experience from five London teaching hospital". *J. Cl..Oncol.,* 2005, *23*, 4192.
[21] Velengtas P., Daling J.R., Malone K.E., Weiss N.S., Williams M.A., Self S.G. *et al.*: "Pregnancy after breast carcinoma: outcomes and influence on mortality". *Cancer,* 1999, *85*, 2424.
[22] Blakely L.J., Buzdar A.U., Lozada J.A., Shullaih S.A., Hoy E., Smith T.L. *et al.*: "Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence". *Cancer,* 2004, *100,* 465.
[23] Kroman N., Jensen B.M,. Melbye M., J Wohlfahrt J., Mouridsen H.T.: "Should women be advised against pregnancy after breast-cancer treatment?" *Lancet,* 1997, *350,* 319.
[24] Mignot L.: "Desire for a child after breast cancer (in French)". *Gynecol. Obstet. Fertil.,* 2000, *28,* 547.
[25] Emens L.A., Davidson N.E.: "Adjuvant hormonal therapy for premenopausal women with breast cancer". *Clin. Cancer. Res.,* 2003, *9,* 486s.
[26] Berliere M., Galant C., Marques G., Piette P., Duck L., Fellah L *et al.*: "LH-RH agonists offer very good protection against the adverse gynaecological effects induced by tamoxifen". *Eur. J. Cancer,* 2004, *40*, 1855.
[27] Blumenfeld Z.: "Ovarian cryopreservation versus ovarian supression by GnRh analogues: primum non nocere". *Hum. Reprod.,* 2004, *19,* 1924.

[28] Falcone T., Mohamed A.B.: "Fertility and pregnancy outcome after malignancy". *Curr. Opin. Obstet. Gynecol.*, 2005, *17*, 27.
[29] El Hussein E., Tan S.L.: "Successful in vitro fertilization and embryo transfer after treatment of invasive carcinoma of the breast". *Fertil. Steril.*, 1992, *58*, 194.
[30] Oktay K., Buyuk E., Davis O., Yermakova I., Veeck L., Rosenwaks Z.: "Fertility preservation in breast cancer patients: IVF and embryo cryopreservation after ovarian stimulation with tamoxifen". *Hum. Reprod.*, 2003, *18*, 90.
[31] Oktay K., Buyuk E., Libertella N., Akar M., Rosenwaks Z.: "Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation". *J. Clin. Oncol.*, 2005, *23*, 3858.
[32] Prest S.J., May E.E., Westley B.R.: "The estrogen-regulated protein TFF1, stimulates migration of human breast cancer cells". *FASSEB. J.*, 2002, *16*, 592.
[33] Oktay K., Buyuk E., Veeck L., Zaninovic N., Xu K., Takeuschi T. *et al.*:"Embryo development after heterotopic transplantation of cryopreserved ovarian ovarian tissue". *Lancet*, 363, 837.
[34] Donnez J., Dolmans M.M., Demylle D., Jadoul P., Pirard C., Squifflet J. *et al.*: "Livebirth after orthotopic transplantation of cryopreserved ovarian tissue". *Lancet*, 2004, *364*, 1405.
[35] Jeremias E., Bedaiwy M.A, Gurunluoglu R., Biscott C.V. Siemionow M., Falcone T.: "Heterotopic autotransplantation of the ovary with microvascular anastomosis: a novel surgical technique". *Fertil. Steril.*, 2002, *77*, 1278.
[36] Esfandiani N., Falcone T., Bedaiwy M.A., Agarwal A., Jeremias E., Sharma R.K.: "Autologous transplantation of cryopreserved ovary induces the generation of antiovary antubodies in sheep". *Fertil. Steril.*, 2003, *80*, 1062.
[37] Danforth D.N.: "How subsequent pregnancy affects outcome in women with a prior breast cancer?". *Oncology*, 1991, *5*, 23.
[38] Sankila R., Heinavaara S., Hakulinen T.: "Survival of breast cancer patients after subsequent term pregnancy: "Healthy mother effect". *Am. J. Obstet. Gynecol.*, 1994, *170*, 818.
[39] Mignot L., Morvan F., Berdah J., Querleu D., Laurent J.C., Verhaeghe M. *et al.*: "Pregnancy after breast cancer: results of a case control study (in French)". *Presse. Med.*, 1986, *15*, 1961.
[40] Mueller B.A., Simon M.S., Deapen D., Kamineni A., Malone K.E., Daling J.R.: "Childbearing and survival after breast cancinoma in young woman". *Cancer*, 2003, *98*, 1131.
[41] Cheek J.H.: "Cancer of the breast in pregnancy and lactation". *Am. J. Surg.*, 1973, *126*, 729.
[42] Clark R.M., Chua T.: "Breast cancer in pregnancy: the ultimate challenge". *Clin. Oncol.*, 1989, *1*, 11.
[43] Cooper D.R., Butterfield J.: "Pregnancy subsequent to mastectomy for cancer of the breast". *Ann. Surg.*, 1970, *17*, 429.
[44] Harvey J.C., Rosen P.P., Ashikari R., Robbins G.H., Kinne D.V.: "The effect of pregnancy on the prognosis of carcinoma of the breast following radical mastectomy". *Surg. Gynecol. Obstet.*, 1981, *153*, 723.
[45] Lethaby A.E., O'Neill M.A., Mason B.H., Holdaway I.M., Harvey V.J.: "Overall survival from breast cancer in women pregnant or lactating at or after diagnosis". *Int. J. Cancer*, 1996, *67*, 751.
[46] Gelber S., Coates A.S., Goldhirsch A., Castiglione-Gertsch M., Marini G., Lindtner J. *et al.*: "Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer". *J. Clin. Oncol.*, 2001, *19*, 1671.
[47] Von Schoultz E., Johansson H., Wilking N., Rutquist L.E.: "Influence of prior and subsequent pregnancy on breast cancer prognosis". *J. Clin. Oncol.*, 1995, *13*, 430.
[48] Lemon H.M., Kumar P.F., Peterson C., Rodriquez-Sierra J.F., Abbo K.M.: "Inhibition of radiogenic mammary carcinoma in rats by rats by estriol and tamoxifen". *Cancer*, 1989, *63*, 1685.
[49] Averette H.E., Mirhashemi R., Moffat F.L.: "Pregnancy after breast cancer: the ultimate medical challenge". *Cancer*, 1999, *85*, 2301.
[50] Botelho F., Clark D.A.: "How might pregnancy immunize against breast cancer?". *Am. J. Reprod. Immunol.*, 1998, *29*, 279.
[51] Rosenberg L., Thalib L., Adami H.O., Hall P.: "Childbirth and breast cancer prognosis". *Int. J. Cancer*, 2004, *111*, 772.
[52] Largent J.A., Ziogas A., Anton-Culver H.: "Effect of reproductive factors on stage ,grade and hormone receptor status in early-onset breast cancer". *Breast. Cancer. Res.*, 2005, *7*, 541.
[53] Cullinane C.A., Lubinski J., Neuhausen S.L., Ghadirian P., Lynch H.T., Issacs C. *et al.*: "Effect of pregnancy as a risk factor for breast cancer in BRCAI/BRCAII mutation carrieres". *Int. J. Cancer*, 2005, *117*, 988.

Address reprint requests to:
M. KASUM, M.D.
Gynaecological clinic
School of Medicine
University of Zagreb
Zagreb (Croatia)