

Klinika za ženske bolesti i porode Medicinskog fakulteta Sveučilišta i KBC-a u Zagrebu

## THE INFLUENCE OF SUBSEQUENT PREGNANCY ON THE PROGNOSIS OF BREAST CANCER

### UTJECAJ KASNIJE TRUDNOĆE NA PROGNOZU RAKA DOJKE

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*Review*

*Key words:* breast cancer, treatment, pregnancy, prognosis

**SUMMARY.** The overall incidence of breast cancer is the highest in perimenopausal and older women but rare in the reproductive age. However, with the increasing trend toward delay in childbearing that is visible in many developed countries, in addition to possibilities of better diagnostic methods, it could be expected the higher incidence of breast cancer in this age group than it was earlier. The paper presents an overview of literature regarding the effect of a pregnancy on survival subsequent to diagnosis of breast cancer. On contrary to earlier studies the findings from recent researches demonstrate that there is no justification for a therapeutic abortion, and the survival of women with breast cancer is not decreased by subsequent pregnancy. The survival of breast cancer patients is not decreased by subsequent pregnancy because they have good survival rates, often the same or better, with favourable relative risks, and a lower recurrence of metastases, in comparison with non-pregnant group. Therefore, the prognosis of the breast cancer does not seem to be influenced adversely by subsequent pregnancy, although the issue of pregnancy with regard to subclinical metastases remain questionable.

*Pregled*

*Ključne riječi:* rak dojke, liječenje, prognoza, trudnoća

**SAŽETAK.** Rak dojke je najčešći zloćudni tumor u žena, predstavlja drugi razlog smrtnosti po učestalosti od malignih bolesti. Rak dojke se javlja najčešće u žena u perimenopauzi i kasnije, rjeđe se opaža i u reproduktivnoj dobi kod žena mlađih od 40 godina. Epidemiološke studije su pokazale da u mnogim razvijenim zemljama postoji opći trend odgađanja rađanja, čemu pridonose brojni razlozi, kao što su obrazovni, profesionalni, osobni, društveno-ekonomski te problemi sa zanošenjem. Istodobno, zahvaljujući boljem standardu i unapređivanjem razvoju znanosti u tim zemljama, za očekivati je bolju zdravstvenu skrb, što se odražava u ranijoj i boljoj dijagnostici i liječenju bolesti. Na taj su način suvremene dijagnostičke metode omogućile ranije i češće otkrivanje raka dojke u populaciji žena kasnije fertile dobi, koje su odgodile rađanje i kojima još predstoji reproduktivska uloga. Stoga sve veća pojavnost raka dojke i brojnija populacija žena kasnije fertile dobi kojoj još predstoji rađanje, stvaraju problem i opravdanu zabrinutost kako bi se trudnoća mogla odraziti na prognozu i tijek maligne bolesti. Problem utjecaja kasnije trudnoće nakon liječenja raka dojke od vitalne je važnosti za ženu koja želi rađati, no isto tako nije manja odgovornost ni liječnika koji joj treba pružiti adekvatnu pomoć. Poznato je da su u prošlosti trudnoće nakon liječenja raka dojke smatrane rizičnim zbog čega su izbjegavane i nisu preporučivane, a u slučaju zanošenja namjerno su prekidane, zbog pretpostavke da bi trudnoća mogla nepovoljno utjecati na tijek bolesti. Nasuprot povijesnim stavovima kada je terapijski pobačaj bio pravilo, danas je stav dijametralno promijenjen jer je utvrđeno da prekid trudnoće ne predstavlja nikakvu prognostičku prednost za rak dojke. Iznimno je terapijski pobačaj još uvijek indiciran kod sumnje na oštećenje embrija zbog uporabe intenzivne adjuvantne terapije, u slučaju progresije bolesti ili zbog psihološko-socijalnih razloga trudnice. Danas se općenito smatra da trudnoća nakon liječenja raka dojke ne predstavlja rizičan čimbenik za novu pojavu bolesti, promatrano kroz stopu preživljenja, relativnih rizika i pojavu kasnijih metastaza, dok je opće preživljenje u žena koje su zatrudnile i rodile, jednako ili čak bolje u odnosu na žene koje nisu kasnije zanijele. Štoviše, uz trudnoću nakon liječenog raka dojke spominju se znatno rjeđe pojave lokalnih recidiva ili kasnih metastaza bolesti. Promatrajući vremenski razmak od dijagnoze raka dojke i kasnije trudnoće dogovorno je utvrđen interval između 2 i 5 godina, što je ovisno o stupnju proširenosti bolesti. Smatra se da je bolja prognoza bolesti s većim preživljenjem ukoliko je dulja stanka od pojave raka dojke do trudnoće zbog čega je veća vjerojatnost da bi se izbjegli recidivi, premda se i kraće pauze do trudnoće kod najranijih oblika bolesti nisu pokazale rizičnim. Pretpostavlja se da se povoljan učinak kasnije trudnoće nakon liječenja raka dojke može pripisati »per se« zdravijim ženama, antiestrogenom učinku estriola te zajedničkim tumorskim i fetalnim antigenima koji imunološkom reakcijom stvaraju protutijela protiv tumorskih stanica. Ipak, mogući učinak kasnije trudnoće kod eventualno neprepoznatih supkliničkih ili mikrometastaza nije još razjašnjen, zbog čega ostaje predmetom budućih istraživanja.

## Introduction

Breast cancer is the most common female malignancy in many western countries, affecting 205,000 newly diagnosed cases in the United States in 2002. It is the second most common cause of cancer death in women, with 40,000 deaths in the same year.<sup>1</sup> Because it generally affects women in the perimenopausal and postmenopausal age group, its occurrence in women 30 to 40 years of age is a relatively rare phenomenon. About 6,5% of all

breast cancers are diagnosed by the age of 40 and 21,8% occurred in women under 50 years.<sup>2</sup> In Croatia in women 25 to 44 years of the age the incidence 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 pregnancies after completed treatment of breast cancer.<sup>3</sup>

The National Center for Health Statistics notes that the rate of childbirth among women older than 30 years more than doubled between 1970 and 1986. Furthermore,

the American women have postponed their first child-bearing experience from the median age of 26,2 in 1972 to the age of 29,1 years in 2000.<sup>4–6</sup> The increasing trend toward delay in childbearing from 30 to 40 years of age for different reasons (educational, professional, personal, socioeconomic, and fertility) noticed in the United States and many modern countries, in addition to improved diagnostic and therapeutic methods, is concordant with the increasing incidence of breast cancer in women who have not yet completed their family.<sup>7</sup> 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. Because the incidence of premenopausal women delaying childbearing with breast carcinoma is increasing, they may have concerns regarding preservation of ovarian function and possible risks of future childbearing on the prognosis of disease, what could be of paramount importance not only for the patient, but also for the doctor from whom she seeks advice. Breast cancer patients need well-founded advice about how pregnancy and other reproductive events may influence their lives and future risks of the disease.<sup>4</sup>

Owing to many investigators of predominantly retrospective case control or observational studies and case series, no data are available to suggest that subsequent pregnancy after breast cancer will hasten or induce breast-cancer recurrence.<sup>5,8–15</sup> Moreover, in several studies in the patients who conceived following treatment of breast cancer, a lower appearance of local recurrences and distant metastases have been noticed.<sup>16–18</sup> Because most of these retrospective studies are with incomplete data, small sample sizes, and a potential problem of selection bias, they are usually difficult for interpretation for oncologist, who rely on research data to provide the most informed counsel to their patients.<sup>8</sup> Although in the past and in the early 1950s was noticed a better outcome in patients following a therapeutic abortion, current opinion is that there is no justification for termination of pregnancy. A therapeutic abortion could be indicated and may be relevant only in the patient who has rapidly progressing breast cancer, in occasion of eugenic reasons following to intensive cytotoxic treatment or for psychological and social reasons.<sup>3,16,19</sup> However, the concern in these patients would be for acceleration of the growth rate or of stimulation of previously dormant micrometastases, as well as of carcinogenesis of a new primary breast carcinoma facilitated by gestational hormones.<sup>20</sup> Theoretic concern of tumor promotion could be only justified when considering the long term exposure to the intense gestational hormones, in the presence of established breast carcinoma with possible micrometastases. Although most reports find that subsequent pregnancy does not affect survival from breast carcinoma, circumspection and cautious consideration is appropriate, when exploring the issue with the individual patient.<sup>7,21</sup>

This paper reviews the literature regarding the effects of pregnancy on survival of the patients and risk of recurrence following treatment of breast carcinoma.

## Survival of patients with pregnancy after breast cancer

Breast carcinoma is for the most part, hormone dependent, and pregnancy is a condition in which hormone levels are at an all-time high.<sup>8</sup> The main concern regarding the possible adverse effect of a subsequent pregnancy on breast carcinoma prognosis, is that hormonal changes might stimulate growth of the remainder breast cancer cells or dormant micrometastases,<sup>20</sup> thereby increasing the risk of recurrence, and consequently how the women should be advised.<sup>13,14</sup> The influence of subsequent pregnancy on the prognosis of the disease is usually regarded through its action on survival of patients, observing survival rates or relative risks, and appearance of recurrence or distant metastases.<sup>6</sup> Overall, the evidences from the literature in any earlier or recent of the published series indicate, that the survival of women with breast carcinoma is not decreased by subsequent pregnancy. Moreover, breast cancer patients who subsequently become pregnant have good survival rates, often the same or sometimes better, than the patients with no subsequent pregnancy.<sup>9,11,13,22–26</sup> The limited data on outcome after subsequent pregnancy in breast carcinoma 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 a better prognosis. In these case control studies cases are defined as women treated for breast cancer who subsequently became pregnant, and controls are women treated for breast cancer without a subsequent pregnancy.<sup>6,7</sup> In non-population based studies employing case-matching methodology, that provided more data to allow for 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 it is compared favourably with the patients with positive lymph nodes in both case control studies and case series (*Table 1.*)

The population-based studies tried to avoid the recollection bias prevalent in the retrospective studies, but they added biases perhaps in the choice of control subjects for the matching. These studies added to the retrospective studies have shown, that a subsequent pregnancy results in an improvement in survival with favourable relative risks between 0.2 (0.1–0.5)<sup>13</sup> and 0.8 (0.3–2.3)<sup>14</sup> (*Table 2.*)

Three Scandinavian studies from different countries have confirmed these beneficial results in survival of patients after breast cancer. Sankila et al.<sup>13</sup> from Finland reported a population-based study of 91 eligible patients with subsequent delivery after the diagnosis of breast cancer to whom 471 controls were matched for stage, age, and year of breast cancer. It was found that the controls had 4.8-fold (95% confidence interval, 2.2 to 10.3) risk of death, compared with those who were delivered after the diagnosis of breast cancer. Because their study was retrospective, they could not assess whether the results were related to the possible beneficial biologic ef-

Table 1. Non-population based studies reporting about survival rates in breast cancer survivors after pregnancy  
 Tablica 1. Populacijski neutemeljena istraživanja koja izvješćuju o stopama preživljenja nakon trudnoće

Author	Year	No of cases	5-year survival				10 – year survival			
			node negative cases	node negative controls	node positive cases	node positive controls	node negative cases	node negative controls	node positive cases	node positive controls
Cooper and Butterfield <sup>24</sup>	1970	32	94%	71%	45%	45%				
Cheek <sup>22</sup>	1973	10	50%							
Harvey et al. <sup>25</sup>	1981	41					80%		79%	
Mignot et al. <sup>11</sup>	1986	68	97%	92%	90%	53%				
Clark and Chua <sup>23</sup>	1989	136	76%	63%						
Sankila et al. <sup>13</sup>	1994	91	96%	77%	79%	49%	96%	67%	79%	42%
Lethaby et al. <sup>26</sup>	1996	14	100%	80%	50%	50%				
Gelber et al. <sup>9</sup>	2001	94	92%	85%			86%	74%		

Table 2. Population-based studies reporting relative risks of survival in breast cancer after pregnancy in comparison to nonpregnant patients  
 Tablica 2. Populacijski utemeljena istraživanja koja izvješćuju o relativnim rizicima preživljenja kod raka dojke nakon trudnoće u usporedbi bolesnicama koje nisu zatrudnile

Author	Year	No of cases	Relative risk of survival (95% confidence interval)
Sankila et al. <sup>13</sup>	1994	91	0.2 (0.1–0.5)
Von Schoultz et al. <sup>15</sup>	1995	50	0.48 (0.18–1.29)
Kroman et al. <sup>10</sup>	1997	173	0.55 (0.28–1.06)
Velentgas et al. <sup>14</sup>	1999	53	0.8 (0.3–2.3)
Gelber et al. <sup>9</sup>	2001	108	0.44 (0.21–0.96)
Mueller et al. <sup>12</sup>	2003	438	0.54 (0.41–0.71)
Blakely et al. <sup>8</sup>	2004	47	0.70 (0.25–1.95)

fects of pregnancy itself. Therefore, it was concluded that their results were related to a selection bias and called it »healthy mother effect« (i.e., that only women who feel healthy give birth, and those who are affected by the disease do not). In a Swedish study by Von Schoultz et al.<sup>15</sup> the relative hazard for women who became pregnant after diagnosis of breast cancer in comparison without a subsequent pregnancy was 0.48 (95% confidence interval, 0.18 to 1.29), which suggested a possible decreased risk of distant dissemination. They found no evidence that pregnancy after breast cancer diagnosis adversely influenced the clinical course of the disease. In the third study from Denmark Kroman et al.<sup>10</sup> found among 173 women with a full-term pregnancy after treatment of breast cancer, a non-significantly reduced relative risk of death of 0.55 (95% confidence interval, 0.28 to 1.06), compared with women who had had no full-term pregnancy after adjustment for age, diagnosis, stage of disease, and reproductive history before diagnosis. However, because women with a poor outlook were believed to avoid pregnancy, they noticed a potential problem of selection bias in the exposed group, what has been the main concern about the interpretation of results reported previously.<sup>13</sup>

Six years ago several studies in United States have reported similar results. Velentgas et al.<sup>14</sup> reported that the age-adjusted relative risk of death among 53 pregnant women after breast cancer was 0.8 (95% confidence interval, 0.3 to 2.3), compared with 265 matched controls. Although their findings were based on a small

number (5) of deaths, there was no conclusion that pregnancy has an adverse effect on survival. However, the observed percentage of pregnancies that ended in miscarriage (24%) was higher 70% than expected, what might have been probably attributed to an underlying higher risk of spontaneous abortion. A similar study by Gelber et al.<sup>9</sup> found among 108 women a decreased relative risk of death of 0.44 (95% confidence interval, 0.21 to 0.96) with a subsequent pregnancy, after diagnosis of early-stage breast cancer, compared with 188 matched controls. It was suggested that the superior survival seen in their and other series may merely reflect a health patient selection bias, but is also consistent with an antitumor effect of the pregnancy. In a large study performed by Mueller et al.<sup>12</sup> among 438 women younger than 45 years with primary invasive breast cancer and subsequent birth, compared to 2775 matched controls, there was found a decreased hazard of death with relative risk of 0.54 (95% confidence interval, 0.41 to 0.71). It was concluded that subsequent childbearing is unlikely to increase the risk of mortality, and that their results together with growing evidences from other studies may provide some reassurance to young women with breast cancer. In a recent study by Blakely et al.<sup>8</sup> in 2004 among 47 women with breast cancer and posttreatment pregnancy, the hazard ratio for disease recurrence was 0.70 (95% confidence interval, 0.25 to 1.95). Although there was no evidence that subsequent pregnancy after adequate therapy for breast cancer is associated with an increased mortality or disease recurrence, but the high rate of spontaneous abortion of 29% was found. The high rate of miscarriage was explained by the age of the women and changes to ovarian function that can occur after chemotherapy, and/or radiotherapy. Velentgas et al.<sup>14</sup> similarly have reported a spontaneous abortion rate as high as 24%, whereas Kroman et al.<sup>10</sup> have found a rate as low as 10%.

Excluding the effects of pregnancy after breast cancer on survival rates and relative risks, other outcome measures include recurrence and incidence of distant metastases. Several authors<sup>8,15,17,27</sup> have reported about the influence of pregnancy on recurrence and distant metastasis. Sutton et al.<sup>17</sup> reported a *recurrence rate* of 28% in the pregnancy group and 46% in the non-pregnant group. Similarly, Malamos et al.<sup>27</sup> presented a rate of local recurrence of 14% in the pregnant group, and 39% in the

non-pregnant group. Blakely et al.<sup>8</sup> in 2004 also reported a recurrence rate of 23% for women who experienced pregnancy, and 54% for women who did not. With regard on *distant metastasis* Von Schoultz et al.<sup>15</sup> using registry data reported a rate of 8% among all patients who became pregnant, compared with a rate of 24% among patients without a subsequent pregnancy. Therefore, it is evident that pregnancy may not have an adverse effect on the incidence of recurrence or distant metastasis in patients previously treated for breast cancer.

### Interval from diagnosis of breast cancer to pregnancy

When looking for the mean interval from diagnosis of breast cancer to pregnancy and whether this affects survival, it is difficult to give advice on how short a delay could be recommended as »safe« for the treatment. The definition of this time interval is variable, because some studies use the length from moment of diagnosis to time of delivery with exclusion of abortions, whilst others use time from diagnosis of breast cancer to diagnosis of pregnancy which then include all abortions.<sup>6</sup> Of the previous studies a delay of at least 2 years from diagnosis to pregnancy has been recommended<sup>11,12,20</sup> and nearly one-third of women in reproductive age who develop breast cancer will later have one or more pregnancies, and 70% of these will occur within 5 years of treatment.<sup>5,19</sup> Clark and Reid<sup>28</sup> found that survival was better with a longer interval between cancer diagnosis and pregnancy. They reported a 5-year survival of 54% in those who became pregnant within 6 months of diagnosis, and 78% in those who waited between 6 months and 2 years. Similarly, Clark and Chua<sup>23</sup> found a 92% 5 years survival rate for those with an interval of 2 years, and 59% for those with a 6-month interval. Gelber et al.<sup>9</sup> reported a better survival rate in those women who had a subsequent pregnancy (overall 5-year survival of 92% versus 85% in cases versus controls, respectively), even though 43% of cases completed a pregnancy within 1 year of diagnosis. Although it is evident from many studies<sup>9,13,22–26</sup> that the prognosis of the breast cancer does not seem to be influenced by subsequent pregnancy, Mignot<sup>19</sup> has recommended that it would be reasonable to wait for 2 or 3 years before pregnancy, when the risk of relapse is high (patients with positive nodes or negative nodes grade III). In order to prevent an undesired pregnancy during this period of 2 to 5 years when the risk of relapse is present the use of barrier contraceptives has been included.<sup>3,17,19,29–31</sup> However, when the risk of recurrence is quite low (microinvasive or low grade with negative nodes tumor), no delay between treatment of breast cancer and pregnancy is necessary to preserve the good prognosis.<sup>19</sup>

### Hypothesis regarding survival

A good survival rate often the same or better, that has been consistently observed in reviews, for the patients who become pregnant subsequent to a diagnosis of breast cancer, than in patients with no subsequent pregnancy,

may in part be to the bias of retrospective studies. The women who do become pregnant may be healthier than women who do not, so there may be some inherent selection bias. In a study by Blakely et al.<sup>8</sup> women who later became pregnant had earlier stage disease, fewer positive lymph nodes, had estrogen receptor-negative tumors more often, and were younger than women who did not have subsequent pregnancies. Unfortunately, the biologic effect, if any, on improvement of survival is clearly not understood. Whether the disproportionally high rise during pregnancy of estriol, a relative weak estrogen and possibly an antagonist of estrone and estradiol, confers protection remains to be determined.<sup>3,32</sup> A fetal antigen hypothesis has been proposed to account for a causal influence of pregnancy on survival of women after breast cancer. It is postulated that breast carcinoma cells and fetal cells share common antigens what represent the base for isoimmunisation that occurs during pregnancy. Averette et al.<sup>33</sup> have suggested that fetal antigens raised during pregnancy can elicit a memory response through the immune system, and that this can prevent the development of disease through an immune response to subclinical metastases. This hypothesis was supported by Botelho and Clark<sup>34</sup> who confirmed the presence of tumor specific antigen, MUC1, on both fetal and breast cancer tissue.

### Conclusions

The evidences from the literature have shown that the overall survival in the patients treated for breast cancer who become pregnant following the interval of 2 to 5 years is not decreased, than it is characterized with good survival rates, favourable relative risks and lower recurrence of metastases in comparison with the controls. Therefore contrary to earlier reports, currently there is no justification for a therapeutic abortion except in the situation of rapidly progressing breast cancer, eugenic reasons due to intensive cytotoxic treatment, and psychological-social reasons. However, the issue of pregnancy with regard to subclinical recurrences remain questionable. Therefore, further research with larger, prospective, and multicenter studies are needed for detailed analysis, which may answer these questions.

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