

## Pregnancy After Breast Cancer

a report by

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### Introduction

Breast cancer is the most frequent malignant disease in women in the Western world and its incidence is increasing in both industrialized and developing countries.

Although the incidence of breast cancer rises with age, approximately one-quarter of newly diagnosed breast cancer patients are pre-menopausal, and 6.5% of the cases occur in women under 40 years of age. The disease is very rare in women under 30 years. Several *in vitro* and *in vivo* observations clearly show a correlation between the development of breast cancer and hormones. Early menarche and late menopause have been associated with an increased incidence of breast cancer parity appears to decrease the risk, but breast cancer frequency is increased immediately after pregnancy.

A major concern related to the possibility of a pregnancy after breast cancer is the fear that silent micrometastases still present after primary treatment of breast cancer may be re-activated by the hormonal changes experienced during pregnancy, and negatively affect the outcome. Furthermore, breast cancer at a young age is considered to have a more aggressive biological behavior and an unfavorable prognosis compared with the disease in older premenopausal patients. These facts are making the task of counseling patients on subsequent pregnancies particularly hard.

Adjuvant therapies after primary treatment of breast cancer consisting of chemotherapy, hormonal therapy, or both, and lately antibodies as well, are applied to most of the patients to prevent recurrence. Transient or definitive amenorrhea is one of the side effects of these therapies (see *Table 1*), and it has been associated with a more favorable outcome particularly in patients with receptor-positive disease. The frequency of chemotherapy-related amenorrhea increases with increasing age (8% for women <35; 78% for women above the age of 40). Patients with receptor-positive disease generally also receive long adjuvant endocrine therapies (~5 years), which may well interfere with a

desire of pregnancy considering the decrease of fertility in the general population after the age of 35.

### Desire of Pregnancy in Survivors

Great emphasis has been placed on physical and psychological rehabilitation of breast cancer patients. Fertility and possible pregnancies after breast cancer should be part of the initial discussion with each premenopausal patient.

Little data are available on breast cancer survivors having children after treatment. Dow<sup>6</sup> reported the data on 20 women: answering to semi-structured interviews, participants indicated that they were eager to resume their life goals, which were stalled by breast cancer. For these women, having children was a high priority at the time of diagnosis and was related to the belief of being 'cured', to the fact of being well enough to look forward to a future, and to the reconnection with their peers, friends, and family. Having children was a strong stimulus to 'get well' again. Participants expressed concerns about the potential for disease recurrence and the need to be vigilant. Participants also reported the severe concerns about their decision to become pregnant expressed by some family members.

### Pregnancy After Breast Cancer

The majority of the reports on pregnancy after breast cancer are case-control studies (see *Table 2*).

In the Velentgas<sup>10</sup> report on 53 patients, the age-adjusted relative risk (RR) of death associated with subsequent pregnancy was 0.8 (95% confidence interval (CI) 0.3–2.3), showing that pregnancy did not have a negative influence on survival after breast cancer.

In a large Danish registry study,<sup>11</sup> 173 of 5,725 women with primary breast cancer aged 45 years or younger who became pregnant after treatment were identified. No increase in the risk of death from breast cancer was observed in association with pregnancy after diagnosis.

Women who had a full-term pregnancy after treatment had a non-significant reduced risk of death (RR=0.55, 95% CI 0.28–1.06) compared with women with no full-term pregnancy (p=0.08).

Gelber<sup>12</sup> identified 94 patients with 137 pregnancies after breast cancer diagnosis and adjuvant treatment, and her observation did not show an adverse effect of pregnancy on survival. At five and 10 years from diagnosis, overall survival among patients with pregnancy was 92% ±3% and 86% ±4% respectively, and for a matched comparison group survival was 85% ±3% and 74% ±4% respectively.

A Finnish population-based study identified 91 breast cancer patients with subsequent deliveries and matched them with 471 control subjects. Breast cancer survivors with subsequent pregnancy had statistically better survival rates than controls with no subsequent birth.<sup>13</sup>

Von Schoultz reported, in 2,119 women with breast cancer (<50 years old), a total of 50 pregnancies and observed that the RR of distant dissemination for women who became pregnant after breast cancer was not elevated (0.48; p=0.14).<sup>14</sup>

The interval between diagnosis of breast carcinoma and pregnancy has been recognized as a relevant factor by some authors. Clark<sup>15</sup> noted that patients who became pregnant within six months from diagnosis had a five-year survival of 54% compared with 78% for patients with a later pregnancy (six months to two years). This trend was also reported by Clark and Chua who found a 92% survival rate at five years for women with an interval of at least two years from treatment to pregnancy, and 59% for those with an interval of six months or less.<sup>16</sup>

In the International Breast Cancer Study Group (IBCSG) report, 43% of women completed pregnancy

**Table 1: Rates of Chemotherapy-induced Amenorrhea**

Groups	Adjuvant Chemotherapy	Incidence of Amenorrhea (at least ≥3 months)
IBCSG (1)	Classic CMF x 6	61% (<40 yrs) 95% (≥40 yrs)
St Luke's (2)	AC x 4	34%
BCIRG (3)	FAC x 6	32.8%
	TAC x 6	51.4%
MD Anderson (5)	Doxorubicin-containing	59%
NCIC (4)	CEF x 6	51%

CMF = cyclophosphamide, methotrexate, 5FU; AC = doxorubicin, cyclophosphamide; FAC = 5FU, doxorubicin, cyclophosphamide; TAC = docetaxel, doxorubicin, cyclophosphamide; CEF = cyclophosphamide, epirubicin, 5FU.

within two years of diagnosis but no adverse effect could be observed for these patients.<sup>12</sup>

Due to the particular treatments received after breast cancer, women becoming pregnant may experience a higher rate of abortion or miscarriages.

Blakely<sup>17</sup> observed 10 spontaneous or elective abortions and four miscarriages (29%) among 383 patients, a higher incidence than in other reports that may be explained by the older age of the women (65% patients age >30 years).

Sanders reported on 72 pregnancies in 41 women treated for breast cancer. Sixty-one per cent of the pregnancies ended with a live birth and the remaining 39% in miscarriages, terminations, or ectopic pregnancies.<sup>18</sup> Woolas observed a live birth rate of 50% in his series.<sup>19</sup> These results are comparable with the most recent data reported by Falconer and Ferns – between 1987 and 1998 they identified 40 women who conceived or delivered a child following treatment for cancer. All women had undergone a combination of therapies including surgery, chemotherapy, and radiotherapy and there was no indication for an increased risk (in terms of gestation length, delivery outcome, or weight of the child at birth).<sup>20</sup>

**Table 2: Studies on Breast Cancer After Pregnancy**

Author	Number of Patients with Pregnancy	Observation Time	5-year Survival	10-year Survival Node Negative/positive	HR Pregnancy/Non-pregnancy
Ribeiro <sup>7</sup>	57	1941–1980	69%	64% / 26%	-
Mignot <sup>8</sup>	68	1940–1985	-	90% / 71%	-
Clark and Chua <sup>16</sup>	136	1931–1985	-	64%	-
Ariel and Kemper <sup>9</sup>	46	1950–1980	-	76% / 56%	-
Sankila <sup>13</sup>	91	1967–1989	-	93%	0.20
Von Schoultz <sup>14</sup>	50	1971–1988	-	-	0.48 (distant dissemination)
Kroman <sup>11</sup>	173	1978–1995	-	-	0.55 (full-/not full-term delivery)
Velentgas <sup>10</sup>	53	1983–1992	-	-	0.80
Gelber <sup>12</sup>	94	1981–2000	92%	86%	0.44

### Risk of Teratogenic Effects and Possible Problems of Development in Offspring After Treatment for Breast Cancer

Most adjuvant treatments for breast cancer are potentially highly teratogenic. The incidence of malformations in the general population is 3%. The commonly used chemotherapy drugs are generally metabolized and excreted within a few days and almost all are able to cross the placenta. The risk of malformations is therefore only increased if pregnancy occurs during or immediately after treatment. The first trimester is most crucial because of organogenesis. The risk of major malformations during this period is 10% for single-agent and 25% for combination chemotherapy.

Sutton reviewed 227 patients younger than 35 years treated with adjuvant chemotherapy (5-fluorouracil,

Little is known about the offspring's outcome when a pregnancy begins while on tamoxifen. However, adverse effects have been reported in animals (increased mammary tumorigenesis) and ambiguous genitalia have been observed in humans.

There are no data regarding pregnancy after termination of five years of tamoxifen, after pure estrogen antagonist administration (e.g. fulvestrant), or after other hormones.

Also noteworthy is the fact that no increase in the rate of birth defects has been observed in 1,056 offspring of individuals who received various treatments for a number of different cancers during adolescence.<sup>24</sup> Similarly, among 5,847 offspring of childhood cancer survivors, there appeared to be no excessive risk of non-hereditary cancer.<sup>25</sup> It appears unlikely, therefore, that pregnancy after completion of

*Although the incidence of breast cancer rises with age, approximately one-quarter of newly diagnosed breast cancer patients are pre-menopausal.*

doxorubicin, and cyclophosphamide (FAC), for a median duration of seven months), and observed 33 pregnancies in 25 patients (median interval between the last dose of chemotherapy and pregnancy was 12 months (range 0–87 months)). Ten pregnancies were terminated, two patients had spontaneous abortions, 19 pregnancies resulted in full-term deliveries and two patients were pregnant at the time of the report. No malformations were observed in the 19 offspring.<sup>21</sup>

A report from the Charing Cross Hospital showed a high rate of still-birth and Cesarean section rate for 1,211 patients treated with cytotoxic chemotherapy.<sup>22</sup>

Malamos performed a survey in three hospitals in Athens. Since 1978, 5,798 women with breast cancer were registered; 243 were 35 years old or younger and 21 got pregnant (14 full-term deliveries, seven elective abortions) after treatment consisting of chemotherapy and radiation (median interval from diagnosis to pregnancy, 31 months (range seven to 100 months)). As far as offspring were concerned, no anatomical abnormalities were detected at birth or during follow-up (median, 38 months (range – 12 to 168)).<sup>23</sup>

Adjuvant therapies also frequently include long-term endocrine manipulations.

breast cancer therapy would pose a major direct health threat to the offspring.

### Conclusion and Outlook

Available data do not suggest a negative influence of a subsequent pregnancy on outcome of breast cancer.

The interval between breast cancer diagnosis and pregnancy may have some influence on the further course of breast cancer and patients should be advised to postpone pregnancy for about two years if possible.

Patients with a prior breast cancer generally have a slightly higher incidence of abortion and miscarriages, which may be due to the older age of these patients and possibly to the late effect of breast cancer treatment.

Prior treatment for breast cancer does not seem to increase the incidence of malformation and of development disorders in offspring.

Data on these important topics are still very scarce, and international cooperation will be needed in order to gather more information for the benefit of young breast cancer patients. ■

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