ORIGINAL ARTICLE

Presentation, Management and Outcome of 32 Patients with Pregnancy-Associated Breast Cancer: A Matched Controlled Study

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■ **Abstract:** Pregnancy-associated breast cancer (PABC) is a rare and challenging problem. We sought to describe epidemiology, management and outcome of women in whom breast cancer was diagnosed during pregnancy or within one year after delivery. Thirty-two women with PABC were referred to two European Union oncology centers between 1995 and 2007, 16 during pregnancy and 16 within 1 year after delivery. Data concerning diagnosis, management, delivery and fetal and maternal outcome were recorded. A group of 32 patients (matched controls) presenting with nonpregnancy-associated breast cancer (non-PABC) was matched for age at diagnosis, tumor size and stage to each PABC patient. Differences in outcome between the PABC and non-PABC groups were then assessed. Histological features were similar in both groups, except that estrogen receptor-negative tumors were more common in the PABC group. Three patients received chemotherapy and two others underwent surgery during pregnancy, with no excess toxicity or severe maternal/fetal adverse effects. All children in the PABC group were healthy, except for one exposed to epirubicin in utero and born with rectal atresia. Overall survival was similar in PABC and non-PABC patients ($p = 0.449$). The subgroup of patients with breast cancer diagnosed within one year after delivery showed a shorter time to relapse than controls or patients with gestational cancer ($p = 0.0178$). PABC is a special situation, necessitating individualized, multi-disciplinary management. Prognosis is similar for women with nongestational cancer matched for age and stage though poorer outcome postpartum should be further investigated. ■

Key Words: breast cancer, chemotherapy, outcome, pregnancy, pregnancy-associated breast cancer, prognosis

Pregnancy-associated breast cancer (PABC) is a clinical entity that represents a challenge for physician and patient alike. Because women are postponing childbearing to a later reproductive age, the number of patients with the diagnosis of breast carcinoma during or within 12 months from completion of pregnancy is increasing. The average age of patients with breast carcinoma in pregnancy is between 35 and 38 years (1). With an incidence of 1–3 cases per 10,000 pregnancies, it is the second most frequent malignancy occurring during gestation after cervical cancer (2). However, the impact of pregnancy and lactation on tumor biology on the management and prognosis of patients with breast cancer remains unclear (3). Most investigators define PABC as breast cancer occurring during gestation, lactation or within 1 year from delivery (4). In keeping with this convention and providing comparable data we used this definition and presented epidemiology, management and outcome data on 32 patients with PABC diagnosed in two oncologic centers of the European Union treated in the past 12 years.

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MATERIALS AND METHODS

From 1995 to 2007, 32 patients with PABC (group A) from two medical centers (10 from the Ioannina University Hospital, Ioannina, Greece and 22 from the

University Hospital Motol, Prague, Czech Republic) were included in this retrospective study. Of these 32 patients, 16 were diagnosed during pregnancy (group B) and 16 were diagnosed within 1 year after delivery (group C). We examined patient case sheets and recorded the following data: patient demographic characteristics, stage of pregnancy at the time of diagnosis, histological characteristics of the tumor, management, delivery data and data on neonatal and maternal outcome.

A grade scoring system was established according to the Nottingham grading system. Tumor estrogen and progesterone receptor status were tested immunohistochemically by means of the mouse monoclonal anti-Human ER/PR antibodies (DAKO, Glostrup, Denmark). Hormone receptor status was considered positive when 10% or more of tumor cells exhibited staining. Her2/neu protein expression was tested with the HercepTest Kit (DAKO). Her2/neu 3+ was considered positive; in case of equivocal results (i.e., 2+) gene amplification was sought by means of fluorescent in situ hybridization (FISH).

Each patient with PABC was matched to a patient presenting with nonpregnancy-associated breast cancer (non-PABC) according to age at diagnosis, tumor size, axillary lymph node status and presence or absence of metastatic deposits (matched controls, group D). The patient match was tested by comparing median values for age and tumor size using the Wilcoxon test. Differences in groups A and D concerning histopathological features (such as grade, ER/PR status and Her2/neu status) were tested with the chi-squared test of independence. Survival analysis was performed for time to relapse (TTR) and overall survival (OS) time, and survival curves were constructed according to the Kaplan–Meier product-limit method and compared by the log-rank test.

RESULTS

Patient characteristics and tumor histological parameters are presented in Table 1. The median age at diagnosis was 33.7 years (range 25.9–41.6), average gravidity 2.4 years and parity 1.8 years. The most frequent histological type of malignancy was ductal carcinoma, which occurred in 97% of the PABC patients. The mean size of the primary tumor at diagnosis was 33.9 mm (range 6–100), grade 2.4. Estrogen receptor expression was observed in 36.7% of the gestational tumors and progesterone receptor in 36.7%. Her2/neu protein overexpression or gene amplification was noted in 33.3% of the cases and involved axillary lymph nodes in 65.5% in the PABC group.

Table 1. Characteristics of Group A (Patients with PABC) and Group D (Non-PABC Patients)

	PABC	Non-PABC	p-value
Number of patients	32	32	NS
Age			
Median	33.7	33.6	
Localization			
Right	16	19	NS
Left	16	13	
Histology			
Ductal	31	31	NS
Lobular	0	1	
Ductolobular	1	0	
Size			
<2 cm	6	11	NS
>2 cm	26	21	
Grade			
I	2	3	NS
II	15	14	
III	15	15	
ER			
Positive	11	20	0.03
Negative	19	11	
PR			
Positive	11	17	NS
Negative	19	14	
Her2/neu			
Positive	10	11	NS
Negative	20	20	
Lymph node status			
Positive	18	21	NS
Negative	11	11	
Metastatic disease			
Positive	6	6	NS
Negative	26	26	

PABC, pregnancy-associated breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER/2, Her2/neu.

Table 2 summarizes the management data in breast cancer patients diagnosed during pregnancy. Gestational age was the most important factor in determining the selected treatment procedure. Three patients received chemotherapy (single-agent epirubicin in two patients and FEC in one patient), all during the second and third trimesters of pregnancy. After completion of pregnancy, all patients subsequently received full-dose combination chemotherapy, including alkylators, anthracyclines and taxanes. Two pregnant women underwent surgical resection of their tumor (one a breast-conserving procedure and the other a modified radical mastectomy) with axillary lymph node clearance during the second and third trimesters of pregnancy. The remaining 13 patients underwent surgical extirpation of their tumor (mastectomy in seven and breast-conserving surgery in six) after delivery, with the exception of three patients who harbored metastatic

Table 2. Management of Patients with Breast Cancer Diagnosed during Pregnancy (Group B)

		Therapy					
ID	WP	Surgery	Chemotherapy	Radiotherapy	Hormonal therapy	Regiment description	Surgery
1	33	Yes	Yes			AC × 4, T × 3	RMM/ALND
2	16	Yes (18)	Yes (23)	Yes		E × 4, T × 4	BC/ALND
3	34		Yes			FEC × 3	Not done
4	25	Yes	Yes (33)			E × 2, T × 4, Tr × 35	BC/ALND
5	37	Yes	Yes	Yes		FAC × 4, D × 2, Tr × 60	RMM/ALND
6	16	Yes	Yes		Yes	FAC × 4, D × 3	BC/SLNB
7	18	Yes	Yes			AT × 3, AT × 2	BC/SLNB
8	22	Yes (23)	Yes	Yes	Yes	AC × 4, T × 4	RMM/ALND
9	36	Yes	Yes			AC × 3	BC/ALND
10	24	Yes	Yes (24)			FEC × 3	RMM/ALND
11	11	Yes	Yes	Yes		E × 3, CMF × 3, wT × 9	RMM/ALND
12	12	Yes	Yes	Yes	Yes	EC × 4	BC/ALND
13	33	Yes	Yes	Yes		E × 3, T × 3, CMF × 3	RMM/ALND
14	28	Yes	Yes			EC × 4, T × 4	RMM/ALND
15	22	Yes	Yes			VTr, Cp/Tr, CB/G/Tr	BC/not done
16	20	Yes	Yes			E × 6, T, Vt × 3	M/not done

WP, week of pregnancy of the diagnosis; CHT, chemotherapy; RT, radiotherapy; RMM, radical modified mastectomy; BC, breast-conserving surgery; M, mastectomy; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; A, doxorubicin; E, epirubicin; C, cyclophosphamide; CP, capecitabine; CB, carboplatin; D, docetaxel; F, 5-fluorouracil; G, gemcitabine; M, methotrexate; P, cisplatin; T, paclitaxel; wT, weekly paclitaxel; V, vinorelbine; Tr, trastuzumab.

disease. Breast or chest wall external beam radiotherapy was implemented in six patients after delivery and following termination of lactation. Chemotherapy administered in our three pregnant patients was well-tolerated, with no excess of severe hematologic or nonhematologic toxicities encountered, despite administration of standard doses of cytotoxic drugs. No adverse sequellae were observed in either mother or fetus from the anesthesia or surgical procedures performed in our two pregnant patients.

Table 3 presents management data in patients with breast carcinoma diagnosed within a one-year period after delivery. Management of the malignant disease was significantly more straightforward in these women 3–52 weeks after delivery, as cessation of lactation was the only precaution required regarding potential impact on the offspring. With the exception of one woman lost to follow-up, all patients were managed with surgical extirpation of the primary tumor. Administration of combination chemotherapy and external beam radiotherapy was performed in seven cases.

Information on type of delivery and neonatal and maternal outcome are summarized in Table 4.

Table 3. Management of Patients with Breast Cancer Diagnosed within 1 year after Delivery (Group C)

		Therapy					
ID	WAD	Surgery	Chemotherapy	Radiotherapy	Hormonal therapy	Regiment description	Surgery
17	19	Yes	Yes			CMF × 6	RMM/ALND
18	5	Yes	Yes	Yes		PA × 1, AC × 3	RMM/ALND
19	14	Yes	Yes	Yes		AT × 1, AC × 2, AC × 3	RMM/ALND
20	3					Lost to follow-up	
21	36	Yes	Yes	Yes		FAC × 4, T × 1, D × 2, AV × 3	RMM/ALND
22	12	Yes	Yes	Yes	Yes	AC × 4, T × 4, D × 6	RMM/ALND
23	8	Yes	Yes	Yes		AC × 4, T × 4	RMM/SLNB,ALND
24	34	Yes	Yes	Yes		AC × 4, T × 10, VG × 4	BC/SLNB,ALND
25	32	Yes	Yes			AC × 3, AT × 2, T × 1	RMM/ALND
26	52	Yes	Yes	Yes	Yes	AT × 3, TAC × 3	RMM/ALND
27	16	Yes	Yes	Yes		AT × 3	BC/ALND
28	42	Yes	Yes			FAC × 6	RMM/ALND
29	20	Yes	Yes	Yes	Yes	E × 3, T × 3, CMF × 3	RMM/ALND
30	32	Yes	Yes			FEC × 6	RMM/ALND
31	8	Yes	Yes			CMF × 6	RMM/ALND
32	12		Yes			ET × 6	Biopsy

WP, week of pregnancy of the diagnosis; CHT, chemotherapy; RT, radiotherapy; RMM, radical modified mastectomy; BC, breast-conserving surgery; M, mastectomy; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; A, doxorubicin; E, epirubicin; C, cyclophosphamide; CP, capecitabine; CB, carboplatin; D, docetaxel; F, 5-fluorouracil; G, gemcitabine; M, methotrexate; P, cisplatin; T, paclitaxel; wT, weekly paclitaxel; V, vinorelbine; Tr, trastuzumab.

Table 4. Outcome of the Patients and Newborns

ID	Delivery/abortion (gestational age)	Birth weight (g)	Newborn outcome	Mother outcome (weeks)	BRCA testing
Group B					
1	Cesarean section (33)	1,890	Normal	Alive	Negative
2	Cesarean section (35)	2,540	Rectal atresia	Alive	Sent
3	Cesarean section (36)	2,775	BRCA 1	Dead (17)	BRCA 1
4	Spontaneous (39)	3,740	Normal	Alive	BRCA 1
5	Spontaneous (40)	3,090	Normal	Relapse (22)	Sent
6	Abortion (18)	NA	NA	Alive	Sent
7	Abortion (20)	NA	NA	Alive	Sent
8	Abortion (24)	NA	NA	Alive	Sent
9	Spontaneous (36)	2,840	Jaundice	Alive	Sent
10	Ongoing	Ongoing	Ongoing	Alive	Sent
11	Spontaneous (11)	NA	NA	Alive	Not checked
12	Abortion (12)	NA	NA	Alive	Not checked
13	Spontaneous (36)	3,150	Normal	Alive	Not checked
14	Spontaneous (36)	2,500	Normal	Alive	Not checked
15	Cesarean section (39)	3,300	Normal	Alive	Not checked
16	Spontaneous	Not available	Normal	Dead (126)	Not checked
Group C					
17	Spontaneous	3,600	Normal	Relapse (435)	BRCA 1
18	Cesarean section	Not available	Normal	Dead (62)	Not checked
19	Spontaneous	Not available	Normal	Dead (258)	Negative
20	Spontaneous	Not available	Normal	Dead (14)	Not checked
21	Spontaneous	3,360	Normal	Dead (55)	BRCA 1
22	Spontaneous	3,130	Normal	Relapse (162)	BRCA 1
23	Cesarean section	2,280	Normal	Alive	Not checked
24	Spontaneous	Not available	Normal	Dead (241)	Sent
25	Spontaneous	3,500	Normal	Alive	Not checked
26	Spontaneous	3,380	Normal	Alive	BRCA 2
27	Spontaneous abortion	NA	NA	Alive	Sent
28	Spontaneous	4,870	Normal	Alive	Sent
29	Spontaneous	3,800	Normal	Dead (133)	Not checked
30	Cesarean section	Not available	Normal	Dead (309)	Not checked
31	Spontaneous	3,700	Normal	Alive	Not checked
32	Spontaneous	3,500	Normal	Dead (171)	Not checked

NA, not applicable.

Eighteen of 32 patients were tested for BRCA mutation. Of eight patients with available test results, six (75%) were positive for germline mutations. Abortions occurred in 4/32 women, with three in group B (cancer during pregnancy). Spontaneous birth occurred in 19 patients, whereas in seven patients a healthy infant was delivered by means of a scheduled cesarean section. The median newborn weight was about 3 kg (range 1,890–4,870 g): their health being normal in 23 of 25 deliveries of available data. One baby presented transient jaundice and one rectal atresia; the one with the atresia was born to a mother who received single-agent epirubicin starting on the 23rd gestational week. Twelve of 32 women had malignant relapse and 10 died at a median follow-up of 142 months. Three relapses occurred in group B and nine in group C, where the number of deaths was two and eight in groups B and C, respectively.

Groups A (32 women with PABC) and D (matched controls) were found to be well matched for age, stage, tumor size, grade, progesterone receptor and HER2 status though estrogen receptor-negative tumors were more frequent in women with PABC. Twelve malignant relapses and nine deaths occurred in group D. Median follow-up times for groups A and D were 142.5 and 214.8 weeks, respectively. No statistically significant difference in TTR was found between groups A and D ($p = 0.143$, Fig. 1). The median TTR in group A was 165, whereas in group D the median was not reached. When group A was divided into group B (breast cancer during pregnancy) and group C (breast cancer within 1 year after delivery), a statistically significant worse prognosis was noted in group C (median TTR not reached) but not in group B (median TTR 51.5) ($p = 0.0178$, Fig. 1). No statistically significant differences, however, were observed in OS between groups A (median OS 309) and D (median OS 449) ($p = 0.449$, Fig. 2) or among groups B (median OS not reached), C (median OS 258) and D (median OS 449) ($p = 0.468$).

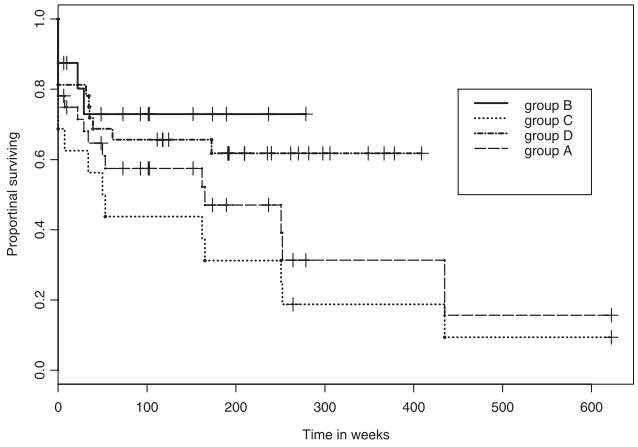

Figure 1. Time-to-relapse curves in group A (patients with PABC), group B (patients with breast cancer during pregnancy), group C (patients with breast cancer within 1 year from delivery) and group D (controls with non-PABC).

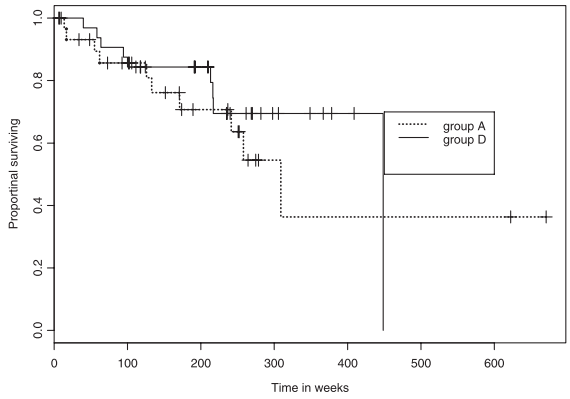

Figure 2. Overall survival curves for groups A (patients with PABC) and D (controls with non-PABC).

DISCUSSION

There is a minor shift towards a lower incidence of breast cancer in the group of women aged below 40 years recorded between the years 1985 and 2003 in the Czech Republic. In 1985, there were 6.7% of all patients with breast cancer under 40 years, whereas in 2003 the figure was 3.4% of all patients (5). On the other hand, the average age of primiparous women has shifted dramatically towards older age. In 1985, the average age of primiparous and multiparous women was 22.3 and 24.6 years, respectively; the same parameters in 2003 were 25.9 and 28.1 years. This means that as childbearing is delayed until older age, in which breast cancer incidence is markedly higher, the risk of breast carcinoma associated with pregnancy is expected to increase.

According to the literature, there is a comparable representation of the histological types of breast carcinoma in pregnant and nonpregnant women (6–8), whereas positive regional lymph nodes were found more often in pregnant women (59–83%) than in nonpregnant women (38–54%) (9). In our PABC patient group 65.5% harbored node-positive tumors, a figure lying in the high end of reported incidence of axillary involvement in breast cancer series. Some published studies have reported a higher frequency of estrogen-negative tumors. Bonnier et al., for instance, reported that 42% of gestational tumors were estrogen receptor-negative as compared with 21% in their control group. Other studies, which have focused on tumor expression of Her2/neu protein, reported that the number of positive Her2/neu tumors in pregnancy was greater (58%) when compared with a control group (10–25%) (10). Our data seem to confirm the high incidence of estrogen receptor-negative tumors (59%), which is probably a biological characteristic of breast cancer affecting most young women rather than pregnant women per se. On the contrary, we observed Her2/neu overexpression in less than a third of our pregnant women, a finding consistent with quoted incidences in non-PABC populations.

Because treatment is strictly individual, the essential part of the treatment strategy in every case of gestational cancer should be based on a good communication with the patient and family. Co-operation of oncosurgeons, oncologists, radiotherapeutists, pathologists and perinatologists is a key issue for successful, individualized patient management. To our knowledge, there is no evidence indicating better outcome through the termination of pregnancy (11). Radical modified mastectomy with axillary lymphadenectomy is favored because of the associated possibility to omit radiotherapy during pregnancy. Despite a propensity for greater tumor size at diagnosis, probably because of diagnostic delays, breast-conserving surgery can be performed when indication criteria are fulfilled (12). There are varying opinions on the use of sentinel lymph node biopsy (SLNB) with ^{99m}Tc. Kaufmann et al. do not recommend the usage of radioisotope because of unknown teratogenic effects (13), whereas Gentilini et al. propose that the maximal radiation dose of 0.00043 Gy associated with the procedure is well below the threshold teratogenic dose (14). SLNB with blue dye can avoid the risks of radiation.

Chemotherapy used in the first trimester is associated with an increased risk of miscarriage or congenital

Table 5. Literature Review of Case–Control Series of Patients with PABC

Author	Years	PABC	Cancer during pregnancy	Cancer after delivery	Matched patients	Outcome
Petrek, 1991	1960–1980	56	56		166	No survival difference
Zemlickis, 1992	1958–1987	118	118		269	No survival difference
Ishida, 1992	1970–1988	192	72	120	192	Worse prognosis in PA group
Chang, 1994	1979–1988	21			199	No survival difference
Nugent, 1995	1970–1980	19	19		157	No survival difference
Lethaby, 1996	1976–1985	20	10	10	362	Worse survival when diagnosed during lactation, no difference in pregnant patients
Bonnier, 1997	1960–1993	154	92	62	308	Worse prognosis in PA group
Ibrahim, 2000	1992–1996	72	72		216	No survival difference
Zhang, 2003	1957–1990	88			176	No survival difference
Halaska, 2008	1995–2007	32	16	16	32	No survival difference

PABC, pregnancy-associated breast cancer.

malformation of the fetus. However, during the second and third trimesters, relatively low risks for the fetus were reported (15,16). Berry et al.'s prospective study, which used a standard protocol of chemotherapy in 24 pregnant patients after the first trimester (FAC: fluorouracil 1,000 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2), found only three cases of preterm delivery (15). Another prospective patient cohort study included 57 women treated with FAC regimen. One child had Down's syndrome and two had congenital abnormalities (club foot, congenital bilateral ureteral reflux) (17). A retrospective study described similar results in 28 patients treated with chemotherapy in the period after the first trimester of pregnancy (18), whereas a study with 40 patients treated with antracyclines or cyclophosphamide after the first trimester reported no neonatal or maternal complications (19). Thus far, not enough evidence has been accumulated on taxane use in pregnancy though fetal toxicity has been noted in animal models. Nevertheless, there were no complications observed in individual human cases, with the sole exception of transitory anhydramnios (20,21). When cytostatics are used during pregnancy, it is important to plan delivery two to three weeks after the last cycle of chemotherapy in order to avoid maternal and fetal myelosuppression. A relation of rectal atresia (which occurred in one child in our series) to exposure to epirubicin, a highly lipophilic compound, during the 2nd trimester of pregnancy is highly improbable. Longer follow-ups of children exposed to chemotherapy in utero are needed to determine late effects on normal tissues. Breastfeeding is contraindicated during chemotherapy because most cytostatics are released into the milk, a fact confirmed in a recent international meeting of experts outlining therapeutic guidelines (22).

As summarized in Table 5, a majority of the authors found no difference between patients with PABC and patients with nongestational breast cancer matched for stage and age (23–31). Accordingly, an unfavorable prognosis has been attributed to late diagnosis rather than distinct tumor biological behavior. Few studies have specifically compared subgroups of PABC patients (e.g., those with breast cancer during pregnancy and those with breast cancer diagnosed within 1 year after delivery). Comparing OS in patients with breast cancer during pregnancy, lactating women with breast cancer and matched controls, Lethaby et al. found a worse prognosis in patients with cancer diagnosed during lactation (27). In our series a trend toward a worse prognosis for patients diagnosed with breast cancer within 1 year after the delivery was noted, though this did not translate into an OS difference, probably because of the small sample size. This finding, if confirmed in subsequent work in a larger series, could reflect persistence of diagnostic delays, distinct tumor biology, host immune dysfunction or an aberrant hormonal milieu. Data registration is needed to expand clinical experience on which basic research could be based and lead to a better understanding of tumor and host biology in gestational cancer.

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