F, V & V in ObGyn, 2011, 3 (3): 183-188

Original paper

Postpartum breast cancer behaves differently

N. Van den Rul, S.N. Han, K. Van Calsteren, P. Neven, F. Amant

Multidisciplinary Breast Centre, Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium.

Correspondence at: Frederic Amant, Gynaecological Oncology, Department of Obstetrics and Gynaecology, University Hospitals Leuven, B-3000 Leuven, Belgium.
E-mail: frederic.amant@uzleuven.be
F. Amant is Sr. Clinical Investigator for the Research Fund-Flanders

Abstract

Background and Aim: Previous studies suggest a worse prognosis for postpartum breast cancer (PPBC) diagnosed within the first 12 months following delivery. We investigated this hypothesis in our setting through a retrospective pilot study.
Methods: A retrospective multicentre paired case-control study of breast cancer patients diagnosed under age 45 from the UZ Leuven database or affiliated centres. We compared disease outcome of women with a PPBC and those without a pregnancy associated breast cancer (PABC). They were matched for the following prognostic markers: age at diagnosis, tumour type, characteristics and stage. Kaplan-Meier statistics were applied for overall and disease free survival.
Results: 53 PPBC cases were matched with 103 controls. All PPBC patients were diagnosed with an invasive ductal carcinoma. Axillary lymph nodes were involved in 56.6% of cases and 13% were primary metastasized at diagnosis. A third was triple-negative and another third was HER-2-positive.The 5-year overall survival was 60% and 84% respectively for PPBC cases and control group. 5-year disease free survival was respectively 53% and 68%.
Conclusions: We confirm that postpartum breast cancer behaves more aggressively than the matched non-PABC group. Longer follow-up and extension of the study group are necessary to confirm these findings.

Key words: Breast cancer, Prognosis, Postpartum, Matched case-control study

Introduction

PABC is defined as breast cancer diagnosed during pregnancy or within one year following delivery. Breast cancer is the most common pregnancy-associated cancer (Van Calsteren *et al.,* 2010). Between 0.2 and 3.8% of all breast cancer patients are diagnosed during pregnancy (DiFronzo and O'Connell, 1996) and 1 in 3000 pregnancies is affected by a breast cancer (du Bois *et al.,* 1993). Incidence is increasing due to a higher maternal age at pregnancy (Nettleton *et al.*, 1996; Andersson *et al.*, 2009, Han *et al.,* 2010).

The discussion on pregnancy as an independent adverse prognostic factor in PABC is still ongoing. Several series have shown that PABC patients have more advanced disease. Possible explanations for this observation include diagnostic delay (due to physiologic alterations), treatment delay (due to fear for treating pregnant cancer patients) and also a more aggressive tumour biology (Ishida *et al.*, 1992).

In case of breast cancer during pregnancy, current retrospective studies show that maternal prognosis and survival is similar to non-pregnant patients when matched for age and stage (Stensheim *et al.,* 2009). The three years survival rate for pregnant patients with stages I to III is similar compared to non-pregnant patients.

On the other hand, patients diagnosed with breast cancer in the postpartum, may have a worse outcome, even when adjusted for age and extent of disease. (Lethaby *et al.,* 1996; Stensheim *et al.,* 2009). Our current study focuses on outcome of PPBC exclusively. We compared (epidemiology and) disease

outcome of PPBC after delivery or abortion with matched controls of non-PABC. The hypothesis was that diagnosis in the postpartal period negatively affects prognosis of breast cancer. We report results of this study and review the available literature.

Materials and methods

Study set-up

This is a retrospective, multicentre paired case-control study of breast cancers diagnosed under age 45 between January 2000 and January 2011 in UZ Leuven or affiliated hospitals. Eligible cases were patients diagnosed with an invasive breast cancer in the first year after pregnancy, irrespective of gestational age. The control group consisted of women with non-PABC breast cancer. Each case was matched for age at diagnosis (with a maximum deviation of 2 years), tumour type, characteristics and stage. Half of the control group consisted of parous and half of nulliparous women. For cases in which more than one control patient matched the PPBC patient, selection was based on conformity of hormonal receptor status and the closest date of diagnosis. It was impossible to match for hormonal receptors because of the scarcity of young breast cancer patients. Because of the prognostic importance of triple-negative receptors, matching for these receptors did take place.

The following data were collected: age at diagnosis, parity, date of delivery, tumour type, adjuvant treatment, date and type of recurrence, and date of last follow-up. The project was approved by the local institutional review board and is a part of the Cancer in Pregnancy research project (www.cancerinpregnancy.org).

Tumour stages are defined between 0-IV based on American Joint Committee on Cancer Staging, 7th edition (Edge *et al.*, 2010), and determined according to the pathological staging in adjuvant and metastatic settings. In neo-adjuvant settings the stage was determined according to the clinical staging.

Table I. — Characteristics of PPBC[1] patients and control breast cancer patients.

Characteristics	PPBC group (n = 53)	Control group (n = 103)
Age (y)		
Minimum	26	25.5
Maximum	42	42
Mean	32.9	33.9
Median	32	33
Weeks after pregnancy		
Mean	23.9	Not applicable
Median	26	
Tumour histology (%)		
IDA	53 (100)	103 (100)
Other	0	0
Stages (%)		
I	12 (22.6)	26 (25.2)
II	21 (39.6)	39 (37.9)
III	13 (24.5)	25 (24.3)
IV	7 (13.3)	13 (12.6)
Axillary lymph node involvement at diagnosis (%)	30 (56.6)	57 (55.3)
Distant metastasis (%)	13.3	12.6
Hormonal receptors[2] (%)		
PPN	12 (22.7)	41 (39.9)
PNN	4 (7.5)	6 (5.8)
NPN	2 (3.8)	1 (0.9)
PNP	1 (1.9)	1 (0.9)
NNP	8 (15.1)	12 (11.7)
PPP	6 (11.3)	11 (10.7)
NNN	16 (30.2)	29 (28.2)
Unknown	4 (7.5)	2 (1.9)

[1]*PPBC: Postpartum-associated breast cancer*
[2]*Hormonal receptors: 1st location defines estrogen receptor, 2nd location progesterone receptor, 3rd location HER-2 amplification. P = positive, N = negative. Eg: NNN: triple negative breast cancers.*

Statistical analysis

The overall survival functions of the two groups of breast cancer patients were analyzed using the Kaplan-Meier method. The variable used to assess the prognosis was the overall length of survival, which is defined as the interval between breast cancer diagnosis and the patient's death. P-values were set for differences in prognosis between the PPBC-group and the control groups. Analysis was performed using MedCalc® (version 11.5.1.0).

Literature

Literature was searched for in scientific databases (Medline, Cochrane, Embase) with following search terms: breast cancer, premenopausal, pregnancy-associated breast cancer, lactation, tumour biology, pregnancy, survival, and outcome.

Results

Characteristics

Out of 1046 breast cancer patients in the UZ Leuven database, aged 45 or younger at diagnosis, 41 PPBC patients were identified. There were another 15 PPBC patients from local hospitals that

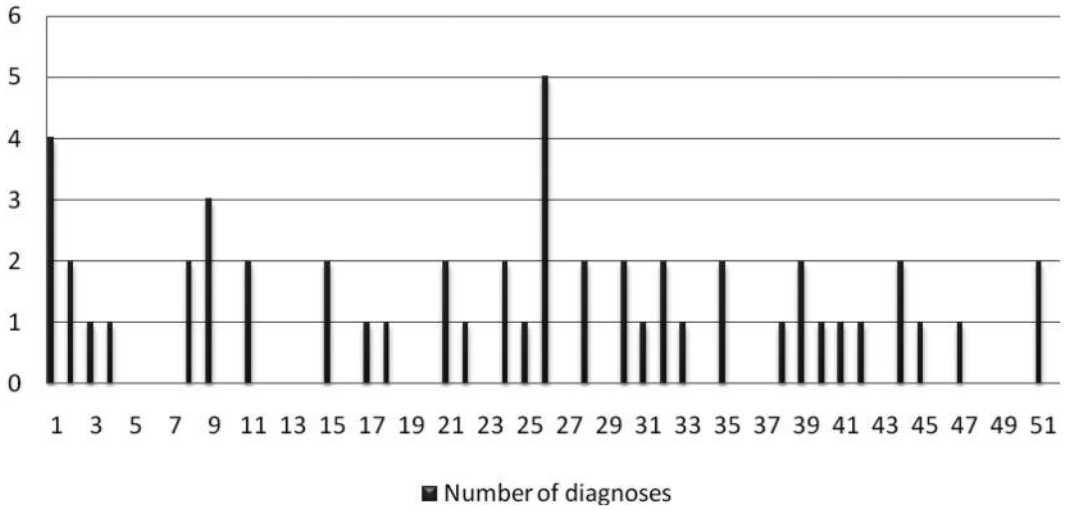

Fig. 1. — Number of breast cancer diagnoses within weeks after delivery/abortion

could be included. In total, the study group consisted of 53 PPBC patients. One patient was excluded because she had a breast sarcoma which couldn't be matched for in the control groups. Two other patients were excluded because follow-up data were unavailable. 4 patients were diagnosed within one year after spontaneous abortion, 49 after delivery.

Based on matching criteria, 103 women without pregnancy association, were selected as controls. 3 patients couldn't be matched for with a parous or a nulliparous woman. Nevertheless, their data were used in the results. Figure 1 illustrates the distribution of the time between delivery or abortion and the breast cancer diagnosis in the PPBC group. Table I shows the patient characteristics. The PPBC group is nearly equal compared to the control group concerning age at diagnosis, axillary lymph node involvement, presence of distant metastasis at diagnosis and tumour staging. Hormone receptor status differed between PPBC group and controls, but triple negative tumours were equal in study group and controls. There were less estrogen and progesterone positive tumours in the PPBC-group. Tumour histology was invasive ductal adenocarcinoma in all patients.

Overall survival

In Table II, the 2-year and 5-year survival of PPBC patients is compared to those of the controls. 5-year survival was 60% in the PPBC group survived compared to 84.7% in the control group. In Table III, survival per stage is presented.

The Kaplan-Meier survival estimator was used because of a difference in follow-up periods between the patients (Fig. 2 and 3). The P-value of this Kaplan-Meier equation is 0.0127 between PPBC group and controls.

Table II. — Comparison of survival between PPBC[1] patients and controls with same prognostic markers and with a group of premenopausal women.

	PPBC[1] group n = 53	**Control group** n = 103	**Karithala *et al.* premenopausal women** n = 268
2-year survival	81.4% (35/43)	93% (93/100)	
5-year survival	60% (18/30)	84.3% (59/70)	81.1%
Disease free survival (5 y)	53.3% (16/30)	67.7% (50/74)	65.2%

[1]*PPBC: Postpartum-associated breast cancer*

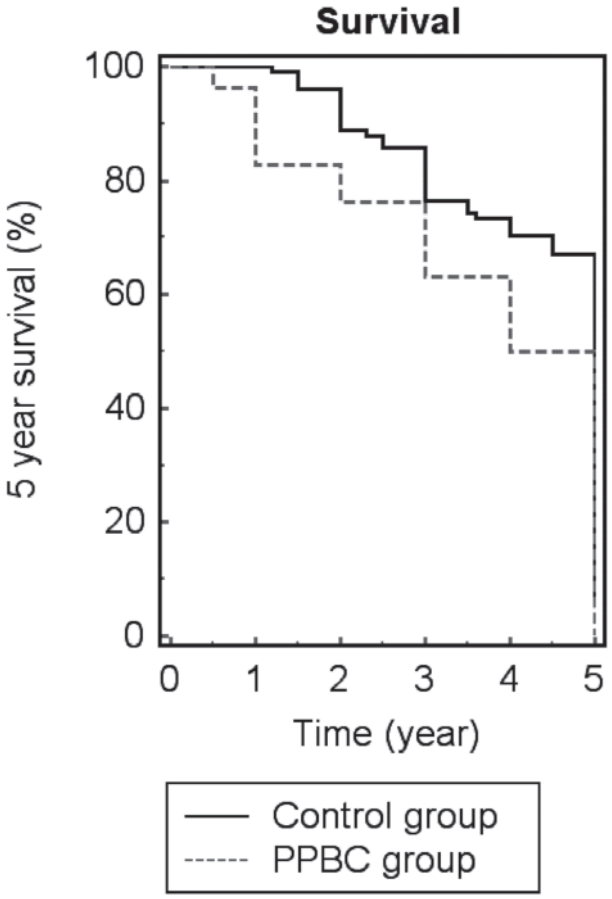

Fig. 2. — Kaplan-Meier overall survival functions for postpartum-associated breast cancer (PPBC) and the corresponding controls (P-value = 0.0127).

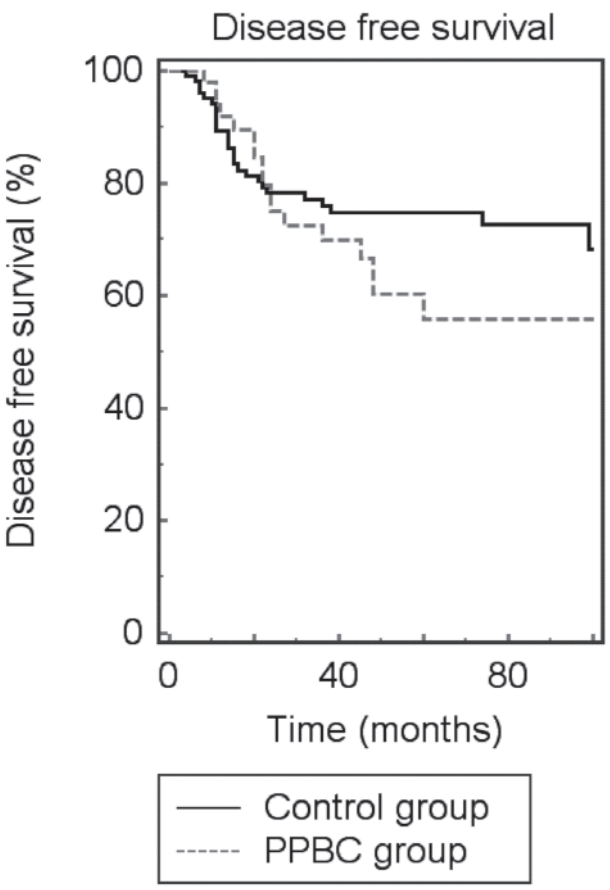

Fig. 3. — Kaplan-Meier graphs regarding DFS of breast cancer in PPBC compared to controls (P-value = 0.2347).

[1] *DFS: Disease free survival*

[2] *PPBC: Postpartum-associated breast cancer*

Discussion

In 1943, Haagensen *et al*. reported that breast cancer which developed during pregnancy or lactation tended to be inoperable. This concept ruled for many years. White concluded in 1954 that the outcome of 700 PABC patients was worse than for their non-pregnant matches. He identified delayed diagnosis and treatment as the main causes. These, together with a more aggressive disease, were considered by Ishida *et al*. (1992) to be responsible for the worse prognosis based on 192 PABC patients compared to 191 controls of the same age. These authors found that the incidence of axillary lymph node involvement and negative hormone receptor status was higher in the PABC group than among the controls. The recent study of Rodriguez *et al*. (2008) based on 797 PABC patients (610 PPBC) and 4177 controls, found that pregnancy significantly (P-value = 0.046) worsened the breast cancer prognosis.

Most investigations concerning the overall survival of PABC patients have concluded a worse prognosis compared to non-pregnant controls. They all focused on pregnancy- and postpartum-related breast cancer. Data per subgroup (during pregnancy or PPBC) were not always available. The aim of this study was to examine the subgroup of PPBC.

The PPBC group consists of 53 patients. 56.6% of them had at least one axillary lymph node involved. Also 13% of patients had metastasis when diagnosed with breast cancer. This confirms findings in other studies who established that a larger proportion of pregnancy-associated cases are more advanced at diagnosis. Compared to the overall breast cancer population (SEER database, 2010) this is high. In the overall breast cancer population metastasized breast cancer at diagnosis accounts for 5%.

In this study a poor prognosis for the overall survival of PPBC patients compared to control patients is shown. Also when compared to literature (Karithala *et al*., 2010) concerning premenopausal women, the PPBC group has a worse outcome regarding 5 year survival and disease-free survival. In the Kaplan-Meier survival analyses (Fig. 2 and 3), a significant difference was shown (P-value = 0.0127). Diagnosis in the postpartal period is to be considered an independent negative prognostic factor for breast cancer survival. The PPBC group appears to have an

Table III. — Proportion of women who died within 5 years according to stage.

Stage	PPBC[1] Total	PPBC[1] Died (%)	Control group Total	Control group Died (%)
I	6	2 (33.3)	14	0 (0)
II	10	3 (30.0)	31	3 (14.3)
III	11	5 (45.4)	19	4 (21.1)
IV	3	2 (66.6)	6	4 (66.0)
Limited follow-up	23		33	

[1]*PPBC: Postpartum-associated breast cancer*

increased risk of recurrence, certainly from 2 years after diagnosis (P = 0.2347).

Multiple theories have been suggested to explain the poor prognosis of postpartum-associated breast cancer. One explanation for the worse prognosis is the increased estrogen level in the body during and shortly after pregnancy. Estrogens are a known breast cancer-promoting factor (Tretli *et al*., 1988). Another explanation suggested by Moreira *et al*. (2010) is the difficulty of diagnosis in these young patients because of the characteristics of mammary tissue. Stensheim *et al*. (2009) points out that a combination of hormonal changes, immunologic suppression and increased vascularisation during pregnancy could play a part in this. Lambe *et al*. (1994) hypothesize that stimulation of the growth of cells that have undergone the early stages of malignant transformation could promote breast cancer development. On the other hand, primiparous women are getting older in general, which means they have more chances of developing cancer (Halaska *et al*., 2009). Bonnier *et al*. (1997) established that a higher frequency of estrogen negative breast tumours occurs in these young women, of which is known that they have a worse prognosis. Some reports suggest that the interval between diagnosis and parturition could be an important factor for prognosis. Guinee *et al*. (1994) proposed that the shorter the interval between pregnancy and diagnosis, the worse the prognosis of breast cancer was. This needs further investigation. In this respect, Asselin-Labat *et al*. (2010) suggested that the transient increase in mammary stem cells during pregnancy which are highly responsive to steroid signalling despite the lack of estrogen and progesterone receptors, could be responsible for this change in aggressiveness of the tumour and therefore the worse prognosis. This is probably mediated through a paracrine pathway from RANK ligand. It has been studied in preclinical mouse models and needs to be studied in humans.

The increased intrinsic aggressiveness of breast malignancies in the postpartum period is probably to be searched on molecular and cellular level. Xu *et al*. (2009) suggest that the aberrant p63, a tumour suppressor gene, and WT-1 expression on myoepithelial cells in the breast cancer cells of PABC is associated with tumour aggressiveness and invasiveness.

Others suggest a pathological tissue remodelling and mammary gland involution in the breast during postpartum which would promote metastasis (Lyons *et al*., 2009; Schedin *et al*., 2007).

The findings of this pilot study should be interpreted with caution. This is a small subgroup of patients, questioning the differences in disease free survival. Another limitation is that only 30 of 53 study patients have been in follow-up for over 5 years. Also no correction for proximity in time to delivery or abortion was made. No correction for differences in treatment were made. Further, due to the retrospective nature of the study, not all risk factors of interest (such as breastfeeding, menarche, age at first pregnancy) were available. Differences in hormone receptor status between study group and controls is considered to be another limitation, for example the studied group contains 28.3% of Her2-amplificated tumours compared to 23.3% in the control group.

In the future there should be a longer follow-up of the PPBC group and the controls, the groups should be expanded allowing univariate and multivariate analyses.

Conclusion

This pilot study shows that women diagnosed with breast cancer during the postpartum period have a worse outcome. It appears that diagnosis of breast cancer in the postpartum period is a negative prognostic marker.

A longer follow-up period and a larger study group are necessary to confirm these findings. Such a study is planned within the frame of the cancer in pregnancy project (www.cancerinpregnancy.org).

Acknowledgements

The authors would like to thank the affiliated hospitals for participation and patient accrual in the current study:
– Dr G. Orye, Jessa Ziekenhuis Hasselt
– Dr A. Roelstraete, OLV Ziekenhuis Aalst
– Dr C. De Rop, Imeldaziekenhuis Bonheiden
– Dr H. Van Den Bulck, Imeldaziekenhuis Bonheiden
– Dr A. Bols, Algemeen Ziekenhuis Brugge
– Dr J. Vlasselaer, Ziekenhuis Oost-Limburg Genk
– Dr P. Vryens, Sint Augustinusziekenhuis Veurne
– Dr JL. Canon, Centre Hopsitalier Notre Dame-Reine Fabiola Charleroi
– Dr A. Pastrijn, St-Pierre Bruxelles
– Dr R. Van Dijck, Heilig Hartziekenhuis Leuven

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