

A retrospective clinical study of patients with pregnancy-associated breast cancer among multiple centers in China (CSBrS-008)

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Abstract

Background: Pregnancy-associated breast cancer (PABC) is a special type of breast cancer that occurs during pregnancy and within 1 year after childbirth. With the rapid social development and the adjustment of reproductive policies in China, the average age of females at first childbirth is increasing, which is expected to lead to an increase in the incidence of PABC. This study aimed to accumulate clinical experience and to investigate and summarize the prevalence, diagnosis, and treatment of PABC based on large multicenter samples in China.

Methods: According to the Chinese Society of Breast Surgery, a total of 164 patients with PABC in 27 hospitals from January 2016 to December 2018 were identified. The pregnancy status, clinicopathological features, comprehensive treatment methods, and outcomes were retrospectively analyzed. Survival curves were plotted using the Kaplan-Meier method.

Results: A total of 164 patients of PABC accounted for 0.30% of the total number of cases in the same period; of which, 83 patients were diagnosed during pregnancy and 81 patients during lactation. The median age of PABC was 33 years (24–47 years). Stage I patients accounted for 9.1% (15/164), stage II 54.9% (90/164), stage III 24.4% (40/164), and stage IV 2.4% (4/164). About 9.1% (15/164) of patients were luminal A. Luminal B patients accounted the most (43.3% [71/164]). About 15.2% (25/164) of patients were human epidermal growth factor receptor 2 (Her-2) overexpression and 18.9% (31/164) of patients were triple-negative breast cancer. For pregnancy breast cancer, 36.1% (30/83) of patients received direct surgery and 20.5% (17/83) received chemotherapy during pregnancy. About 31.3% (26/83) chose abortion or induction of labor. The median follow-up time was 36 months (3–59 months); 11.0% (18/164) patients had local recurrence or distant metastasis and 3.0% (5/164) died.

Conclusions: It is safe and feasible to standardize surgery and chemotherapy for PABC.

Keywords: Pregnancy-associated breast cancer; Clinicopathological feature; Treatment; Prognosis

Introduction

Pregnancy-associated breast cancer (PABC) is a special type of breast cancer that occurs during pregnancy and within 1 year after childbirth. PABC can be divided into PABC during pregnancy and postpartum PABC.^[1] PABC accounts for 0.2% to 3.8% of all breast cancers, including 10% to 20% of all breast cancers in patients <30 years.^[2–4] With the rapid social development and the adjustment of reproductive policies in China, the average age of females at first childbirth is increasing, which is expected to lead to an increase in the incidence of PABC. A total of 164 cases of PABC in 27 hospitals were collected in this study through the Chinese Society of Breast Surgery to investigate the prevalence of PABC in

China and to accumulate and summarize the experience with the clinical diagnosis and treatment of PABC in China.

Methods

Clinical data

A total of 60,998 newly diagnosed breast cancer patients were treated at 27 hospitals nationwide between January 2016 and December 2018, including 164 patients with pathologically confirmed PABC, accounting for 0.3% of the total number of breast cancer cases during the same

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period. Among these PABC cases, 83 occurred during pregnancy, including 14 cases during early pregnancy (<12 weeks of gestation), 38 cases during mid-pregnancy (12–28 weeks of gestation), and 31 cases during late pregnancy (>28 weeks of gestation) and 81 occurred during lactation.

Follow-up

Follow-up visits were conducted via outpatient visits or telephonic interviews. The follow-up deadline was November 31, 2020, and the median follow-up duration was 36 months (3–59 months). Survival curves were plotted based on the follow-up data. Disease-free survival (DFS) was defined as the time from the pathological diagnosis of PABC to relapse or metastasis. Overall survival (OS) was defined as the interval between the pathological diagnosis of PABC and the date of death or the last follow-up.

Statistical methods

The results were analyzed using IBM Statistics SPSS 20 (IBM Corp., Armonk, NY, USA). Survival curves were plotted using the Kaplan-Meier method.

Results

Clinical and pathological characteristics

A total of 164 patients with a median age of 33 years (24–47 years) were included in this study. Among them, 15 (8.2%) had a family history of malignancies and ten (5.4%) had a family history of breast cancer. There were six patients (3.7%) in stage 0, 15 (9.1%) in stage I, 51 (31.1%) in stage IIa, 39 (23.8%) in stage IIb, 27 (16.5%) in stage IIIa, 8 (4.9%) in stage IIIb, five (3.0%) in stage IIIc, four (2.4%) in stage IV, and nine (2.4%) in an unknown stage. There were 54 cases (33.0%) of N0, 71 cases (43.3%) of N1, 19 cases (11.6%) of N2, and five cases (3.0%) of N3. Invasive ductal carcinoma of the breast was the most common pathological type, accounting 71.3% (117/164). There were two cases (1.2%) of histological grade G1, 51 (31.1%) of G2, and 49 (30.0%) of G3. There were 15 cases (9.1%) of luminal A type, 48 (29.3%) of luminal B type (Her2–), 23 (14.0%) of luminal B type (Her2+), 25 (15.2%) of human epidermal growth factor receptor 2 (Her-2)-positive breast cancer, and 31 (18.9%) of triple-negative breast cancer (TNBC). The clinicopathological characteristics of the patients are summarized in Table 1.

Outcomes of patients with PABC during pregnancy

The 83 patients with PABC during pregnancy included 14 patients in early pregnancy, 38 in mid-pregnancy, and 31 in late pregnancy. All patients with PABC in early pregnancy chose surgical or medical abortion to terminate their pregnancy. Among the patients with PABC in mid-pregnancy, 12 patients chose medical abortion and 26 delivered successfully. All patients with PABC in late pregnancy delivered successfully. All neonates had normal

Table 1: The clinicopathological characteristics of the 164 patients with PABC.

Characteristics	Number of patients	Percentage (%)
Family history		
Yes	10	6.1
No	154	93.9
Stage		
Stage 0	6	3.7
Stage I	15	9.1
Stage II		
IIa	51	31.1
IIb	39	23.8
Stage III		
IIIa	27	16.5
IIIb	8	4.9
IIIc	5	3.0
Stage IV	4	2.4
Unknown	9	5.5
T stage		
Tis	13	7.9
T0	1	0.6
T1	29	17.7
T2	82	50.0
T3	19	11.6
T4	11	6.7
Unknown	9	5.5
N stage		
N0	54	33.0
N1	71	43.3
N2	19	11.6
N3	5	3.0
Unknown	15	9.1
Histopathology subtype		
Invasive ductal carcinoma	117	71.3
Invasive lobular carcinoma	3	1.8
Others	44	26.8
Histological grade		
G1	2	1.2
G2	51	31.1
G3	49	30.0
Unknown	62	37.8
Immunohistochemistry		
ER positive	86	52.4
PR positive	70	42.7
Her2+	48	29.3
Ki-67 positive (<20%)	25	15.2
Ki-67 positive (≥20% and <40%)	48	29.3
Ki-67 positive (≥40%)	71	43.3
Unknown	20	12.2
Molecular subtype		
Luminal A	15	9.1
Luminal B (Her2–)	48	29.3
Luminal B (Her2+)	23	14.0
Her2+	25	15.2
TNBC	31	18.9
Unknown	22	13.4

ER: Estrogen receptor; PABC: Pregnancy-associated breast cancer; PR: Partial remission; TNBC: Triple-negative breast cancer.

Apgar scores, indicating good development, with 23 neonates weighing >2500 g and 21 neonates weighing <2500 g.

Treatment for PABC during pregnancy

Among the 83 patients with PABC during pregnancy, 30 (36.1%) underwent surgical treatment during pregnancy, including eight who received breast-conserving surgery and 22 who received modified radical mastectomy; 17 (20.5%) received chemotherapy during pregnancy, including six who received neoadjuvant chemotherapy and 11 who received adjuvant chemotherapy (eight received weekly chemotherapy with paclitaxel and nine received chemotherapy with epirubicin + cyclophosphamide). Among the six patients who received neoadjuvant chemotherapy, one patient with progressive disease after initial chemotherapy received direct surgical treatment, three patients with stable disease after initial chemotherapy achieved partial remission after receiving a different chemotherapy regimen, and two patients had partial remission after initial chemotherapy. Among the 17 patients who received chemotherapy during pregnancy, recurrence and metastasis occurred in four patients, including two who received adjuvant chemotherapy and two who received neoadjuvant chemotherapy. The treatment regimens are shown in Table 2.

Follow-up

Follow-up visits were performed for 164 PABC patients. The median follow-up duration was 36 months (3–59 months). Among the patients, 18 were lost to follow-up, with a loss to follow-up rate of 11.0%. Among the patients with PABC during pregnancy, two had local recurrence, six had distant metastasis (including two cases of liver metastasis, three cases of bone metastasis, and one case of skin metastasis), and three died. Among the patients with PABC during lactation, four had local recurrence, six had metastasis (including one case of brain metastasis, one case of adrenal metastasis, one case of lumbar metastasis, one case of liver metastasis, and two cases of liver metastasis with bone metastasis), and two died. There were a total of 18 cases (11.0%) of local recurrence and distant metastasis and five cases (3.0%) of death in the 164 patients with PABC. The follow-up data are shown in Tables 3 and 4.

The Kaplan-Meier survival curves of the patients with PABC during pregnancy and those of the patients with PABC during lactation were compared, and the *P* value was 0.525 for DFS and 0.346 for OS. In the comparison of patients with Ki-67 <20%, patients with Ki-67 ≥20% and <40%, and patients with Ki-67 ≥40%, the *P* value was 0.179 for DFS and 0.391 for OS. Similarly, in the comparative analysis of Her-2-positive patients and Her-2-negative patients, the *P* value was 0.638 for DFS and 0.364 for OS. The survival curves are shown in Figures 1–3. In addition, the Kaplan-Meier survival curves of the 83 patients with PABC during pregnancy who terminated their pregnancy and those of patients who continued their pregnancy [Figure 4] were compared, and the *P* value was 0.138 for DFS and 0.910 for OS, with no significant difference.

A total of 85 children of 138 patients with PABC during pregnancy or lactation who delivered successfully were followed up for development. The children included 39 boys and 46 girls with an average age of 29 months (19–72 months). Their heights and weights were all within the normal ranges.

Discussion

PABC occurs during pregnancy and lactation. It affects the health of the mother and the fetus and should receive extensive attention. The definition of PABC varies in different studies. In a 2012 meta-analysis of 30 studies on PABC, eight studies defined PABC as breast cancer diagnosed during pregnancy, five studies defined PABC as breast cancer diagnosed during lactation, and 15 studies defined PABC as newly occurring breast cancer during pregnancy or within 1 year after childbirth.^[5] A meta-analysis conducted in 2016 suggested to extend the definition of PABC to include new occurrences of breast cancer during pregnancy and within 5 years after childbirth.^[6] Currently, the mainstream definition of PABC is newly occurring breast cancer during pregnancy and within 1 year after childbirth,^[7] which is the subject of this clinical study.

The incidence of PABC is low (0.2%–3.8%) in foreign studies, and it ranks third among cancers commonly diagnosed during pregnancy and lactation.^[8] A multicenter study involving 16 countries showed that PABC ranked first among cancers diagnosed during pregnancy.^[9] No multicenter clinical study of PABC has been conducted in China. A large single-center retrospective study performed at the Tianjin Medical University found that PABC accounted 0.36% of all breast cancer cases.^[10] The present study included 164 PABC patients from 27 hospitals nationwide, accounting 0.3% of the total cases of breast cancer during the same period.

The median age of onset of PABC in this study was 33 years, which was consistent with a previous large-scale study.^[11] Currently, the relationship between PABC and family history of breast cancer is inconclusive. In this study, 5.4% of the PABC patients had a family history of breast cancer; this is similar to the proportion of people with a family history of breast cancer in the general population, suggesting that a family history of breast cancer may not be associated with PABC.^[12,13]

This study showed that patients in stages III and IV accounted to 26.8% (44/164). Current studies suggest that the late stages are associated with delayed diagnosis and that the diagnosis of PABC is typically delayed by 1 to 13 months.^[14] Hyperplasia of the mammary glands during pregnancy and lactation increases tissue density, making small masses undetectable by conventional palpation; furthermore, the use of X-ray and other imaging examinations is limited due to their negative impact on the fetus, and pregnancy-related hormone fluctuations may stimulate tumor growth and progression. All these factors affect the early diagnosis of PABC. The literature has reported that a 1-month delay in treatment may increase the risk of lymph node involvement by 0.9%.^[15] Breast ultrasound is safe, simple, and non-radioactive.

Table 2: Treatment conditions of 17 breast cancer patients accepting chemotherapy during pregnancy period.

Number of sequence	Age (years)	Gestational age at diagnosis	Histopathological subtype	Histological grade	Ki-67 (%)	Molecular subtype	Chemotherapy regimen	Efficacy evaluation	Post-surgery assessment	Mode of delivery	Neonatal condition				Follow-up of mother			
											Gestational age at birth	Gender	Weight at birth (g)	Height at birth (cm)	Apgar score	Neonatal condition	Recurrence and metastasis	Treatment
Adjuvant chemotherapy																		
1	27	2 weeks + 5 days	IDC	G3	80	IIA TNBC	P	-	-	Natural labor	36 weeks + 1 day	Male	2800	48	9	Premature delivery, good	Live without tumor	-
2	29	19 weeks + 6 days	IDC	-	30	IIA Luminal B	EC	-	-	Natural labor	38 weeks	Male	3900	50	9	Normal	Live without tumor	-
3	30	26 weeks + 2 days	IDC	G3	30	I Luminal B	T	-	-	Cesarean section	35 weeks + 1 day	Male	2350	49	9	Premature delivery, good, low birth weight infants	Live without tumor	-
4	32	28 weeks	IDC	G3	40	IIB Luminal B (Her2+)	EC	-	-	Natural labor	37 weeks + 3 days	Female	2640	49	9	Good, emergency labor	Live without tumor	-
5	32	31 weeks	IDC	G2	30	IIA Her2+	EC	-	-	Natural labor	37 weeks + 2 days	Male	3050	50	9	Good	Live without tumor	-
6	33	24 weeks	IDC	G3	85	IIIC TNBC	P	-	-	Cesarean section	36 weeks + 1 day	Female	2330	50	9	Premature delivery, low birth weight infants	Live without tumor	-
7	35	18 weeks + 5 days	IDC	G3	40	IIA Luminal B	T	-	-	Cesarean section	34 weeks + 2 days	Female	2390	48	9	Small notch in left ventricular, low birth weight infants	Live without tumor	-
8	36	23 weeks + 1 day	IDC	-	25	- Luminal B	EC	-	-	Cesarean section	35 weeks	Female	2450	49	9	Premature delivery	Bone metastasis	Not yet
9	39	24 weeks	IDC	G3	40	IIIA Luminal B	P	-	-	Cesarean section	30 weeks	Female	1800	46	8	Premature delivery	Bone metastasis	Chemotherapy + endocrine therapy
10	39	29 weeks	IDC	G3	20	IIA Luminal B (Her2+)	P	-	-	Cesarean section	35 weeks + 3 days	Male	2400	50	9	Premature delivery, low birth weight infants	Live without tumor	-
11	40	19 weeks + 1 day	IDC	G2	40	IIA Luminal B	P	-	-	Cesarean section	42 weeks	Female	3000	47	9	Normal	Live without tumor	-
Neo-adjuvant chemotherapy																		
1	27	16 weeks	Invasive micropapillary carcinoma	G3	30	IIIA Luminal B	P	After 6*PD, efficacy was evaluated. Then given operation, 4*EC was given	PD	Cesarean section	35 weeks + 2 days	Female	2100	46	9	Premature delivery, low birth weight infants	Live without tumor	-
2	31	15 weeks	IDC	G3	35	IIB Luminal B	EC	After 2*ddEC, evaluated as SD and changed to chemotherapy regimen DPH	PR	Cesarean section	36 weeks + 4 days	Male	2810	46	10	Premature delivery	Live without tumor	-
3	32	32 weeks	IDC	G3	15	IIIB Luminal B (Her2+)	EC	After 2*ddEC, evaluated as SD and changed to chemotherapy regimen DPH	PR	Cesarean section	35 weeks + 3 days	Female	2300	50	9	Premature delivery, good	Skin metastasis	Pyrotinib
4	38	27 weeks	IDC	G3	90	IIA TNBC	EC	After 1*EC, evaluated as PD. Then TP was replaced after termination of pregnancy	PR	-	31 weeks	-	-	-	-	-	Live without tumor	-
5	34	21 weeks + 1 day	IDC	-	40	IIB Luminal B	EC	PR	PR	Cesarean section	35 weeks	Female	3000	50	9	Premature delivery	Live without tumor	-
6	28	19 weeks	IDC	-	80	IIIA TNBC	EC-wp	PR	PR	Natural labor	35 weeks + 4 days	Male	2000	46	9	Premature delivery	Local recurrence	2020,10 surgery

ddEC: Dose-dense epirubicin and cyclophosphamide; EC: Epirubicin + cyclophosphamide; EC-wp: Epirubicin + cyclophosphamide-weekly paclitaxel; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; PD: Progressive disease; PR: Partial remission; SD: Stable disease; TNBC: Triple-negative breast cancer.

Table 3: Follow-up results of 164 patients with PABC.

Item	Recurrence or metastasis	Death
Breast cancer in pregnancy (<i>n</i> = 83)	8 (9.6)	3 (3.6)
Skin metastasis	1 (1.2)	
Liver metastasis	2 (2.4)	
Bone metastasis	3 (3.6)	
Local recurrence	2 (2.4)	
Breast cancer in lactation (<i>n</i> = 81)	10 (12.3)	2 (2.5)
Brain metastasis	1 (1.2)	
Adrenal metastases	1 (1.2)	
Liver metastasis	1 (1.2)	
Liver and bone metastasis	2 (2.5)	
Lumbar metastasis	1 (1.2)	
Local recurrence	4 (4.9)	

PABC: Pregnancy-associated breast cancer.

Table 4: Follow-up of 23 cases of recurrence, metastasis, and death.

Number of sequences	Age	Gestational age at diagnosis	Histopathological subtypes	Histological grade	T	N	M	Stage	Ki-67 index (%)	Molecular subtype	Treatment strategy	Prognosis
Breast cancer in pregnancy												
1	30	6 weeks	Invasive carcinoma	G2	T3	N1	M0	IIIA	70	TNBC	Stop pregnancy-chemotherapy-radical mastectomy	Bone metastasis
2	28	19 weeks	Invasive carcinoma	-	2	2	0	IIIA	80	TNBC	Chemotherapy-delivery-chemotherapy-radical mastectomy	Local recurrence
3	32	32 weeks	IDC	G3	T4d	N1	M0	IIIB	15	Luminal B (Her2+)	Chemotherapy-delivery-chemotherapy-radical mastectomy	Skin metastasis
4	32	32 weeks	Invasive carcinoma	G2	T3	N1	M0	IIIA	40	Luminal B	Delivery-chemotherapy-radical mastectomy-chemotherapy	Liver metastasis
5	36	23 weeks + 1 day	Invasive carcinoma	-				IIIC	25	Luminal B	Radical mastectomy-chemotherapy-delivery-chemotherapy	Bone metastasis
6	39	24 weeks	IDC	G3	T3	N1	M0	IIIA	40	Luminal B	Chemotherapy-delivery-radical mastectomy	Bone metastasis
7	33	32 weeks	IDC	G3	T2	N2	M0	IIIA	70	Her2+	Delivery-chemotherapy-radical mastectomy	Recurrence on the left breast
8	34	25 weeks	IDC	G2	T2	N2	M0	IIIA	40	Luminal B (Her2+)	Chemotherapy-delivery-radical mastectomy	Liver metastasis
9	33	28 weeks	IDC	G2				IIIA	30	Her2+	Stop pregnancy-chemotherapy-radical mastectomy	Death
10	30	36 weeks	Invasive carcinoma	G2	T3	N1	M0	IIIA	45	TNBC	Neo-adjuvant chemotherapy-surgery-chemotherapy-radiotherapy	Death
11	37	28 weeks	IDC	G3	4	3	0	IIIC	20	TNBC	Neo-adjuvant chemotherapy-surgery	Death
Breast cancer in lactation												
1	35	Postpartum 13 months, drug abortion 2 months	Intraductal carcinoma	-	Tis	N0	M0	O	15	Her2+	Others	Lumber metastasis
2	29	Postpartum 4 months	IDC	-	T2	N1	M1	IV	20	Her2+	Neo-adjuvant chemotherapy-surgery	Adrenal metastasis
3	38	Postpartum 10 days	IDC	G2	T4d	N3a	M0	IIIC	30	Luminal B	Neo-adjuvant chemotherapy-surgery	Liver metastasis, bone metastasis
4	32	Postpartum 4 weeks	IDC	-	T2	N0	M0	IIA	30	Luminal B (Her2+)	Neo-adjuvant chemotherapy-surgery	Axillary recurrence
5	27	Postpartum 12 months	IDC	G3	T2	N1	M0	IIB	50	TNBC	Chemotherapy + sentinel lymph node dissection	Local recurrence
6	34	Postpartum 4 months	IDC	G2	T2	N1	M1	IV	60	Luminal B	Delivery-chemotherapy-radical mastectomy	Liver metastasis
7	34	Postpartum 20 months	Invasive carcinoma	G2	T4d	N2a	M0	IIIB	60	Luminal B	Neo-adjuvant chemotherapy-radical mastectomy	Chest wall recurrence
8	32	Postpartum 32 weeks	IDC	-	T1	N1	M0	IIA	50	Luminal A	Enlarge mastectomy + chemotherapy	Recurrence on the left breast
9	31	Postpartum 6 months	Invasive carcinoma	-	T2	N0	M0	IIA	40	Luminal B (Her2+)	Chemotherapy-radical mastectomy	Brain metastasis
10	34	Postpartum 2 months	ILC	-	T2	N1	M0	IIB	40	Her2+	Neo-adjuvant chemotherapy + target therapy-surgery	Liver metastasis, bone metastasis
11	27	Postpartum 20 days	IDC	G2	T2	N1	M1	IV	40	Luminal B (Her2+)	Chemotherapy-modified radical mastectomy	Death
12	36	Postpartum 2 weeks	Invasive carcinoma	-	T2	N1	M1	IV	70	Luminal B	Delivery-surgery-chemotherapy	Death

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; TNBC: Triple-negative breast cancer.

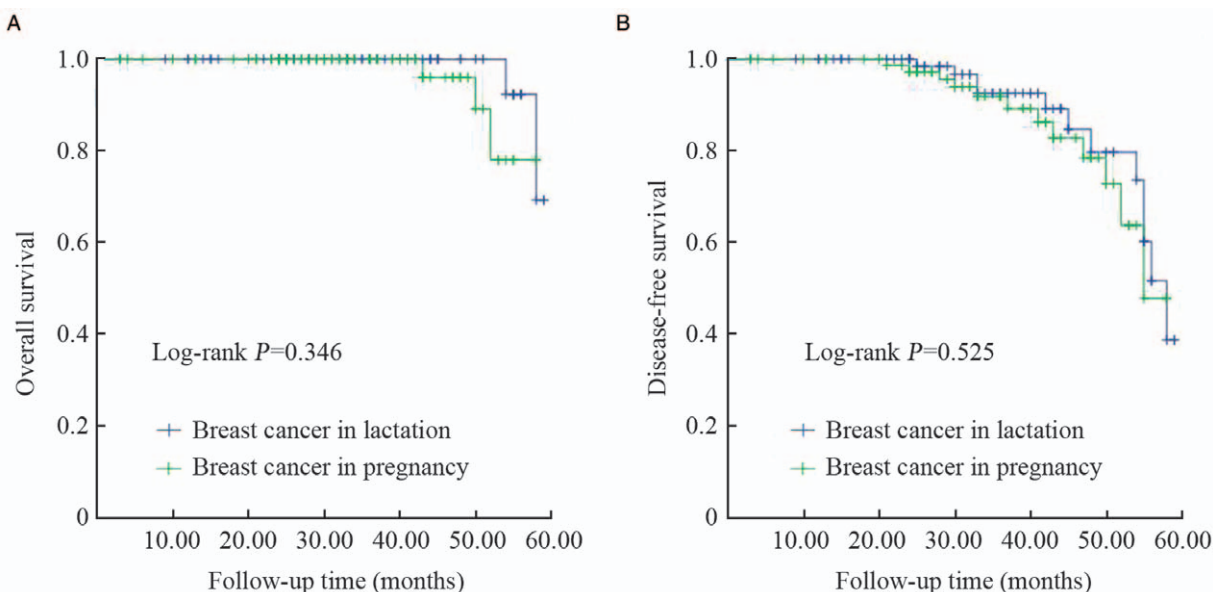


Figure 1: The OS and DFS analysis of the patients with PABC during pregnancy and those of the patients with PABC during lactation. DFS: Disease free survival; OS: Overall survival; PABC: Pregnancy-associated breast cancer.

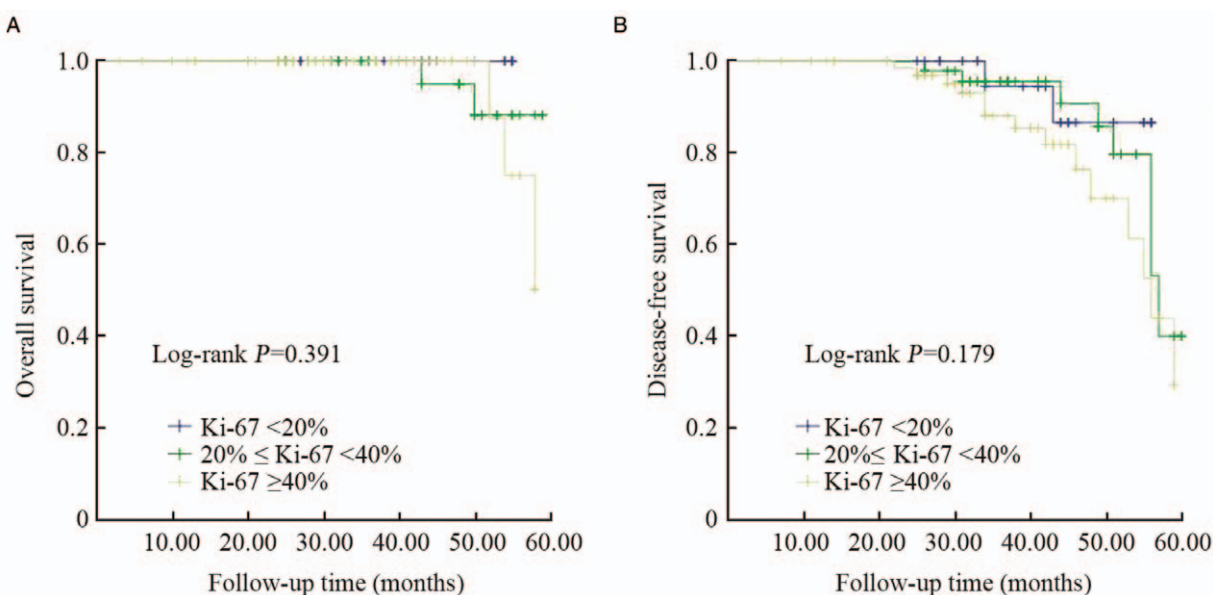


Figure 2: The OS and DFS analysis of the subgroups with different Ki-67 index. DFS: Disease free survival; OS: Overall survival.

Therefore, it can be used as the first-choice method for the diagnosis of PABC. In addition, mammography with protective measures has also been proven safe for the fetus, but its sensitivity is not high because of the increased density of the mammary glands. For suspected clinical patients, the above examinations should be performed as soon as possible, and if necessary, biopsy should be performed to avoid delays in diagnosis and subsequent treatment.

In our study, invasive ductal carcinoma was the most common pathological type, accounting 71.3% of all cases.

Histological grades G2 and G3 accounted 61.1% of all histological grades. The estrogen receptor (ER)- and progesterone receptor (PR)-positive rates were not high (52.4% and 42.7%, respectively), and the Her-2-positive rate was 29.3%. The results were consistent with the results of similar studies conducted abroad. PABC tends to have a high histological grade and the expression of ER and PR is low.^[10,14] In addition, patients with Ki-67 <20%, patients with Ki-67 ≥20% and <40%, and patients with Ki-67 ≥40% accounted 15.2%, 29.3%, and 43.3% of the Ki-67-positive patients, respectively. Regarding molecular subtypes, the most common types are

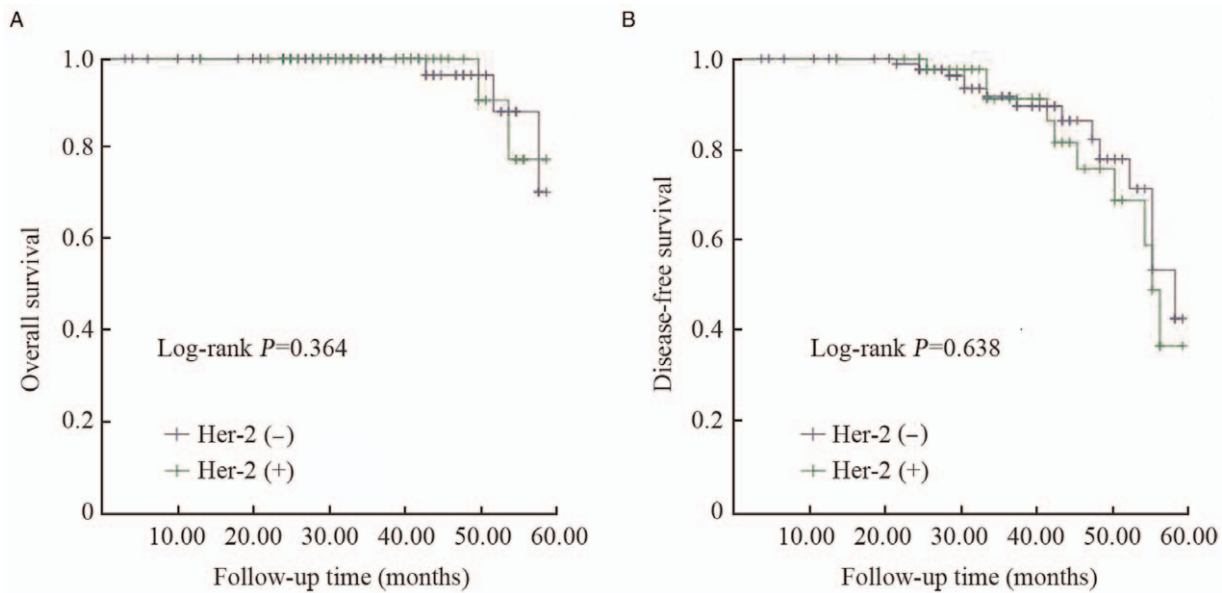


Figure 3: The OS and DFS analysis of the Her2+ and Her2- subgroups. DFS: Disease free survival; OS: Overall survival.

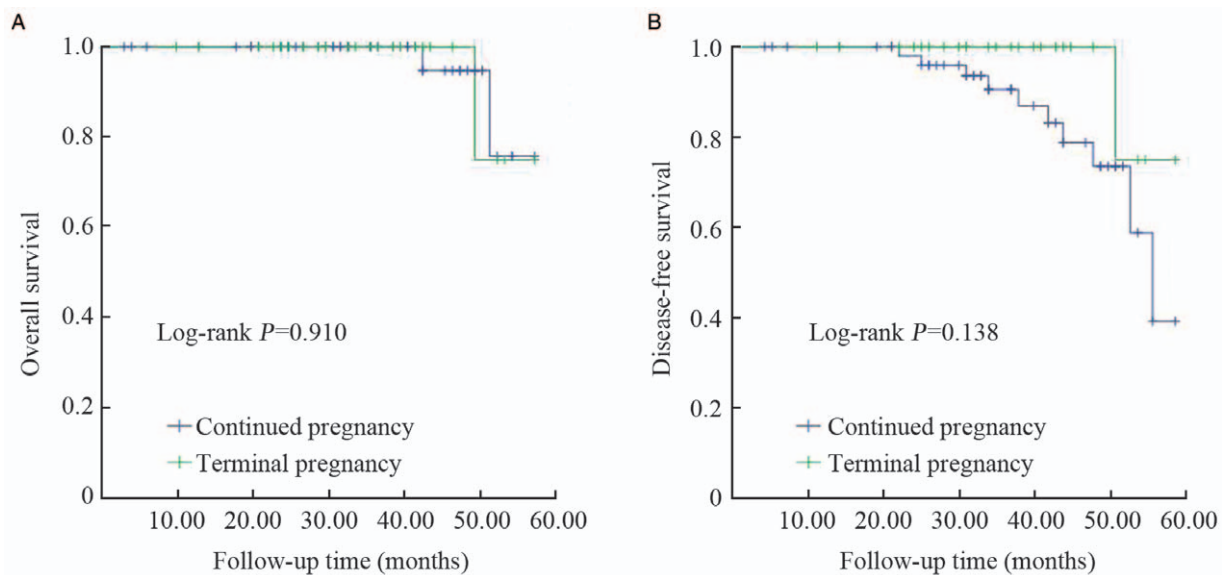


Figure 4: The OS and DFS analysis of the 83 patients with PABC during pregnancy who terminated their pregnancy and those of patients who continued their pregnancy. DFS: Disease free survival; OS: Overall survival; PABC: Pregnancy-associated breast cancer.

still controversial, and some studies believe that TNBC and Her-2 overexpression types are the most common. In our study, luminal B was the most common type, and the proportions of TNBC and Her-2 overexpression were also high, which is supported by other studies.^[10,14,16,17] Through gene expression profiling, some scholars have found that compared with non-PABC patients, patients with PABC had epithelial cells with enhanced expression of genes associated with invasion and recurrence that had a complex relationship with ER and PR.^[18] Other literature has reviewed the mechanisms underlying the development of PABC, including various hypotheses such as hormonal effects, immune changes, and inflammatory responses which await further investigation.^[14]

While the treatment of PABC during lactation is similar to that for non-PABC, PABC during pregnancy is difficult to treat because of the restrictions associated with pregnancy.^[19] Regarding the decision to pursue surgery or chemotherapy during pregnancy, surgery can theoretically be performed at any time. Among the 57 patients in this study who continued their pregnancy, 30 chose to undergo surgery during pregnancy; most of them selected modified radical mastectomy, although a few selected breast-conserving surgery. There were no significant adverse events in the mother or the fetus after surgery. When it is administered during pregnancy, chemotherapy is usually performed in the middle and late stages of pregnancy, and the safety of mother and fetus can be ensured.^[20] Because

chemotherapy in early pregnancy is likely to cause fetal malformations, and chemotherapy in late pregnancy can easily cause bone marrow suppression in the fetus after delivery, it is contraindicated during early and late pregnancy (after 35 weeks or 3 weeks before delivery).^[1] In this study, 17 patients with PABC during pregnancy underwent chemotherapy, including two patients in late pregnancy and 15 patients in mid-pregnancy, and all neonates were healthy. Most of these patients received weekly chemotherapy with anthracycline + cyclophosphamide, and a few of them received weekly chemotherapy with small-dose paclitaxel, mainly because the proportions of anthracycline, cyclophosphamide, and paclitaxel that can pass through the placental barrier are <8%, the lowest among chemotherapeutic drugs. More than 50% of carboplatin can pass through the placental barrier; thus, it ranks highest among chemotherapeutic drugs. Approximately 25% of cyclophosphamide can pass through the placental barrier, and although its effect on fetal development is relatively small in mid- and late pregnancy, it tends to cause fetal malformations when administered in early pregnancy.^[1] Therefore, weekly chemotherapy with anthracycline + cyclophosphamide was the main chemotherapy method used in this study, and no obvious complications of mother or hypoplasia of fetus were observed during chemotherapy. In addition, endocrine therapy, targeted therapy, and radiotherapy are prohibited during pregnancy because they can easily affect fetal development or threaten the life of the fetus.

A total of 26 (31.3%) patients terminated the pregnancy. Whether termination of pregnancy can change the prognosis is still controversial. Most studies showed no difference in prognosis between the patients who terminated their pregnancy and those who continued their pregnancy.^[21] In this study, among 57 patients who continued their pregnancy, eight had recurrence and metastasis and two died. In contrast, among 26 patients who terminated their pregnancy, only one patient died and no patient had recurrence or metastasis. Survival analysis showed that the DFS of the patients who continued their pregnancy was worse, but not significantly worse than that of patients who terminated their pregnancy, and their OS was not significantly different. Therefore, termination of pregnancy is not recommended for women with PABC during pregnancy unless chemotherapy is required in early pregnancy under certain circumstances. Regarding the impact of PABC on neonatal outcomes, a US study based on big data showed that the risks of intrauterine growth restriction, congenital abnormality, and intrauterine fetal death were similar in patients with PABC and patients with non-PABC patients, but the risks of premature birth and premature rupture of membranes were higher in patients with PABC.^[22] A total of 57 patients who continued their pregnancy were selected for this study, and 11 of them who were in late pregnancy (close to 39 weeks of gestation gave birth) before receiving any treatment. The remaining 46 patients gave birth after receiving chemotherapy or/and surgery during pregnancy, and 89.1% of patients were diagnosed in mid-pregnancy. Among the neonates delivered by the 57 patients with PABC during pregnancy, 23 (37.7%) neonates with normal body weight (>2500 g) and

21 (34.4%) neonates with body weight <2500 g had Apgar scores >8 points, and the birth conditions of 13 neonates were unknown. This result is basically similar to those of previous studies.

The prognosis of PABC is still controversial. Previous studies have reported that the prognosis of patients with PABC is worse than that of non-PABC patients because of the diagnosis delay, treatment delay, and hormone stimulation, and pregnancy and lactation are independent factors for a poor prognosis in patients with breast cancer.^[5,6] However, some studies have reported that when age, tumor stage, hormone receptor expression, and other factors were matched, the prognosis of patients with PABC and that of non-PABC patients were not significantly different.^[23,24] In this study, the median follow-up duration was 36 months. Among the 164 patients with PABC, 18 (11.0%) had local recurrence and distant metastasis, and five (3.0%) died. Studies have shown that breast cancer detected during lactation is associated with a worse prognosis,^[25] perhaps because the persistent presence of inflammatory stimuli during the process of mammary gland involution leads to changes in the tumor microenvironment and promotes the migration and metastasis of tumor cells. The comparison of survival conditions between patients with PABC during pregnancy and patients with PABC during lactation showed that the prognosis of the latter group was slightly worse. However, follow-ups found no significant difference between the groups. In this study, 23 patients with recurrence, metastasis, or death were analyzed. The 11 cases of PABC during pregnancy were initially diagnosed as stage III breast cancer. The 12 cases of PABC during lactation included one case of stage 0 (8.3%, 1/12), four cases of stage IV (33.3%, 4/12), five cases of stage II (41.6%, 5/12), and two cases of stage IIIC (16.6%, 2/12). No patient with PABC during pregnancy had stage IV PABC, perhaps because the absence of systemic evaluation due to pregnancy made it difficult to detect distant metastasis. Four cases of stage IV PABC during lactation were all T2N1M1, which may also be associated with breast cancer being prone to distant metastasis. TNBC and luminal B (9/11) were the dominant molecular subtypes of PABC during pregnancy. Luminal B type and Her-2-positive breast cancer (10/12) were the dominant molecular subtypes of PABC during lactation. In addition, the Ki-67 value-added index is closely related to the prognosis of breast cancer, and a higher Ki-67 index generally indicates a worse prognosis.^[26,27] Therefore, the Ki-67 index was divided into three levels in this study: Ki-67 <20%, Ki-67 ≥20%, and <40%, and Ki-67 ≥40%. Patients with Ki-67 ≥40% had a worse, but not significantly worse, prognosis than patients with Ki-67 ≥20% and <40%, and patients with Ki-67 ≥20% and <40% had a worse, but not significantly worse, prognosis than patients with Ki-67 <20%. Similarly, the comparison of survival between the Her-2-positive patients and the Her-2-negative patients showed that the Her-2-positive patients had a worse, but not significantly worse, prognosis than the Her-2-negative patients, possibly because of the small sample size and the short follow-up duration in this study. More PABC cases and longer follow-up durations are needed to further improve the survival analysis.

Regarding the growth and development of the children of PABC patients, some studies showed that the children of PABC patients who received chemotherapy during pregnancy had no significant difference in neurological and cardiac development and functions compared with normal children.^[28] In this study, 85 children were followed up. No obvious abnormalities in nerve and heart growth and development were observed in the children of PABC patients who received chemotherapy or surgical treatment during pregnancy or the children of PABC patients who did not receive any treatment during pregnancy. However, further studies are needed because of the large number of children lost to follow-up and the relatively short follow-up duration.

PABC is a special type of breast cancer. Standardized surgery and chemotherapy for PABC during pregnancy are safe for mother and fetus. However, our conclusions still need to be confirmed by large-scale studies and long-term follow-up data. With the adjustment of national birth control policies, the incidence of PABC may increase. Early detection, early diagnosis, and standardized treatment of PABC are very important.

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Conflicts of interest

None.

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