A One-center Study of Sixteen Patients with Pregnancy-associated Breast Cancer: Clinicopathological Characteristics and Survival

Gebelikle İlişkili Meme Kanserli 16 Hastaya Dair Tek Merkez Çalışması: Klinikopatolojik Özellikler ve Sağkalım

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Abstract

Aim: Cancer treatment is of special importance during pregnancy, concerning the health of both mother and baby. Treatment of pregnancy-associated breast cancer (PABC) has become even more important today because women tend to delay pregnancy to later ages and because of women who desire to conceive while under treatment for breast cancer. This retrospective study is aimed at investigating the clinical, radiological and histopathological characteristics and PABC treatment outcomes of patients who had long-term follow-up.

Materials and Methods: Sixteen women diagnosed with PABC were included in this study. We evaluated the clinicopathological characteristics, gestational history, and survival outcomes of the patients who had been treated and followed up for breast cancer during pregnancy and the first postnatal year at Istanbul University Institute of Oncology in 2010–2017.

Results: The median patient age was 32 (21–41) years. The median gestational week of diagnosis in pregnant patients was 26 (11–35) weeks while the mean time elapsed after delivery until diagnosis in postpartum patients was 9.3 (±3.6) months. The median follow-up time was 47.5 (5–99) months. The mean disease-free survival (DFS) and overall survival (OS) were calculated because the median DFS and OS could not be computed. The mean OS and DFS values were 87.8±7.3 and 77.6±8.5 months, respectively.

Discussion and Conclusion: Breast cancer in pregnancy is a special health condition that should be treated and followed up by a multidisciplinary team. Primary surgical intervention should not be delayed. While chemotherapy could be administered safely in the first and second trimesters, radiotherapy and targeted and endocrine treatments should be postponed until after delivery. Reporting and long-term follow-up of cases of pregnancy and cancer concurrence is essential for increasing the relevant knowledge.

Keywords: pregnancy; breast cancer; diagnosis; survival

Öz

Amaç: Gebelikte kanser tedavisi hem anne hem de bebek sağlığı açısından özel bir öneme sahiptir. Günümüzde kadınların gebeliği ileri yaşlara ertelemesi ve meme kanseri tedavisi almakta olan kadınların gebelik isteği nedeniyle GİMK tedavisi giderek önem kazanmaktadır. Bu retrospektif çalışma ile uzun süreli izlemi olan vakaların klinik, radyolojik ve histopatolojik özelliklerini ve GİMK tedavisi sonuçlarını incelemek amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya GİMK tanısı almış olan 16 kadın hasta dahil edilmiştir. 2010–2017 döneminde İstanbul Üniversitesi Onkoloji Enstitüsünde gebelik sırasında veya postnatal birinci yılda meme kanseri tanısıyla tedavi ve takip edilen hastaların klinikopatolojik özellikleri, gestasyonel öyküleri ve sağkalım sonuçları değerlendirilmiştir.

Bulgular: Medyan hasta yaşı 32 (21–41) yıldı. Gebe hastaların tanı anındaki medyan gebelik haftası 26 (11–35) hafta iken postpartum hastalarda doğumdan sonra meme kanseri tanısına kadar geçen ortalama süre 9,3 (±3,6) ay idi. Medyan takip süresi 47,5 (5–99) aydı. Medyan genel sağkalım (GS) ve hastalıksız sağkalım (HS) değerlerine ulaşılamadığı için ortalama GS ve HS hesaplandı. Ortalama GS ve HS değerleri sırasıyla 87,8±7,3 ve 77,6±8,5 ay idi.

Tartışma ve Sonuç: Gebelikte meme kanseri takip ve tedavisi multidisipliner bir ekip tarafından yapılması gereken özel bir sağlık sorunudur. Primer cerrahi müdahale geciktirilmemelidir. Kemoterapi ikinci ve üçüncü trimesterde güvenle uygulanabilirken radyoterapi, hedefe yönelik tedaviler ve endokrin tedavileri doğum sonrasına ertelenmelidir. Gebelik ve kanser birlikteliği vakalarının bildirilmesi ve uzun süreli takibi ilgili bilgi birikiminin artması bakımından çok önemlidir.

Anahtar Sözcükler: gebelik; meme kanseri; tanı; sağkalım

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INTRODUCTION

Cancer treatment is of special importance during pregnancy, concerning the health of both mother and baby. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or the first postnatal year. Its treatment is of increasing importance today because women tend to delay pregnancy to later ages and because of women who desire to conceive while under treatment for breast cancer. Concurrence of cancer and pregnancy is observed most frequently in breast cancer, with a reported incidence of 1.3 per 10,000 live births (1). PABC is diagnosed during pregnancy in 0.2 to 3.8% of women under the age 50 (2), and the average age of diagnosis is 32 to 34 years (3). Women's delay of pregnancy to later ages is a factor contributing to its increasing incidence (4). PABC is a serious form of cancer due to young patient age, delayed diagnosis, advanced stage, and/or aggressive histological profile in many cases. It has not been established, however, whether PABC has poorer prognosis compared to non-pregnancy-associated cancer at equivalent stages and in presence of similar prognostic factors (5,6). This retrospective study was designed aimed at investigating the outcomes and clinical, radiological and histopathological characteristics of patients who had long-term follow-up due to PABC.

MATERIALS AND METHODS

This retrospective study included female patients who had been treated and followed up for breast cancer during pregnancy and the first postnatal year at Istanbul University Institute of Oncology in 2010–2017. The data of age, symptoms, gestational or postnatal time of diagnosis, oncological treatments performed, management of pregnancy, maternal and neonatal results, and survival outcomes were obtained by reviewing the patient files. Histopathological tumor characteristics obtained from the pathology reports were recorded. Tumor type, histological grade, estrogen receptor (ER) and progesterone receptor (PR) status, HER2 expression, and nodal involvement data were also recorded. DFS was described as the time from the pathological diagnosis of breast cancer to recurrence or the last time the patient was seen, while OS as the time from the pathological diagnosis to death or the last visit. SPSS 21.0 software (SPSS Inc., Chicago, IL, US) was used for the statistical analyses. To assess the survival outcomes, the Kaplan–Meier method was used. No ethics committee approval was sought due to the retrospective nature of the study.

RESULTS

We identified sixteen patients with PABC. Of these, 10 (62.5%) had been diagnosed during pregnancy, 6 (37.5%) in the first postnatal year. General characteristics of the patients are shown in Table 1. The median gestational week of diagnosis in pregnant patients was 26 (11–35) weeks while the mean time elapsed after delivery until diagnosis in postpartum patients was 9.3 (±3.6) months.

Only three patients had complications associated with pregnancy; one of them gave birth to a non-viable fetus in the 22nd gestational week, one to a premature baby in the 32nd week, and one to a low-birth-weight baby.

The primary complaint of all patients was a palpable mass in the breast, and one patient had additional inflammatory alterations. While all of the pregnant patients were diagnosed radiologically by ultrasonography (USG) only, USG, mammography (MMG) and, when necessary, positron-emission tomography (PET) were used in the diagnosis of the postpartum patients.

In all patients, the histological type was invasive ductal carcinoma. Most of the tumors (75%) were grade 3. Immunologically, 43.75% of the tumors were of the luminal B subtype, 37.5% with high HER2 expression, and 18.75% triple-negative, with no case of luminal A cancer. Nodal involvement was present in 62.5% of the patients. At the time of diagnosis, most of the patients (50%) had stage-III and one had stage-IV cancer. Of the pregnant patients, six underwent surgery during pregnancy and four after delivery. Of the six patients, one underwent breast-conserving surgery (BCS) combined with axillary curettage (AC) in the 12th week, one BCS in the 28th week, one BCS with sentinel lymph node biopsy (SLNB) in the 11th week, one modified radical mastectomy (MRM) in the 29th week, one MRM in the 33rd week, and the last MRM with AC in the 30th week.

Table 1. Clinicopathological and gestational characteristics of the sixteen patients with PABC	
Number of patients n (%)	16 (100)
Pregnant	10 (62.5)
Postpartum	6 (37.5)
Median patient age (years)	32.0 (21–41)
Gestational time elapsed until diagnosis (weeks) in pregnant patients	26 (11–35)
Time elapsed after delivery until diagnosis (months) in postpartum patients	9.3±3.6
Birth, n (%)	
Full-term	14 (87.5)
Preterm	2 (12.5)
Tumor localization, n (%)	
Right	6 (37.5)
Left	10 (62.5)
Tumor size (cm)	4.3±3.5
Histological grade, n (%)	
II	4 (25)
III	12 (75)
ER or PR positivity, n (%)	7 (43.75)
HER2 expression, n (%)	9 (56.25)
Molecular subtype, n (%)	
Luminal B	7 (43.8)
High HER2 expression	6 (37.5)
Triple-negative	3 (18.8)
Node status, n (%)	
N0	6 (37.5)
N1	4 (25)
N2	3 (18.8)
N3	3 (18.8)
Stage, n (%)	
I	2 (12.5)
II	5 (31.25)
III	8 (50)
IV	1 (6.3)
Ki-67, (%)	42.5 (30–90)

The patient who aborted in the 22nd week had a history of obesity, secondary focal segmental glomerulosclerosis, and chronic renal failure. She had undergone BCS with AC in the 12th week and then received one course of adjuvant chemotherapy with doxorubicin and cyclophosphamide (AC regimen). After the abortion, her chemotherapy was continued with three courses of AC and four courses of docetaxel.

Three patients received anthracycline-based chemotherapy during pregnancy. Those diagnosed with breast cancer after delivery and those who were diagnosed and underwent surgery during pregnancy were treated after delivery similarly to non-pregnant patients with breast cancer. Oncological therapeutic management of the sixteen patients with PABC are summarized in Table 2. One patient who had a palpable mass in the breastfeeding period was considered inoperable due to metastasis.

All except three patients received radiotherapy. Of the three patients, one was not treated radiologically because her cancer was at stage IV at the time of diagnosis, one because of the distant metastasis observed shortly after the completion of adjuvant chemotherapy, and the last because she was treated by MRM for her cancer at stage I.

Follow-up data were present for all of the sixteen patients. Two died from breast cancer during the follow-up, one of whom was the patient with stage-IV cancer at the time diagnosis. The other was the patient who developed local recurrence and then widespread metastasis shortly after the MRM she underwent in the 30th gestational week. Of the three patients whose cancer recurred, two were still on chemotherapy while one was lost due to disease progression with local recurrence and widespread metastasis. The median follow-up time for our cohort was 47.5 (5–99) months. The

Table 2. Oncological therapeutic management of the sixteen patients with PABC

Pregnant patient	Gestational time elapsed until diagnosis (weeks)	Stage	Oncological treatment	RT	OS (months)	DFS (months)	Current state
1	11	II	12th week BCS + AxC + 22nd week abortion + 4c AC + 4c DOS	Yes	95	95	Alive, disease-free
2	15	II	4c neo AC + delivery + 12-week (PAC+HER) + MRM + one-year HER	No	77	18	Alive, recurrent
3	28	I	28th week BCS + delivery + 12-week (PAC+HER) + 1-year HER		58	58	Alive, disease-free
4	11	I	11th week BCS + SLNB + 3c AC + delivery + 12-week (PAC+HER) + 1-year HER	Yes	17	17	Alive, disease-free
5	24	III	4c neo AC + delivery + 12-week neo (PAC+ HER) + BCS + AxC + 1-year HER	Yes	27	27	Alive, disease-free
6	16	III	6c neo AC + delivery + 12-week neo PAC + MRM	Yes	39	39	Alive, disease-free
7	29	III	32nd week premature birth + MRM +3c AC + 4c DOS	Yes	99	77	Alive, recurrent
8	33	III	33rd week MRM + delivery + 4c AC + 12-week PAC		5	5	Alive, disease-free
9	35	II	35th week BCS + SLNB + delivery + 3c FEC + 3c DOS	Yes	60	60	Alive, disease-free
10	30	III	30th week + AxC + 1c neo FAC + delivery + 2c FAC + 4c DOS	No	12	7	Deceased (recurrent)
Postpartum patient	**Time elapsed after delivery until diagnosis (months)**	**Stage**	**Oncological treatment**	**RT**	**OS (months)**	**DFS (months)**	**Current state**
1	12	II	BCS + 4c AC + 12-week PAC	Yes	56	56	Alive, disease-free
2	3	III	MRM + 4c AC + 4c (DOS+HER) + 1-year HER	Yes	84	84	Alive, disease-free
3	7	III	BCS + AxC + 4c AC + 12-week (PAC+HER) + 1-year HER	Yes	75	75	Alive, disease-free
4	12	III	MRM + 4c AC + 12-week (PAC+HER) + 1-year HER	Yes	29	29	Alive, disease-free
5	12	IV	(inoperable) + 4c AC + 12-week (PAC+HER) + lifelong HER	No	36		Deceased
6	10	I	BCS 4c AC +12-week PAC	Yes	37	37	Alive, disease-free

AC: doxorubicin+cyclophosphamide; AxC: axillary curettage; BCS: breast-conserving surgery; c: course of; DFS: disease-free survival; DOC: docetaxel; FAC: 5-fluorouracil+doxorubicin +cyclophosphamide; FEC: 5-fluorouracil+epirubicin+cyclophosphamide; neo: neoadjuvant; MRM: modified radical mastectomy; OS: overall survival; PABC: pregnancy-associated breast cancer; PAC: paclitaxel; RT: radiotherapy; SLBN: sentinel lymph node biopsy; TRAS: trastuzumab

mean disease-free survival (DFS) and overall survival (OS) were calculated because the median DFS and OS could not be computed. The mean OS and DFS values were 87.8±7.3 and 77.6±8.5 months, respectively.

DISCUSSION AND CONCLUSION

In this study we evaluated the clinicopathological characteristics and survival outcomes of sixteen patients who had been treated and followed up due to breast cancer diagnosed during pregnancy or the first postnatal year. Consistently with the literature (3,7–9), the median age of the patients included was 32 (21–41) years. The median gestational week of diagnosis in pregnant patients was 26 (11–35) weeks while the mean time elapsed after delivery until diagnosis in postpartum patients was 9.3 (±3.6) months; and these data were not found consistent with the other studies in the literature reporting slightly earlier diagnoses (5,7,10). In all of the cases, the complaint at the time of diagnosis was a pal-

pable mass. Breast USG was the method of diagnosis preferred for the pregnant patients for not posing risks to the fetus and its safety and diagnostic accuracy. In another study of pregnant women with breast cancer, USG revealed 100% of the breast masses and 90% of the axillary metastases, respectively (11). If mammography is to be used for diagnosis, however, the pelvic area should be protected by a leaden block as much as possible. Contrast-enhanced breast MRI with gadolinium-containing agents is not recommended for use in pregnant women with suspected breast cancer.

Pathologically, all the patients had invasive ductal carcinoma, with poor prognosis. Grade-3 and stage-III tumors made up 75% and 50% of all tumors, respectively. Nodal involvement was present in most of the patients. These poor prognostics were found consistent with the literature (7,10,12,13). A majority of the tumors (56.3%) did not express hormone receptors.

It had been safely possible for all of the pregnant patients to undergo surgery and even sentinel lymph node biopsy. None of the pregnant patients who underwent MRM or BCS during pregnancy had any surgery-related problem. Breast surgery, though safely practicable during each trimester of pregnancy, should nonetheless be scheduled preferably for after the 12th gestational week when the risk of spontaneous abortion is lower (14) or between the 16th and 20th gestational weeks as recommended by a recently published study (15). It is also possible that adjuvant or neoadjuvant chemotherapy be administered safely during pregnancy; neither the pregnant patients in our cohort who received anthracycline-based chemotherapy nor their fetuses developed any complications. However, chemotherapy is contraindicated before the 12th gestational week because the risk of spontaneous abortion and fetal malformation is high in the first trimester due to organogenesis. Chemotherapy should be avoided in the first trimester of pregnancy unless the mother has an otherwise life-threatening condition (3, 16–18).

Exposure to radiation is also risky in pregnancy due to its potential of causing fetal death, physical and mental retardation, and cancer development (19). Accordingly, our pregnant patients received radiotherapy after delivery. Despite the fact that the median survival time could not be computed and our lack of a control group for assessing the survival outcomes, the mean OS and DFS values for our cohort were 87.3±7.3 and 77.6±8.5 months, respectively, again more favorable only compared to those reported in studies of patients with PABC (7,20). In our group including a high number of patients with stage-III cancer, this might be associated with the recent developments such as frequent use of HER2 treatments and more effective use of the adjuvant and neoadjuvant therapeutic modalities.

Breast cancer in pregnancy is a special health condition that should be treated and followed up by a multidisciplinary team. Primary surgical intervention should not be delayed. Procedures such as mastectomy or breast-conserving surgery are possible. The combination of anthracycline and cyclophosphamide can be administered safely in the second and third trimesters of pregnancy. Although the relevant data are limited, use of taxanes appears to be safe. The last administration of chemotherapy should be three weeks prior to delivery. Radiotherapy and targeted and endocrine treatments should be postponed until after delivery. Reporting and long-term follow-up of cases of pregnancy and cancer concurrence is essential for increasing the relevant knowledge

REFERENCES

1. Smith LH, Dalrymple JL, Leiserowitz GS, et al. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. Am J Obstet Gynecol. 2001;184:1504–12.
2. Wallack MK, Wolf JA, Jr., Bedwinek J, et al. Gestational carcinoma of the female breast. Curr Probl Cancer. 1983;7:1–58.
3. Sukumvanich P. Review of current treatment options for pregnancy-associated breast cancer. Clin Obstet Gynecol. 2011;54:164–72.
4. Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2016. Natl Vital Stat Rep. 2018;67:1–55.
5. Bonnier P, Romain S, Dilhuydy JM, et al. Influence of pregnancy on the outcome of breast cancer: a case-control study. Int J Cancer. 1997;72:720–7.
6. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. Cancer. 1991;67:869–72.
7. Basaran D, Turgal M, Beksac K, et al. Pregnancy-associated breast cancer: clinicopathological characteristics of 20 cases with a focus on identifiable causes of diagnostic delay. Breast Care (Basel). 2014;9:355–9.

8. Genin AS, De Rycke Y, Stevens D, et al. Association with pregnancy increases the risk of local recurrence but does not impact overall survival in breast cancer: a case-control study of 87 cases. Breast. 2016;30:222–7.
9. Langer A, Mohallem M, Stevens D, et al. A single-institution study of 117 pregnancy-associated breast cancers (PABC): presentation, imaging, clinicopathological data and outcome. Diagn Interv Imaging. 2014;95:435–41.
10. Asgeirsson KS. Pregnancy-associated breast cancer. Acta Obstet Gynecol Scand. 2011;90:158–66.
11. Yang WT, Dryden MJ, Gwyn K, et al. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. Radiology. 2006;239:52–60.
12. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013;31:2532–9.
13. Beadle BM, Woodward WA, Middleton LP, et al. The impact of pregnancy on breast cancer outcomes in women<or=35 years. Cancer. 2009;115:1174–84.
14. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer. 2006;106:237–46.
15. Kizer NT, Powell MA. Surgery in the pregnant patient. Clin Obstet Gynecol. 2011;54:633–41.
16. Burstein HJ, Partridge AH, Lesnikoski BA. Treatment of breast cancer during pregnancy. Expert Opin Pharmacother. 2002;3:423–8.
17. Lenhard MS, Bauerfeind I, Untch M. Breast cancer and pregnancy: challenges of chemotherapy. Crit Rev Oncol Hematol. 2008;67:196–203.
18. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol. 2010;28:683–9.
19. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. Arch Surg. 2003;138:91–8.
20. Ali SA, Gupta S, Sehgal R, et al. Survival outcomes in pregnancy associated breast cancer: a retrospective case control study. Breast J. 2012;18:139–44.