Received: 13 October 2019 | Accepted: 14 October 2019

DOI: 10.1111/tbj.13714

ORIGINAL ARTICLE

The Breast Journal WILEY

Pregnancy associated breast cancer

Heather R. Macdonald MD, FACOG[1,2]

[1]Hoag Hospital, Newport Beach, California

[2]Keck School of Medicine, University of Southern California, Los Angeles, California

Correspondence
Heather Macdonald, Department of Surgery, Keck School of Medicine of USC, 16305 Sand Canyon Ave, Suite 160 Irvine, CA 92618.
Emails: Heather.macdonald@hoag.org

Abstract

Pregnancy associated breast cancer (PABC) defined as breast cancer occurring during pregnancy or within the first 1-2 years postpartum. Delay in diagnosis is common. Treatment is timed around gestational age. Surgery and chemotherapy are considered safe after the first trimester. Radiation, anti–her-2, and endocrine therapy are delayed until after delivery due to adverse fetal effects. Iatrogenic prematurity likely causes most long-term fetal sequelae. Multi-disciplinary care and social support are critical for patients and families with PABC.

KEYWORDS

breast mass in pregnancy, cancer in pregnancy, chemotherapy in pregnancy, radiation in pregnancy

1 | DEFINITION AND INCIDENCE

Pregnancy associated breast cancer (PABC) is defined as breast cancer occurring during pregnancy or within the first 1-2 years postpartum.[1] Pregnancy associated breast cancer is estimated to complicate 1 in 3000 pregnancies. It is increasing in incidence as women delay childbearing into the 4th and 5th decades of life. Breast cancer is one of the most common malignancies to complicate pregnancy.

2 | PRESENTATION AND DIAGNOSIS

Pregnancy associated breast cancer presents most commonly as a palpable finding.[1] Delay in diagnosis is well documented.[2] Breast density and nodularity increase with pregnancy, complicating the interpretation of clinical examination and breast imaging.

Diagnostic strategy of a palpable mass in pregnancy includes clinical examination, imaging, and biopsy. Breast ultrasound carries sensitivities and negative predictive values up to 100% in pregnant breasts.[3] If suspicious characteristics are identified, diagnostic mammogram is indicated for further characterization and whole-breast survey. Table 1 lists acceptable radiation threshold in pregnancy and radiation exposures of common imaging modalities.[4,5]

Breast MRI with gadolinium is controversial in pregnancy. MRI imaging without contrast is safe[5] but is of limited use imaging breast tissue. Gadolinium crosses the placenta and enters fetal circulation and amniotic fluid. Long-term fetal effects of gadolinium exposure are unknown. Gadolinium exposure has been associated with increased incidence of rheumatologic or inflammatory conditions.[6] Decision regarding use should be made on a case-by-case basis, weighing risks and benefits.[5] Lactation should not be interrupted after breast maternal gadolinium exposure due to limited breast milk excretion and neonatal ingestion.

Any suspicious breast mass or imaging finding should be biopsied. Milk fistulization in pregnancy is exceedingly rare after needle biopsy.[7] Local anesthetic has no known risk in pregnancy. Pathologists should be alerted to the patient's pregnant state to aid in the interpretation of the biopsied tissue.

3 | HISTOLOGY

71%-100% of PABC reported is infiltrating ductal carcinoma, with all breast cancer subtypes represented.[1,2,8] Pregnancy-associated breast cancer is more likely to be hormone receptor negative and her-2 positive, similar to age-matched controls.

4 | MATERNAL PROGNOSIS

In modern series, the prognosis of PABC is similar to age- and stage-matched controls.[2,9] A meta-analysis found higher mortality and

recurrence rates with PABC but included older studies with delayed and less effective treatments.[10] 21% of PABC is diagnosed at stage I or II versus 54% in nonpregnant women.[2,9] 53%-71% of PABC presents with positive nodes. The worse prognosis of PABC is more likely due to stage at diagnosis and breast cancer subtype than pregnancy itself.[1,2]

Pregnancy termination does not improve maternal prognosis.[9] Several studies found worse survival among women who terminated versus those who continued pregnancy.[11,12] Women with breast cancer early in pregnancy may choose to terminate but it is not a medical recommendation.

5 | MANAGEMENT—SPECIAL CONSIDERATIONS DURING PREGNANCY

Families with PABC need a multi-disciplinary team: breast specialized radiologist, breast surgeon, anesthesiologist, medical oncologist, obstetrician, maternal fetal medicine specialist, pediatrician/neonatologist, and social worker. Communication among team members is of paramount importance. Due to young age at diagnosis, genetic testing for inherited breast cancer syndromes is indicated.

All cancer treatments are scheduled around gestational age to minimize risk to the fetus and mother. The most accurate dating is early transvaginal ultrasound,[13] ideally before 9 weeks gestation.

The social support needs of pregnant mothers and families with breast cancer are complex. Families may also include young children. Social workers should be involved early and often. Maternal mental health should not be neglected.

6 | STAGING

When staging the pregnant woman with breast cancer, of primary concern is fetal radiation exposure. Radiation doses of common staging studies are listed in Table 1. Alternative studies with little or no radiation exposure include right upper quadrant abdominal ultrasound, chest x-ray with abdominal lead shielding and noncontrast MR.

TABLE 1 Fetal radiation exposure

Background fetal radiation exposure through pregnancy	1 mGy
Threshold of acceptable fetal exposure	<50 mGy
Threshold for congenital fetal loss, congenital anomalies, intellectual effects	60-200 mGy
Mammogram 2 views	0.001-0.01 mGy
Chest x-ray	0.0005-0.001 mGy
Chest CT	0.01-0.66 mGy
Bone scan T99	4-5 mGy
Abdominal CT	1.3-3.5 mGy
Pelvic CT	10-50 mGy
Pet CT whole body	10-50 mGy

Note: Adapted from guidelines for diagnostic imaging during pregnancy and lactation. American College of Obstetrics and Gynecology Committee Opinion 723, October 2017.

7 | SURGICAL MANAGEMENT IN PREGNANCY

Surgical management of PABC should be chosen by the same principles as nonpregnant patients.[1,14] Small series have confirmed equivalent survival between pregnant women undergoing breast conservation and mastectomy.[14] If chemotherapy is indicated, postlumpectomy radiation can be given after completion of chemotherapy and delivery without treatment delay.

Small studies support the safety in PABC of staged reconstruction after mastectomy with immediate tissue expander placement.[14] The benefits of immediate breast reconstruction include improved psychologic and aesthetic outcomes.[15] A series of pregnant women who underwent tissue expander placement during pregnancy showed no increase in obstetrical or surgical complications.[16]

Sentinel node biopsy is safe and accurate for clinically node-negative pregnant patients. Fetal radiation exposures after radionucleotide injection are within acceptable levels.[17] Isosulfan blue should be avoided due to lack of fetal safety data (pregnancy category C). Methylene blue is a known fetal teratogen.[18] Axillary clearance should be reserved for known axillary disease,[14] due to risk of lymphedema and likely low therapeutic benefit.[19]

Large studies have established the safety of anesthesia exposure during pregnancy.[20,21] Surgery is generally avoided during the first trimester if possible. Surgery is considered safest during the 2nd trimester, between 12 and 24 weeks. Women beyond 20 weeks should be paced in a left lateral tilt position to displace the gravid uterus off the maternal vena cava and preserve cardiac return. Women undergoing surgery after 24 weeks should receive intraoperative fetal heart monitoring and receive care in a facility with the capacity to intervene for preterm labor care for a preterm infant.

All pregnant women undergoing surgery should have precautions taken to avoid uterine hypoperfusion, maternal hypotension, hypoxia, hypoglycemia, pain, fever, and infection. Acetaminophen and narcotic pain medications are used routinely in pregnancy to treat maternal conditions. Aspirin should be avoided in pregnancy due to fetal effects.[22] NSAIDs should be used with caution due to a possible risk of spontaneous abortion in the first trimester. NSAIDs should not be used in the third trimester due to adverse fetal cardiac effects. Antibiotics should be given for usual surgical indications, and many are safe in pregnancy. As both pregnancy and malignancy increase risk for thrombotic events, thrombotic prophylaxis should be employed during surgery.

8 | SYSTEMIC TREATMENT IN PREGNANCY

8.1 | Special considerations

Physiologic changes of pregnancy that effect the pharmacokinetics of systemic treatment include increasing maternal body weight, plasma volume, hepatorenal perfusion, cytochrome P450 activity (third trimester), and serum albumin concentrations. The fetus and amniotic fluid act as a third space, sequestering the medications from the mother. Despite these challenges, survival is similar between age- and stage-matched pregnant and nonpregnant women, so chemotherapy dosing is not altered during pregnancy.

8.2 | Chemotherapy

Almost all known intravenous cancer therapies cross the placental barrier and have fetal effects, including doxorubicin and cyclophosphamide.[23-25] First-trimester exposure increases fetal loss and congenital anomalies. A 2010 International Consensus Conference recommended cytotoxic treatment be delayed until after 14 weeks.[1]

Chemotherapy exposure in the 2nd and 3rd trimesters only (not before 12 weeks) has not been shown to increase rates of fetal loss or congenital anomalies above background rates of 3%-5%. (9; 23, 24) In the second- and third-trimesters known effects include suppression of fetal hematopoiesis, growth restriction, and sepsis.[23-25] Fetal and neonatal echocardiograms do not show increased fetal cardiotoxicity. There are less data regarding taxane exposure in pregnancy but small series suggest similar safety profiles to doxorubicin and cyclophosphamide when used in 2nd and 3rd trimesters.[26]

Dose-dense chemotherapy improves efficacy of treatment and shorten time to completion of therapy[27] which may have benefit when considering timing of therapy and delivery. However, concerns over managing maternal toxicities including anemia, neutropenia, and infection both in mothers and in neonates have limited its use. A small retrospective cohort study of dose-dense chemotherapy in pregnancy found no difference in fetal or maternal complications with dose-dense approach but was significantly underpowered.[27]

Many commonly used supportive agents are safe in pregnancy with low risks of congenital anomalies including metoclopramide, GCS-F, erythropoietin, ondansetron, methylprednisolone, hydrocortisone, diphenhydramine, and ranitidine.[1,28]

8.3 | Biologic agents

Trastuzumab is contraindicated in pregnancy.[29] Her-2 receptors are expressed on fetal renal epithelium. Trastuzumab decreases fetal urine output and amniotic fluid volume, which increase fetal limb malformations and pulmonary hypoplasia. No studies exist demonstrating safety data for the use of pertuzumab in pregnancy.

8.4 | Endocrine therapy

Tamoxifen is contraindicated in pregnancy (pregnancy category D) due to cases of neonatal ambiguous genitalia and oculoauriculovertebral dysplasia.[30] However, case reports describe use in the metastatic setting without fetal harm. Tamoxifen postpartum may delay milk production, and there is limited safety data regarding tamoxifen safety in lactation.

8.5 | Radiotherapy

Known effects of radiation exposure in utero include fetal loss, fetal malformation, mental retardation, and growth disturbances and are impacted by total dose and gestational age at exposure.[31] Radiation should be delayed to after delivery. A delay of treatment <3 months may be acceptable with calculated a 1% increase per month delay in local recurrence risk.[32]

Radiation risk in pregnancy may be overestimated, especially in first trimester when the developing fetus is low in the maternal pelvis. Radiation doses calculated for potential fetal exposure identify first- and second-trimester levels that are within acceptable thresholds.[4] Lead shielding can reduce doses by 50%-70%. A 2010 International Consensus Conference concluded radiation may be relatively safe in the first and second trimester of pregnancy.[1]

Partial breast radiation techniques may have even lower fetal radiation exposures but there are no published safety data considering this approach in pregnancy.[14]

8.6 | Obstetric care

Coordinated care between obstetrics team and oncologists is of paramount importance as timing of treatment is tied to gestational age. Accurate pregnancy dating is best established by first-trimester ultrasound.[13] Fetuses exposed to chemotherapy should be followed with serial ultrasound for growth.[33] Intraoperative fetal monitoring is indicated for all pregnant women beyond 24 weeks.

The most significant fetal sequelae of PABC are from iatrogenic prematurity.[33] In the absence of maternal benefit, carrying the pregnancy to near term (39 weeks) should be a management goal. Delivery is optimally timed 3 weeks after myelosuppressive chemotherapy is stopped.[33,34] Neonatal sepsis has been reported when delivery has occurred with nadiring maternal and fetal blood counts. The mode of delivery is entirely by obstetric considerations. Neonatal resuscitation team should be presented at delivery. Pediatricians should be aware of antenatal exposure to systemic chemotherapy. Infants

should be assessed for growth, weight, and maturity. Peripartum and postpartum care are routine.

8.7 | Postdelivery care

Special attention should be paid to maternal-neonatal bonding and maternal mental health after delivery. Young women with breast cancer report higher rates of depression, fewer coping skills, and worse quality of life compared with older breast cancer patients.[35] Effect of pregnancy and delivery complicated by cancer on maternal mental health is unknown but likely detrimental. Patients undergoing radiation, surgery, or additional systemic therapy after delivery may be unable to breastfeed, potentially complicating maternal-child bonding.

Contraceptive needs of the mother should be addressed immediately postpartum. 33% of women ovulate before their first menstrual cycle postpartum.[36] Due to young age, chemotherapy may not induce permanent ovarian failure. The intrauterine device (IUD) is as effective as surgical sterilization but reversible.[37] The copper IUD carries no hormonal exposure. Small series have shown safety of progestin-containing IUDs in breast cancer patients.[38] An IUD can be placed at the time of delivery with slightly elevated expulsion rates but significantly better compliance than placement at first postpartum visit.[39]

8.8 | Pediatric outcomes after PABC

Small studies regarding pediatric outcomes of children exposed to chemotherapy in utero show preterm birth correlates with worse developmental outcomes independent of cancer treatment.[40,41] Conversely, outside of prematurity, little increased risk of neurologic, cardiac, or cognitive adverse effects have been seen.[42] Follow-up studies of children who were exposed to breast cancer chemotherapy in utero have not shown increases in intellectual, developmental, or growth defects.

8.9 | PABC treatment by trimester

First trimester Weeks 1-12	Surgery probably safe after 9 weeks with cardiac motion established Chemotherapy, radiation, anti–her-2, and endocrine therapy contraindicated
Second trimester Weeks 13-26	Safest surgical window: 12-24 weeks ACT chemotherapy likely safe (limited taxane data) Serial fetal ultrasounds for growth Radiation, anti–her-2 therapy, and endocrine contraindicated
Third trimester Weeks 27-40	Surgery safe: intraoperative fetal monitoring and neonatal resuscitation capability on site (>24 weeks) Radiation, anti–her-2, and endocrine therapy contraindicated
Delivery	Timed delivery: withhold myelosuppressive therapies within 3 weeks of delivery Avoid iatrogenic prematurity in the absence of clear maternal benefit Delivery by obstetric indications Pediatric team available Contraception
Postpartum 1st 12 weeks	Breastfeeding encouraged unless undergoing additional cancer treatment Radiation may be given
Contraindicated in pregnancy and lactation at anytime	Anti–her-2 therapy Endocrine therapy Radiation

9 | CONCLUSION

Breast cancer during pregnancy is becoming more common as women delay childbearing. Prognosis is driven by young age, stage, and cancer histology more than pregnant state. It is best managed with a multi-disciplinary team. Early and accurate pregnancy dating is critical. During organogenesis (first 9 weeks of pregnancy), treatment increases risks of pregnancy loss and congenital anomaly. After the first-trimester, surgery and chemotherapy can be safely given. Preterm delivery should be avoided if possible, to minimize sequelae for the fetus. Chemotherapy and delivery should be timed to avoid delivery during myelosuppressive period. Anti–her-2 therapy, endocrine therapy, and radiation should be delayed until postpartum. Psychosocial support needs of families should be addressed throughout treatment and delivery.

ORCID

Heather R. Macdonald https://orcid.org/0000-0002-7182-2090

REFERENCES

1. Frederic A, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur J Cancer*. 2010;46:3158-3168.
2. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet*. 2012;379:570-579.
3. Vashi R, Hooley R, Butler R, Geisel J, Philpotts L. Breast imaging of the pregnant and lactating patient: imaging modalities and pregnancy-associated breast cancer. *Am J Roentgenol*. 2013;200:321-328.
4. Mazonakis M, Varveris H, Damilakis J, Theoharopoulos N, Gourtsoyiannis N. Radiation dose to conceptus resulting from tangential breast irradiation. *Int J Radiat Oncol Biol Phys*. 2003;55(2):386-391.
5. American College of Obstetricians and Gynecologists. Guidelines for diagnostic imaging during pregnancy and lactation. ACOG Committee Opinion 723, October 2017.
6. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA*. 2016;316:952-961.
7. Schackmuth EM, Harlow CL, Norton LW. Milk fistula: a complication after core breast biopsy. *Am J Roentgenol*. 1993;161:961-962.

8. Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. *Cancer*. 2003;98:1055-1060.
9. Cardonick E, Dougherty R, Grana G, Gilmandyar D, Ghaffar S, Usmani A. Breast cancer during pregnancy: maternal and fetal outcomes. *Cancer J*. 2010;16(1):76-82.
10. Azim HA, Santoro L, Russell-Edu W, Pentheroudakis G, Pavlidis N, Peccatori FA. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev*. 2012;38(7):834-842.
11. Deemarsky LJ, Neishtadt EL. Breast cancer and pregnancy. *Breast*. 1980;7:17-21.
12. King RM, Welch S, Martin K, Coulam CB. Carcinoma of the breast associated with pregnancy. *Surg Gynecol Obst*. 1985;160:228-232.
13. Papageorghiou AT, Kennedy SH, Salomon EO, et al. International standards for early fetal size and pregnancy dating based on crown-rump length in the first trimester of pregnancy. *Ultrasound Obstet Gynecol*. 2014;44(6):641-648.
14. Toesca A, Gentilini O, Peccatori F, Azim HA, Amant F. Locoregional treatment of breast cancer during pregnancy. *Gynecol Surg*. 2014;11:279-284.
15. Fernandez-Delgado J, Lopez-Pedraza MJ, Blasco JA, et al. Satisfaction with and psychological impact of immediate and deferred breast reconstruction. *Ann Oncol*. 2008;19:1430-1434.
16. Lohrsiriwat V, Peccatori FA, Martella S, et al. Immediate breast reconstruction with expander in pregnant breast cancer patients. *Breast*. 2013;22(5):657-660.
17. Gropper AB, Zabicki Calvillo K, Dominici L, et al. Sentinel lymph node biopsy in pregnancy women with breast cancer. *Ann Surg Oncol*. 2014;21:2506-2511.
18. Masannat YA, Hanby A, Horgan K, Hardie LJ. DNA damaging effects of the dyes used in sentinel node biopsy: possible implications for clinical practice. *J Surg Res*. 2009;154:234-238.
19. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305:569-575.
20. Czeizel AE, Pataki T, Rockenbauer M. Reproductive outcome after exposure to surgery under anesthesia during pregnancy. *Arch Gynecol Obstet*. 1998;261(4):193-199.
21. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5404 cases. *Am J Obstet Gynecol*. 1989;161:1178-1185.
22. Bloor M, Paech M. Nonsteroidal anti-inflammatory drugs during pregnancy and the initiation of lactation. *Anest Analg*. 2013;116(5):1063-1075.
23. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med*. 1992;152(3):573-576.
24. Cardonick E, Usmani A, Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. *Am J Clin Oncol*. 2010;33:221-228.
25. Cardonick E, Lacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol*. 2004;5(5):283-291.
26. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer*. 2013;13:16-23.
27. Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. *Obstet Gynecol*. 2012;120(6):1267-1272.
28. Gil SK, O'Brian L, Koren G. The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis. *Dig Dis Sci*. 2009;54:1835-1838.
29. Witzel ID, Muller V, Harps E, Janicke F, de Wit M. Trastuzumab in pregnancy associated with poor fetal outcome. *Ann Oncol*. 2008;19(1):191-192.
30. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy – case report and literature review. *Gynecol Oncol*. 2001;80(3):405-408.
31. Stewart F. A., Akleyev A. V., Hauer-Jensen M., et al. ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs–threshold doses for tissue reactions in a radiation protection context. *Annals of the ICRP*. 2012;41(1-2):1-322.
32. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and outcome: a systematic review of the literature. *Radiother Oncol*. 2008;87:3-16.
33. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer*. 2006;106(2):237-246.
34. Van Calsteren K, Haynes L, Smet DE, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and neonatal outcomes. *J Clin Oncol*. 2010;28(4):683-689.
35. Adams E, McCann L, Armes J, et al. The experiences, needs and concerns of younger women with breast cancer: a meta-ethnography. *Psychooncology*. 2011;20:851-861.
36. Jackson E, Glasier A. Return of ovulation and menses in post partum non lactating women: a systematic review. *Obstet Gynecol*. 2011;117(3):657-662.
37. Schwartz EB, Hess R, Trussell J. Contraception for cancer survivors. *J Gen Intern Med*. 2009;24(suppl2):401-406.
38. Trinhn XB, Tjalma WA, Makar AP, et al. Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. *Fertil Steril*. 2008;90(1):17-22.
39. Kapp N, Curtis KM. Intrauterine device insertion during post partum period: a systematic review. *Contraception*. 2009;80(4):327-336.
40. Amant F, Vandenbroucke T, Verheecke M, et al. Pediatric outcome after maternal cancer diagnosed in pregnancy. *N Engl J Med*. 2015;373:1834-1834.
41. Murthy RK, Theriault RL, Barnett CM, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. *Breast Cancer Res*. 2014;16:500.
42. Cardonick E, Ginglas MG, Hunter K, Greenspan J. Development of children born to mothers with cancer during pregnancy: comparing in utero chemotherapy exposed children with non exposed controls. *Am J Obstet Gynecol*. 2015;212(5):658.e1-658.e8.

How to cite this article: Macdonald HR. Pregnancy associated breast cancer. *Breast J*. 2020;26:81–85. https://doi.org/10.1111/tbj.13714