



REVIEW

Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences

Fedro Alessandro Peccatori¹, Matteo Lambertini², Giovanna Scarfone³, Lino Del Pup⁴, Giovanni Codacci-Pisanelli⁵

¹Gynecologic Oncology Department, European Institute of Oncology, Milan 20141, Italy; ²Department of Medicine, Institut Jules Bordet and Université Libre de Bruxelles (ULB), Brussels 100, Belgium; ³Department of Obstetrics and Gynecology, IRCCS Ospedale Maggiore Policlinico Mangiagalli, Milan 20121, Italy; ⁴Gynecologic Oncology Department, National Cancer Institute, Aviano 3301, Italy; ⁵Department of Medical and Surgical Science and Biotechnology, University "la Sapienza", Rome 00185, Italy

ABSTRACT

Breast cancer is one of the most frequently diagnosed malignancies during pregnancy. Here, we review the management of women with breast cancer during pregnancy (BCP), focusing on biology, diagnosis and staging, local and systemic treatments, obstetric care and long-term follow-up of children with prenatal exposure to anticancer treatments.

KEYWORDS

Breast cancer; pregnancy; chemotherapy; endocrine therapy; targeted therapy

Introduction

Breast cancer represents the most common tumor diagnosed in women and the most frequent malignancy in women of reproductive age¹. Approximately 7% of all breast carcinomas are diagnosed annually in patients below 40 years, and the incidence is even higher in developing countries². The overall incidence of breast cancer during pregnancy (BCP) varies between 2.4 and 7.3 per 100,000 pregnancies³⁻⁸; however, breast cancer is predicted to become more common due to the current trend of postponing pregnancy to later in life⁹ and evidence suggesting that both the incidence of breast cancer in young women and the occurrence of BCP are increasing^{10,11}.

Biology and prognosis

Breast cancer arising at a young age has potentially unique biological features¹²: as shown by gene-expression profiling, the complexity of this condition seems to go beyond breast cancer subtype distribution¹³. The hormonal milieu during pregnancy with its growth-promoting effects might theoretically result in a more aggressive biology of breast

cancer¹⁴. Although some studies have suggested no major differences in the expression of hormone receptors and HER2 between pregnant and non-pregnant age-matched breast cancer patients¹⁵⁻¹⁷, several studies have shown that BCP seems to be more commonly associated with unfavorable tumor biology such as predominance of triple-negative breast carcinomas (TNBC)¹⁸⁻²⁰, high expression of potentially relevant cancer targets (e.g., PD1/PDL1, SRC, insulin growth factor and Wnt/ β -catenin, RANK ligand), and low prevalence of tumor-infiltrating lymphocytes²¹⁻²³.

The unique biologic features of BCP and the more frequent delay in diagnosis might explain the poor prognosis reported by some authors, even if the immediate postpartum period showed a clear trend toward inferior outcomes compared with outcomes during pregnancy or in women with non-pregnancy-related breast cancer²⁴. Moreover, patients with BCP could be offered "nonstandard" and potentially suboptimal systemic therapies, with a possible negative impact on their prognosis. On the contrary, patients with BCP treated at a single center who received the same standard anthracycline-based chemotherapy regimen during pregnancy had similar clinical outcomes than non-pregnant patients with breast cancer¹⁶. Similar findings were observed in the largest cohort study available¹⁷.

Diagnosis and staging

BCP generally presents at a more advanced stage at diagnosis

Correspondence to: Fedro Alessandro Peccatori

E-mail: fedro.peccatori@ieo.it

Received October 12, 2017; accepted January 3, 2018.

Available at www.cancerbiomed.org

Copyright © 2018 by Cancer Biology & Medicine

than breast cancer in the general population^{25,26}. The possible delay in diagnosis is related to the fact that pregnancy increases breast density and nodularity, making clinical and radiologic examinations more difficult²⁷⁻²⁹. Physicians should thus be aware that a breast lump in a pregnant patient may be associated with a cancer diagnosis; in these cases, imaging and biopsies should be performed without delay²⁵. Histopathological diagnosis based on core biopsy represents the gold standard for BCP and should follow standard procedures as in non-pregnant patients, but the pathologist needs to be informed about the pregnancy status to properly consider alterations that may be caused by the physiological modifications of breast tissue during pregnancy^{11,25}.

Imaging procedures for diagnosis and staging should aim to limit exposure to ionizing radiation^{11,25}. Breast ultrasound and mammography with abdominal shielding can be safely and effectively performed in pregnant patients^{30,31} at all gestational ages; however, contrast-enhanced breast magnetic resonance imaging (MRI) is not recommended due to inadequate data concerning fetal safety with contrast media^{11,25}. Ultrasound represents the preferred imaging modality for staging the abdomen and pelvis, and chest X-ray with abdominal shielding can be performed to stage the chest²⁵. In case of advanced disease or suspected metastasis, diffusion-weighted whole-body MRI without gadolinium can be considered after the first trimester²⁵. Computed tomography, bone scan, and positron emission tomography should be avoided during pregnancy^{11,25}.

Genetic counseling should be offered to pregnant breast cancer patients, especially if there is a family history of breast carcinoma or a TNBC diagnosis, similarly to what is recommended for all young patients with breast cancer³²⁻³⁴.

Local treatment

Surgical management

Surgery can be safely performed at any time during gestation by making careful risk/benefit assessment because of the need for anesthesia. The surgical approach should follow the same guidelines as for non-pregnant cases^{11,25}. Mastectomy is not mandatory for patients with BCP solely on the basis of possible delay in the delivery of radiotherapy^{11,25}. Although the available published data on breast conservation are limited, they support the safety and feasibility of this procedure in pregnant patients³⁵. However, patients diagnosed in the first trimester who desire to conserve the breast should be informed about a possible increased risk of local recurrence due to the long delay in postoperative

radiotherapy³⁵.

According to the American Society of Clinical Oncology (ASCO), clinicians should not recommend sentinel lymph node biopsy (SLNB) in patients with BCP³⁶. However, the use of lymphoscintigraphy with technetium-99 SLNB has been shown to be safe and feasible during pregnancy³⁷⁻⁴⁰. The 1-day protocol is associated with a negligible dose to the fetus (i.e., ≤ 0.014 mGy), much lower than the limit established by the United States (US) National Council on Radiation Protection and Measurements⁴¹. Hence, specific guidelines for patients with BCP suggest that SLNB rather than axillary clearance should be offered whenever indicated^{11,25}.

Blue dye for mapping should be discouraged in pregnant patients due to the low but potentially harmful risk of anaphylactic reaction^{11,25} and the capacity of radiolabeled colloid alone to identify sentinel lymph nodes in 99% of patients.

For breast cancer patients who undergo mastectomy, breast reconstruction with an expander is more feasible and safer than autologous flap-based procedures and should be offered to all patients except those with inflammatory breast cancer^{11,32,42}.

Radiotherapy

Exposure of the fetus to radiotherapy can cause several adverse effects (e.g., intrauterine growth restriction, mental retardation, risk of childhood cancer, fetal death)²⁵. Although some successful cases of radiotherapy for BCP with the subsequent birth of healthy children have been reported, the available data are too limited to draw solid conclusions and it is preferable to postpone its use until the postpartum period^{11,25,35,43}.

Systemic treatment

Chemotherapy

The indication for using chemotherapy in patients with BCP should follow standard recommendation as in the non-pregnant setting and should be based on both tumor biology and tumor stage; however, in this setting, some specific issues should be considered, including gestational age at diagnosis, expected date of delivery, and the preferences of the patient and her family^{11,25}.

In patients with BCP, chemotherapy is contraindicated during the first trimester of gestation, while it can be safely administered in the second and third trimesters^{11,25}.

The first trimester is the period of organogenesis, which is

characterized by high vulnerability to drugs and possible occurrence of spontaneous abortions and major congenital fetal malformations^{11,25}. According to the US National Toxicology Program Monograph, the overall rate of major malformations following exposure to chemotherapy during the first trimester was 14%, with some chemotherapeutic agents (i.e., cyclophosphamide and 5-fluorouracil) being associated with a higher risk of major malformations (18% and 31%, respectively)⁴⁴. Termination of pregnancy is not associated with improved maternal outcome⁴⁵; however, for women with stage IV disease and for those with high-risk early-stage breast cancer diagnosed during the first trimester, termination of pregnancy can be considered to avoid delay in the initiation of cytotoxic therapy. During the second and third trimesters, the administration of chemotherapy is associated with an overall 3% rate of major malformations⁴⁴, similar to the prevalence in the US general population^{46,47}.

Nonetheless, the use of chemotherapy during the second and third trimesters can be associated with an increased number of obstetric and fetal complications, including intrauterine growth restriction, hypertensive disorders of pregnancy, and early delivery in approximately 10%-20% of cases^{11,25}. This relatively higher risk of pregnancy complications calls for a multidisciplinary evaluation of patients undergoing chemotherapy during pregnancy, including careful monitoring of fetal growth and maternal blood pressure (see also next paragraph). Meanwhile, iatrogenic prematurity is associated with impaired cognitive development^{48,49} and should be avoided whenever possible^{11,25}.

Anthracycline-based or anthracycline/taxane-based chemotherapy regimens are standard of care for treating breast cancer^{50,51} and should be recommended also in patients with BCP during the second and third trimesters^{11,25}.

Anthracyclines are the most studied chemotherapy compounds during pregnancy, with more than 400 women with BCP treated with these regimens⁵². Hence, anthracycline-based chemotherapy should be considered as the first choice^{11,25}. In non-pregnant breast cancer patients, the addition of 5-fluorouracil to anthracycline and cyclophosphamide has been shown to be associated with no survival benefit but increased toxicity⁵³; therefore, the combination of doxorubicin or epirubicin and cyclophosphamide (i.e., AC or EC, respectively) should be considered the preferred option also in women with BCP^{11,25}.

Clinical experience with the use of taxanes in patients with BCP is more limited. Docetaxel and paclitaxel are substrates for the placental P-glycoprotein transporter that seems to reduce the amount of drug passing from the placenta into the

fetus; even in experimental models, paclitaxel and docetaxel were shown to persist at low levels in fetal tissues for a long time⁵⁵. A systematic review of women with BCP, including 50 pregnancies with exposure to paclitaxel and docetaxel, showed that taxanes were well tolerated during pregnancy with manageable toxicities⁵⁶. Thus, when clinically indicated, the use of taxanes can be considered during pregnancy^{11,25}. Due to the better toxicity profile and no need for granulocyte colony-stimulating factors (G-CSF) nor premedication with high-dose steroids, weekly paclitaxel should be preferred in women with BCP^{11,25}.

Dose-dense chemotherapy is used in high-risk non-pregnant patients^{57,58}, and one small retrospective cohort study evaluated the feasibility of this treatment during pregnancy⁵⁹. Although the study showed no increased risk of fetal or maternal complications, dose-dense chemotherapy should not be used in women with BCP due to the limited data available and the need for G-CSF support.

Clinicians should be aware that the pharmacokinetics of some cytotoxic drugs (e.g., doxorubicin, epirubicin, docetaxel, and paclitaxel) might be altered during pregnancy^{60,61}. Nonetheless, dose reduction as well as increased doses and treatment intervals should be avoided^{11,25}.

A 3-week interval between the last dose of chemotherapy and the expected date of delivery should be allowed to avoid delivery during the nadir period^{11,25}. Due to the possible occurrence of spontaneous delivery after week 34 of gestation, chemotherapy should be discontinued at week 34 of gestation^{11,25}. Weekly chemotherapy regimens (e.g., weekly epirubicin and weekly paclitaxel) have a lower risk of hematological toxicity and shorter nadir periods; hence, they might be considered as a valid treatment option in pregnant patients, particularly as single-drug treatment in the metastatic setting^{11,25}.

Anti-HER2 agents

Trastuzumab is approved for the treatment of patients with HER2-positive breast cancer in the neoadjuvant, adjuvant, and metastatic settings. However, the HER2 pathway has a crucial role in fetal organogenesis and is also involved in the early conception and implantation phases⁶². Immunoglobulin G antibodies can cross the placenta starting from the second trimester of pregnancy, with a continued increase of passage from then on up to term^{63,64}.

In humans, around 34 breast cancer patients who have been exposed to trastuzumab during pregnancy have been described⁶⁵. When trastuzumab was administered during the

second or third trimester, the pregnancy was complicated with oligohydramnios, resulting in preterm delivery in 5 cases reported⁶⁶. The remaining 29 cases became accidentally pregnant during trastuzumab treatment with consequent exposure during the first trimester^{66,67}. First-trimester exposure was not associated with pregnancy complications or fetal malformations, and no cases of oligohydramnios were described^{66,67}.

Therefore, in contrast to chemotherapy, trastuzumab exposure during the first trimester seems to be not associated with congenital malformations, while exposure beyond the second trimester is likely to produce “on-target” effects, with a high number of cases developing oligohydramnios⁶⁵. Thus, elective administration of trastuzumab should be avoided during pregnancy and postponed until after delivery^{11,25}. No cases of women treated with pertuzumab or T-DM1 during pregnancy have been reported so far⁶⁵, and only one case of lapatinib exposure has been published⁶⁸. Thus, these drugs should not be used in pregnant patients⁶⁵.

Endocrine therapy

In women with BCP, endocrine therapy is contraindicated^{11,25}. Fetal malformations (i.e., craniofacial malformations and ambiguous genitalia) have been described in children with in utero exposure to tamoxifen^{70,71}. Hence, the use of endocrine agents should be postponed until after delivery^{11,25,69}.

Supportive care

Among 5-HT₃ receptor antagonists, ondansetron was shown to be not associated with an increased risk of developing adverse fetal outcomes⁷⁴. Granisetron does not seem to cross the placenta⁷⁵, while no data are available about NK1 receptor antagonists and palonosetron^{72,73}. Steroids are contraindicated during the first trimester because of the risk of cleft palate, while they can be administered during the second and third trimesters¹¹, with a preference for methylprednisolone and hydrocortisone, which are extensively metabolized in the placenta and do not reach the fetus^{11,76}.

The safety of G-CSF during pregnancy is limited to a small retrospective series^{77-79,59}, and they should be used only if strictly indicated^{11,26}.

Obstetric care

As mentioned, cytotoxic chemotherapy can be safely

administered in the second and third trimesters, but can be associated with an increased risk of obstetric and fetal complications. The most common complication associated with chemotherapy exposure is intrauterine growth restriction, with an incidence of 7%–9% up to 22% in the largest case series^{45,80,81}. Other possible obstetric complications, including premature rupture of membranes, can occur in 17%–27% of cases^{45,80,81}.

Pregnancy in cancer patients should be considered and monitored as “high risk”^{11,25}. A multidisciplinary team should be involved in the care of women with BCP from the earliest phase possible. An ultrasound confirming dates with detailed fetal anatomic evaluation before treatment initiation is recommended to rule out preexisting fetal anomalies²⁶. During treatment, fetal ultrasound monitoring is recommended at regular intervals¹¹, and the mother should be accurately evaluated at each chemotherapy cycle, including assessment of arterial blood pressure and proteinuria. The mode of delivery should not differ from usual obstetric indications, and delivery should occur in a tertiary center⁸². Furthermore, the placenta should be sent for histological evaluation to assess possible breast cancer cell contamination⁸³.

Long-term outcomes of children after in utero exposure to anticancer therapies

Reassuring data about the long-term follow-up of babies born from mothers treated for cancer during pregnancy have been reported⁴⁸. With an observation period between 18 months and 20 years, the children’s general health, growth, behavior, and hearing did not differ to those of the general population; moreover, cardiac dimensions and functions were within normal ranges⁴⁸. Cognitive development scores were overall within normal ranges but lower for children who were born preterm than for those born at full term⁴⁸. Another multicenter case-control study confirmed these results⁴⁹. No significant difference in cognitive development was observed between cases and controls; however, the gestational age at birth was correlated with the cognitive outcome in both study groups, confirming that prematurity is correlated with a worse cognitive outcome independent of cancer treatment⁴⁹.

Preterm delivery can lead to several complications also in the general population, and the risk of occurrence of complications increases with decreasing gestational age at birth⁸⁴. Thus, delivery after 37 weeks of gestation is recommended whenever possible, and iatrogenic preterm

delivery should be avoided^{11,25}. Although these findings are encouraging, more data and longer follow-up are necessary to identify possible adverse effects that may not be apparent until later in life, including cardiac function impairment and infertility⁸⁵.

Conclusions

The diagnosis of BCP represents a unique challenge for the patient, her caregivers, and the treating physicians and often raises several religious, moral, or social issues that should be taken into account⁸⁶. The complex medical situation in BCP requires the involvement of a multidisciplinary team from the early phases of its management^{11,25}.

Current guidelines on this topic rely on limited evidence. Hence, further research is required to obtain more conclusive data. Prospective studies for the management of BCP are ongoing in the US and Europe. Since running randomized trials is impossible in this setting, the participation of patients in international registries, such as the one organized in Europe by the International Network on Cancer, Infertility and Pregnancy (<https://www.esgo.org/network/incip/>), will help accrue adequate numbers to provide more robust evidence on the management of women with BCP.

Conflict of interest statement

No potential conflicts of interest are disclosed.

References

- Rosenberg SM, Newman LA, Partridge AH. Breast cancer in young women: rare disease or public health problem? *JAMA Oncol.* 2015; 1: 877-8.
- Ghiassvand R, Adami HO, Harirchi I, Akrami R, Zendehdel K. Higher incidence of premenopausal breast cancer in less developed countries; myth or truth? *BMC Cancer.* 2014; 14: 343
- Smith LH, Dalrymple JL, Leiserowitz GS, Danielsen B, Gilbert WM. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. *Am J Obstet Gynecol.* 2001; 184: 1504-13.
- Stensheim H, Møller B, van Dijk T, Fosså SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol.* 2009; 27: 45-51.
- Andersson TML, Johansson ALV, Hsieh CC, Cnattingius S, Lambe M. Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol.* 2009; 114: 568-72.
- Lee YY, Roberts CL, Dobbins T, Stavrou E, Black K, Morris J, et al. Incidence and outcomes of pregnancy-associated cancer in Australia, 1994-2008: a population-based linkage study. *BJOG.* 2012; 119: 1572-82.
- Eiby S, Kjær SK, Mellekjær L. Incidence of pregnancy-associated cancer in Denmark, 1977-2006. *Obstet Gynecol.* 2013; 122: 608-17.
- Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol.* 2003; 189: 1128-35.
- Johnson JA, Tough S, SOGC GENETICS COMMITTEE. Delayed child-bearing. *J Obstet Gynaecol Can.* 2012; 34: 80-93.
- Merlo DFM, Ceppi M, Filiberti R, Bocchini V, Znaor A, Gamulin M, et al. Breast cancer incidence trends in European women aged 20-39 years at diagnosis. *Breast Cancer Res Treat.* 2012; 134: 363-70.
- Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncol.* 2015; 1: 1145-53.
- Azim Jr HA, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res.* 2014; 16: 427
- Azim Jr HA, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. *Clin Cancer Res.* 2012; 18: 1341-51.
- Schedin P. Pregnancy-associated breast cancer and metastasis. *Nat Rev Cancer.* 2006; 6: 281-91.
- Azim Jr HA, Botteri E, Renne G, Dell'Orto P, Rotmensz N, Gentilini O, et al. The biological features and prognosis of breast cancer diagnosed during pregnancy: a case-control study. *Acta Oncol.* 2012; 51: 653-61.
- Litton JK, Warneke CL, Hahn KM, Palla SL, Kuerer HM, Perkins GH, et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. *Oncologist.* 2013; 18: 369-76.
- Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J, 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.
- Murphy CG, Mallam D, Stein S, Patil S, Howard J, Sklarin N, et al. Current or recent pregnancy is associated with adverse pathologic features but not impaired survival in early breast cancer. *Cancer.* 2012; 118: 3254-9.
- Genin AS, Lesieur B, Gligorov J, Antoine M, Selleret L, Rouzier R. Pregnancy-associated breast cancers: do they differ from other breast cancers in young women? *Breast.* 2012; 21: 550-5.
- Madaras L, Kovács KA, Szász AM, Kenessey I, Tökés AM, Székely B, et al. Clinicopathological features and prognosis of pregnancy associated breast cancer-a matched case control study. *Pathol Oncol Res.* 2014; 20: 581-90.
- Azim Jr HA, Brohée S, Peccatori FA, Desmedt C, Loi S, Lambrechts D, et al. Biology of breast cancer during pregnancy using genomic profiling. *Endocr Relat Cancer.* 2014; 21: 545-54.
- Azim Jr HA, Peccatori FA, Brohée S, Branstetter D, Loi S, Viale G,

- et al. RANK-ligand (RANKL) expression in young breast cancer patients and during pregnancy. *Breast Cancer Res.* 2015; 17: 24
23. Azim HA, Vingiani A, Peccatori F, Viale G, Loi S, Pruneri G. Tumour infiltrating lymphocytes (TILs) in breast cancer during pregnancy. *Breast.* 2015; 24: 290-3.
 24. Azim Jr 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: 834-42.
 25. Peccatori FA, Azim Jr HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013; 24 Suppl 6: vi160-70.
 26. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet.* 2012; 379: 570-9.
 27. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. *Arch Surg.* 2003; 138: 91-9.
 28. Leslie KK, Lange CA. Breast cancer and pregnancy. *Obstet Gynecol Clin North Am.* 2005; 32: 547-58.
 29. Ulery M, Carter L, McFarlin BL, Giurgescu C. Pregnancy-associated breast cancer: significance of early detection. *J Midwifery Womens Health.* 2009; 54: 357-63.
 30. 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. *AJR Am J Roentgenol.* 2013; 200: 321-8.
 31. Vashi R, Hooley R, Butler R, Geisel J, Philpotts L. Breast imaging of the pregnant and lactating patient: physiologic changes and common benign entities. *AJR Am J Roentgenol.* 2013; 200: 329-36.
 32. Paluch-Shimon S, Pagani O, Partridge AH, Bar-Meir E, Fallowfield L, Fenlon D, et al. Second international consensus guidelines for breast cancer in young women (BCY2). *Breast.* 2016; 26: 87-99.
 33. Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol.* 2015; 33: 304-11.
 34. Rosenberg SM, Ruddy KJ, Tamimi RM, Gelber S, Schapira L, Come S, et al. BRCA1 and BRCA2 mutation testing in young women with breast cancer. *JAMA Oncol.* 2016; 2: 730-6.
 35. Toesca A, Gentilini O, Peccatori F, Azim Jr HA, Amant F. Locoregional treatment of breast cancer during pregnancy. *Gynecol Surg.* 2014; 11: 279-84.
 36. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American society of clinical oncology clinical practice guideline update. *J Clin Oncol.* 2014; 32: 1365-83.
 37. Gentilini O, Cremonesi M, Trifirò G, Ferrari M, Baio SM, Caracciolo M, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol.* 2004; 15: 1348-51.
 38. Spanheimer PM, Graham MM, Sugg SL, Scott-Conner CEH, Weigel RJ. Measurement of uterine radiation exposure from lymphoscintigraphy indicates safety of sentinel lymph node biopsy during pregnancy. *Ann Surg Oncol.* 2009; 16: 1143-7.
 39. Gentilini O, Cremonesi M, Toesca A, Colombo N, Peccatori F, Sironi R, et al. Sentinel lymph node biopsy in pregnant patients with breast cancer. *Eur J Nucl Med Mol Imaging.* 2010; 37: 78-83.
 40. Gropper AB, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. *Ann Surg Oncol.* 2014; 21: 2506-11.
 41. Pandit-Taskar N, Dauer LT, Montgomery L, St Germain J, Zanzonico PB, Divgi CR. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. *J Nucl Med.* 2006; 47: 1202-8.
 42. Lohsiriwat V, Peccatori FA, Martella S, Azim Jr HA, Sarno MA, Galimberti V, et al. Immediate breast reconstruction with expander in pregnant breast cancer patients. *Breast.* 2013; 22: 657-60.
 43. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol.* 2005; 6: 328-33.
 44. National Toxicology Program. NTP monograph: developmental effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy. *NTP Monogr.* 2013; 2013: i-214.
 45. Cardonick E, Dougherty R, Grana G, Gilmandyar D, Ghaffar S, Usmani A. Breast cancer during pregnancy: maternal and fetal outcomes. *Cancer J.* 2010; 16: 76-82.
 46. Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, et al. Reporting birth defects surveillance data 1968-2003. *Birth Defects Res A Clin Mol Teratol.* 2007; 79: 65-186.
 47. Martin JA, Hamilton BE, Ventura SJ, Osterman MJK, Kirmeyer S, Mathews TJ, et al. Births: final data for 2009. *Natl Vital Stat Rep.* 2011; 60: 1-70.
 48. Amant F, Van Calsteren K, Halaska MJ, Gziri MM, Hui W, Lagae L, et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. *Lancet Oncol.* 2012; 13: 256-64.
 49. Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, et al. Pediatric outcome after maternal cancer diagnosed during pregnancy. *N Engl J Med.* 2015; 373: 1824-34.
 50. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies-improving the management of early breast cancer: St Gallen international expert consensus on the primary therapy of early breast cancer 2015. *Ann Oncol.* 2015; 26: 1533-46.
 51. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for her2-positive breast cancers: an American society of clinical oncology guideline adaptation of the cancer care Ontario clinical practice guideline. *J Clin Oncol.* 2016; 34: 2416-27.
 52. Lambertini M, Kamal NS, Peccatori FA, Del Mastro L, Azim Jr HA. Exploring the safety of chemotherapy for treating breast cancer during pregnancy. *Expert Opin Drug Saf.* 2015; 14: 1395-408.
 53. Del Mastro L, De Placido S, Bruzzi P, De Laurentiis M, Boni C, Cavazzini G, et al. Fluorouracil and dose-dense chemotherapy in

- adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. *Lancet*. 2015; 385: 1863-72.
54. Smit JW, Huisman MT, van Tellingen O, Wiltshire HR, Schinkel AH. Absence or pharmacological blocking of placental P-glycoprotein profoundly increases fetal drug exposure. *J Clin Invest*. 1999; 104: 1441-7.
 55. Calsteren KV, Verbesselt R, Devlieger R, De Catte L, Chai DC, Van Bree R, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. *Int J Gynecol Cancer*. 2010; 20: 1456-64.
 56. Zagouri F, Sergentanis TN, Chrysikos D, Dimitrakakis C, Tsigginou A, Zografos CG, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer*. 2013; 13: 16-23.
 57. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. *J Natl Cancer Inst*. 2010; 102: 1845-54.
 58. Petrelli F, Cabiddu M, Coinu A, Borgonovo K, Ghilardi M, Lonati V, et al. Adjuvant dose-dense chemotherapy in breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat*. 2015; 151: 251-9.
 59. Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. *Obstet Gynecol*. 2012; 120: 1267-72.
 60. Van Calsteren K, Verbesselt R, Ottevanger N, Halaska M, Heyns L, Van Bree R, et al. Pharmacokinetics of chemotherapeutic agents in pregnancy: a preclinical and clinical study. *Acta Obstet Gynecol Scand*. 2010; 89: 1338-45.
 61. van Hasselt JGC, van Calsteren K, Heyns L, Han S, Mhallem Gziri M, Schellens JHM, et al. Optimizing anticancer drug treatment in pregnant cancer patients: pharmacokinetic analysis of gestation-induced changes for doxorubicin, epirubicin, docetaxel and paclitaxel. *Ann Oncol*. 2014; 25: 2059-65.
 62. Lee KF, Simon H, Chen H, Bates B, Hung MC, Hauser C. Requirement for neuregulin receptor erbB2 in neural and cardiac development. *Nature*. 1995; 378: 394-8.
 63. Simister NE. Placental transport of immunoglobulin G. *Vaccine*. 2003; 21: 3365-9.
 64. Schneider H, Miller RK. Receptor-mediated uptake and transport of macromolecules in the human placenta. *Int J Dev Biol*. 2010; 54: 367-75.
 65. Lambertini M, Peccatori FA, Azim Jr HA. Targeted agents for cancer treatment during pregnancy. *Cancer Treat Rev*. 2015; 41: 301-9.
 66. Zagouri F, Sergentanis TN, Chrysikos D, Papadimitriou CA, Dimopoulos MA, Bartsch R. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013; 137: 349-57.
 67. Azim Jr HA, Metzger-Filho O, de Azambuja E, Loibl S, Focant F, Gresko E, et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). *Breast Cancer Res Treat*. 2012; 133: 387-91.
 68. Kelly H, Graham M, Humes E, Dorflinger LJ, Boggess KA, O'Neil BH, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer*. 2006; 7: 339-41.
 69. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American society of clinical oncology clinical practice guideline update on ovarian suppression. *J Clin Oncol*. 2016; 34: 1689-701.
 70. 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: 405-8.
 71. Braems G, Denys H, De Wever O, Cocquyt V, Van den Broecke R. Use of tamoxifen before and during pregnancy. *Oncologist*. 2011; 16: 1547-51.
 72. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010; 21 Suppl 5: v232-43.
 73. Hesketh PJ, Bohlke K, Lyman GH, Basch E, Chesney M, Clark-Snow RA, et al. Antiemetics: American society of clinical oncology focused guideline update. *J Clin Oncol*. 2016; 34: 381-6.
 74. Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med*. 2013; 368: 814-23.
 75. Julius JM, Tindall A, Moise KJ, Refuerzo JS, Berens PD, Smith JA. Evaluation of the maternal-fetal transfer of granisetron in an ex vivo placenta perfusion model. *Reprod Toxicol*. 2014; 49: 43-7.
 76. Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS, et al. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med*. 2007; 357: 1179-89.
 77. Crawford J, Caserta C, Roila F, ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. *Ann Oncol*. 2010; 21 Suppl 5: v248-51.
 78. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011; 47: 8-32.
 79. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC growth factors: American society of clinical oncology clinical practice guideline update. *J Clin Oncol*. 2015; 33: 3199-212.
 80. Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol*. 2012; 13: 887-96.
 81. Van Calsteren K, Heyns L, De Smet F, Van Eycken L, Gziri MM, Van Gemert W, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol*. 2010; 28: 683-9.
 82. Krishna I, Lindsay M. Breast cancer in pregnancy. *Obstet Gynecol*

- Clin North Am. 2013; 40: 559-71.
83. Pavlidis N, Pentheroudakis G. Metastatic involvement of placenta and foetus in pregnant women with cancer. In: *Cancer and Pregnancy*. Berlin, Heidelberg: Springer; 2008. p.183-94.
84. McCormick MC, Behrman RE. The quiet epidemic of premature birth: commentary on a recent Institute of Medicine report. *Ambul Pediatr*. 2007; 7: 8-9.
85. Partridge AH, Garber JE. Long-term outcomes of children exposed to antineoplastic agents in utero. *Semin Oncol*. 2000; 27: 712-26.
86. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer*. 2006; 42: 126-40.
- Cite this article as:** Peccatori FA, Lambertini M, Scarfone G, Del Pup L, Codacci-Pisanelli G. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. *Cancer Biol Med*. 2018; 15: 6-13. doi: 10.20892/j.issn.2095-3941.2017.0146