International Journal of Gerontology 13 (2019) 111–115
https://doi.org/10.6890/IJGE.201906_13(2).0002

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Review Article

Gestational Breast Cancer: A Literature Review

Chia-Yen Hung [a,b], Wen-Chi Chou [b,c], Po-Sheng Yang [d], Chi-Yuan Tzen [e], Suk-Ping Ng [f], Shih-Hua Liu [g], Guan-Jhe Cai [a], Ying-Wen Su [a*]

[a] *Division of Hematology and Medical Oncology, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan,* [b] *Department of Hematology and Oncology, Chang Gung Memorial Hospital at Linkou,* [c] *College of Medicine, Chang Gung University, Taoyuan, Taiwan,* [d] *Department of General Surgery, Mackay Memorial Hospital, Taipei, Taiwan,* [e] *Department of Pathology, Mackay Memorial Hospital, Taipei, Taiwan,* [f] *Department of Radiology, Mackay Memorial Hospital, Taipei, Taiwan,* [g] *Department of Radiation Oncology, Mackay Memorial Hospital, Taipei, Taiwan*

ARTICLE INFO

Accepted 7 November 2018

Keywords:
breast cancer,
gestational,
pregnancy,
treatment

SUMMARY

With the risk of breast cancer increasing with age and trends in delayed childbearing in modern societies, the diagnosis and management of gestational breast cancer become more imperative and challenging for multi-disciplinary team care.

Studies indexed in the PubMed electronic database on the epidemiology, pathology, diagnosis, treatment, and prognosis of gestational breast cancer were reviewed to summarize the principles for the optimal management of these patients.

The diagnosis of breast cancer during pregnancy requires limited radiation exposure, with compromised precision. Different pathologic behaviors, including a higher prevalence of negative estrogen and progesterone receptor and positive human epidermal growth factor receptor 2/neu expression, were observed. The surgical treatment should be the same as that in non-pregnant women. Certain chemotherapy agents are relatively safe and feasible during the second and third trimesters. Radiotherapy, endocrine therapy, and trastuzumab should be avoided during pregnancy. With proper treatments, the prognosis is similar to that in non-pregnant breast cancer patients.

This article updated the information and consensus regarding gestational breast cancer. However, there has been no prospective randomized controlled trial to address the best diagnosis and management of breast cancer during pregnancy. Further studies are needed to help clinicians to establish the paradigm in breast cancer management during pregnancy.

1. Introduction

Breast cancer is one of the most common cancers in pregnant women.[1] Gestational or pregnancy-associated breast cancer, defined as breast cancer diagnosed during pregnancy, in the first postpartum year, or any time during lactation, is expected to become more common due to the trend in delayed childbearing and the increased risk of breast cancer with age[2–4] with incidence rates of approximately one in 1,000 pregnancies and around 15–35 per 100,000 deliveries.[3,4]

Because prospective investigations are lacking, the conclusions of observational studies are often biased from delayed diagnosis of predominantly late or locally advanced disease, inadequate or delayed first-line treatment, and the presence of more aggressive subtypes of breast cancer such as triple-negative disease in younger adults.[5] It is challenging for clinicians and multi-disciplinary teams to properly administer anticancer treatment without negatively influencing the fetus and the delivery process. Despite these unresolved clinical issues, prospective studies regarding gestational breast cancer are limited. Therefore, we searched and reviewed the available literature and clinical studies to answer clinically relevant questions regarding the management of gestational breast cancer.

2. Methods

The PubMed electronic database was searched for articles published between 2000 and 2018 using keywords including pregnancy, breast cancer, diagnosis, staging, management, surgery, radiotherapy, chemotherapy, prognosis, and neonatal outcome. Due to the lack of randomized studies, cohort series, case series, and case reports were reviewed and summarized. No articles on anesthesiology, psychosocial, or ethical issues were included.

3. Results

3.1. Diagnosis

Delayed diagnosis is common in gestational breast cancer. The average delay ranges from 1–2 months.[4] A delay of one month increases the risk of nodal involvement by 0.9%.[6] Therefore, more clinical attention should be paid to any breast mass persisting for more than two weeks. The reasons for delayed diagnosis include decreased self-awareness of breast lumps due to physiological

* Corresponding author.
E-mail addresses: yingwensu.5896@mmh.org.tw (Y. W. Su)

changes during pregnancy, including engorgement and hypertrophy of breast tissue,[7] and concern for radiation exposure by standard radiologic tools such as mammography.

3.2. Imaging

Breast ultrasonography is the standard diagnostic tool to evaluate palpable breast masses during pregnancy, with high sensitivity and specificity and no fetal radiation exposure risk.[8]

Mammography is not absolutely contraindicated for pregnant women. Under adequate abdominal shielding in a two-view mammogram, the dose of radiation exposure (about 200–400 millirads) can be negligible.[9] Therefore, routine use of abdominal shielding is recommended for all pregnant women undergoing mammography.

Contrasted magnetic resonance imaging (MRI) using gadolinium is generally considered harmful to the fetus as multiple studies have shown an increased incidence of stillbirth and rheumatologic and/or dermatologic disease in fetuses.[10,11] The National Radiological Protection Board suggests avoiding MRI in the first trimester due to limited evidence of its organogenesis safety.[12] Therefore, MRI without gadolinium contrast, rather than computed tomography scan with concern regarding fetal radiation exposure, may be considered beyond the first trimester for primary or metastatic site evaluation, such as the chest, abdomen, brain, or even bone.[4,12,13] Moreover, chest radiography, with an estimated exposure dose of approximately 0.06 millirads per exam, is considered to have a low radiation exposure risk to the fetus under adequate fetal shielding. Abdominal ultrasonography is a safe and feasible method to evaluate liver metastasis. Information regarding the safety and efficacy of positron emission tomography is limited and inconclusive.[14] Although radionuclide bone scans are reportedly safe for the fetus,[15] these scans should be reserved for when MRI is unavailable or to resolve controversial observationson MRI, and a “low-dose” bone scan (i.e. a half-dose compensated by a doubled acquisition time) is favored with a lower fetal radiation exposure (approximately 0.08 rad).[16]

3.3 Pathology

As in non-pregnant women, biopsy, including core needle, incisional, or excisional biopsies, is the gold standard method for the definitive diagnosis of gestational breast cancer and is relatively safe for pregnant women.[4,17] Core needle biopsy is preferred, with a high sensitivity rate up to 90%.[18] The pathologist must be cautious about the potential to misread hyperproliferative breast changes.

The predominant histology in gestational breast cancer is invasive ductal carcinoma,[19] but more aggressive or clinically less favorable features are noted, with more negative estrogen and progesterone receptor expression, positive human epidermal growth factor receptor (HER)-2/neu expression, and higher grade or higher Ki-67 scores.[20]

3.4. Treatment

The treatment principles for gestational breast cancer follow those for non-pregnant women; however, the decision is often individualized with the consideration of both maternal and fetal safety.

Pregnancy termination did not improve the survival outcome for gestational breast cancer; some evidence even showed worse survival in patients with early termination.[21] The decision for termination should be individualized with considerations of the ability to raise the offspring, the potential risk to the fetus, and future fertility.

3.4.1. Surgery

Surgery, including modified radical mastectomy and breast-conserving surgery together with axillary lymph node dissection (ALND), is the definitive treatment for localized gestational breast cancer and is considered safe in all trimesters, with minimal fetal risk by contemporary techniques.[4,8] The role of sentinel lymph node dissection is controversial due to the uncertain safety of the radioisotope,[16,22] although some data revealed comparable outcomes with ALND in nodal negative patients with rapid clearance and negligible radioactivity in the body under a one-day protocol (injected ^{99m}Tc-labeled colloid on the day of surgery).[23,24]

3.4.2. Radiotherapy

As a general principle, radiotherapy should be avoided until after delivery because of the increased risk of embryonic death and radiation-induced health effects, such as miscarriage, malformations, growth or mental retardation, and carcinogenesis.[25,26] The estimated dose to the fetus from breast or chest wall radiation following a dose of 50 Gy was 2.1–7.6 centigrays (cGy) in the first trimester, 2.2–24.6 cGy during the second trimester, and 2.2–58.6 cGy during the third trimester.[27] Delays in radiotherapy result in outcomes similar to those with earlier initiation in patients at the second and third trimester;[28,29] therefore, no justification exists for radiotherapy during pregnancy or therapeutic abortion, which may be relevant only in patients with rapidly progressing disease such as inflammatory breast cancer or metastatic disease.

3.4.3. Chemotherapy

The indication for chemotherapy in patients with pregnancy should be the same as that in patients who are not pregnant, with consideration of the pharmacokinetic changes during pregnancy and principles to reduce toxicity to the growing fetus from chemotherapeutic agents.

Generally speaking, chemotherapy dose calculations in pregnant patients should follow the body surface area principle (i.e., adjusting with increased body weight).[30] However, physiological changes during pregnancy, including increased total blood volume and “third space” volume from amniotic fluid, increased hepatic and renal clearance, decreased gastric motility, as well as decreased plasma levels of albumin, may affect drug metabolism and clearance in pregnancy, with uncertain significance under no-dose-adjustment studies based on physiological changes.[16,30,31]

The proper timing for the administration of chemotherapy is critical for the growing fetus. Fetal exposure to chemotherapy in the first trimester has the highest risk for spontaneous abortion, teratogenesis, and fetal congenital malformation, with a reported incidence rate up to 16%[8,32] compared with relatively lower incidence rates (around 1.3%) in the second and third trimesters.[31] Therefore, administrating chemotherapy in the first trimester is generally prohibited. Moreover, to avoid neutropenia in newborns, chemotherapy is usually not administered in the 2–4 weeks prior to the due date.[6]

For individual chemotherapeutic agents, the current suggestions are mainly based on retrospective studies or case reports, with limited credibility and possible reporting bias.

A prospective study reported that anthracycline-based chemotherapies, including doxorubicin and cyclophosphamide; fluorouracil, doxorubicin, and cyclophosphamide (FAC); or fluorouracil, epirubicin, and cyclophosphamide (FEC) as the most common agents used in breast cancer treatment, are relatively safe without significant short-term complications when used during the second or third trimesters.[33]

Alkylating agents, including cisplatin, carboplatin, and cyclophosphamide, are reportedly safe when used after the first trimester.[30,34] In a systemic review, intrauterine growth restriction, preterm birth, oligo-/poly-hydramnios, and ventriculomegaly were reported as possible fetal side effects with intrauterine platinum exposure.[34]

The anti-metabolite, methotrexate, is commonly used in combination with fluorouracil and cyclophosphamide (known as the CMF regimen) and is contraindicated in all stages of pregnancy due to its abortifacient and teratogenic risks.[31,35] The majority of 5-fluorouracil (5-FU) experiences during pregnancy are based on the combined treatment with doxorubicin/epirubicin and cyclophosphamide (FAC or FEC regimen). According to the National Toxicology Program, only 1.2% of cases exposed to 5-FU in the second and third trimesters presented with clubfoot or hemihypertrophy of the lower extremities.[36] Capecitabine and gemcitabine both belong to Food and Drug Administration (FDA) pregnancy category D, with sparse data available.[34,36]

The use of anti-microtubule agents, including paclitaxel and docetaxel, are feasible in pregnancy after the first trimester, with limited risks to the mother or fetus.[16] Data regarding the safety of vinorelbine, eribulin, and ixabepiloneare lacking.

3.4.4. Other treatments

Trastuzumab, as a backbone treatment for all HER-2/neu-overexpressed patients, is contraindicated during pregnancy due to an increased risk of oligohydramnios or anhydramnios-related fetal deaths, pulmonary hypoplasia, and fetal developmental abnormalities.[37] The use of lapatinib is currently not recommended in pregnancy because of limited evidence.[38] The ongoing prospective study, MotHER, is designed to investigate the uncertain safety issue for pertuzumab and ado-trastuzumab emtansine, which are both currently classified as FDA pregnancy category D.

Hormonal therapy with tamoxifen is contraindicated during pregnancy as it increases the risk of vaginal bleeding, miscarriage, congenital abnormalities, and even fetal death.[39] Aromatase inhibitors and luteinizing hormone-releasing hormone (LHRH) agonists are both contraindicated in pregnancy as FDA pregnancy category X, with negative effects such as abortion for LHRH agonists in animal studies.[40,41]

3.4.5. Adjunctive medication

Anti-emetic agents, including selective serotonin (5-HT3) antagonists, neurokinin-1 antagonists, promethazine, metoclopramide, and steroids, are generally considered safe to use during pregnancy.[42] Furthermore, both granulocyte colony-stimulating factor (G-CSF) and recombinant erythropoietin are relatively safe[42] under indirect evidence of the safe use of G-CSF in the management of neonatal neutropenia[43,44] and unexplained recurrent miscarriage.[45]

3.5. Prognosis

The prognosis for gestational breast cancer was similar to that for non-pregnant women according to current evidence,[4,46] with even better survival outcomes shown in one study.[47]

Regarding the prognosis for infants, the current evidence also indicates comparable development outcomes in cardiac, cognitive, and general aspects between children born to mothers diagnosed with cancer during pregnancy and those of the same gestational age without uterine chemotherapy or radiation exposure.[33,48]

3.6. Other issues

3.6.1. Breastfeeding

Breastfeeding appears to be safe and feasible, and itis usually

Table 1
Summary of gestational breast cancer.

Imaging	➢ Breast ultrasonography: gold standard ➢ Mammography: contraindicated ➢ Non-contrasted MRI: avoid in first trimester - Contraindicated: gadolinium (MRI contrast) ➢ PET: inconclusive ➢ "Low-dose" bone scan: considered favorable with preventive procedures
Pathology	➢ Biopsy: gold standard (specifically, core needle biopsy) - More negative ER/PR and positive HER-2/neu expression - Higher grade or score of Ki-67
Treatment	
- Surgery	Same as for non-pregnant women - MRM or BCS+ALND - Sentinel lymph node dissection: controversial (radioisotope: uncertain safety)
- Chemotherapy	Relatively safe and feasible during the second and third trimesters - Relatively safe: anthracycline-based regimen, cisplatin, carboplatin, cyclophosphamide - Feasible: taxane - Contraindicated:methotrexate - FDA pregnancy category D (positive human fetal risk): capecitabine, gemcitabine - No data available: vinorelbine, eribulin, ixabepilone
- Radiotherapy	contraindicated
- Endocrine therapy	contraindicated
- Anti-HER-2 agents (trastuzumab, lapatinib)	contraindicated
Prognosis	Similar to that of non-gestational breast cancer mothers and infants - Breastfeeding: safe and feasible (usually in the contralateral breast) - Breastfeeding: avoided during chemotherapy, endocrine therapy, and treatment with trastuzumab and lapatinib - Subsequent pregnancy: avoid conceiving within two years after the completion of anti-cancer treatment

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; MRM, modified radical mastectomy; PET, positron emission tomography; PR, progesterone receptor.

successful in the contralateral breast,[49] without evidence to influence prognosis.[50]

The current consensus recommends against breastfeeding during chemotherapy, endocrine therapy, and treatment with trastuzumab and lapatinib. Most of the cytotoxic chemotherapy agents are excreted in breast milk, especially cyclophosphamide, methotrexate, and doxorubicin.[4,51] Taxane, as a lipophilic agent, should also be used with caution due to its accumulation in milk.[16] These agents might contribute to neonatal neutropenia or pancytopenia in breastfed infants.[4,51]

3.6.2. Pregnancy after breast cancer

Based on current evidence, there is no negative impact on the prognosis of subsequent conception in women who have undergone successful anti-cancer treatment.[52,53] A meta-analysis revealed that pregnancy did not compromise the overall survival, even suggesting a protective effect.[54] However, worse case scenarios, such as relapse during subsequent pregnancy or while the children are still young, should be evaluated before making a decision for subsequent pregnancy.[4]

The current consensus suggests avoiding conceiving within at least two years after the completion of anti-cancer treatment.[4,55]

4. Conclusion

With proper treatment, patients with gestational breast cancer should have the same prognosis as those who are not pregnant. Therefore, unnecessary delay of optimal treatment should be avoided.

The diagnosis and treatment of gestational breast cancer patients remain a challenge for clinicians. The treatment plan for gestational breast cancer should be individualized with consideration of the physical and emotional well-being of mothers and the health of the fetus. Surgery and many chemotherapeutic agents, including anthracyclines and taxanes, are relatively safe and feasible for use beyond the first trimester. Radiotherapy, endocrine therapy, and trastuzumab should be avoided during pregnancy. Breastfeeding and subsequent pregnancy are possible after adequate consultation. We summarised the conclusion in Table 1 according to the current evidence.

However, due to the lack of prospective randomized controlled trials in this field, standard treatment guidelines cannot be determined from this literature review. Relevant studies with stronger evidence are urgently required to assist clinicians in understanding and establishing a paradigm for the management of breast cancer during pregnancy.

Declarations of interest

None.

References

1. Antonelli NM, Dotters DJ, Katz VL, et al. Cancer in pregnancy: A review of the literature. Part II. *Obstet Gynecol Surv.* 1996;51(2):135–142.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7–30.
3. Andersson TM, Johansson AL, Hsieh CC, et al. Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol*. 2009; 114(3):568–572.
4. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: A literature review. *Arch Surg*. 2003;138(1):91–98; discussion 99.
5. Guinee VF, Olsson H, Moller T, et al. Effect of pregnancy on prognosis for young women with breast cancer. *Lancet*. 1994;343(8913):1587–1589.
6. Nettleton J, Long J, Kuban D, et al. Breast cancer during pregnancy: Quantifying the risk of treatment delay. *Obstet Gynecol*. 1996;87(3):414–418.
7. King RM, Welch JS, Martin JK, Jr., et al. Carcinoma of the breast associated with pregnancy. *Surg Gynecol Obstet*. 1985;160(3):228–232.
8. Navrozoglou I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: A mini-review. *Eur J Surg Oncol*. 2008;34(8):837–843.
9. Behrman RH, Homer MJ, Yang WT, et al. Mammography and fetal dose. *Radiology*. 2007;243(2):605; author reply 605–606.
10. Ray JG, Vermeulen MJ, Bharatha A, et al. Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA*. 2016;316(9):952–961.
11. Bellin MF, Webb JA, Van Der Molen AJ, et al. Safety of MR liver specific contrast media. *Eur Radiol*. 2005;15(8):1607–1614.
12. Shellock FG, Crues JV. MR procedures: Biologic effects, safety, and patient care. *Radiology*. 2004;232(3):635–652.
13. Rosenthal DI. Radiologic diagnosis of bone metastases. *Cancer*. 1997; 80(8 Suppl):1595–1607.
14. Takalkar AM, Khandelwal A, Lokitz S, et al. 18F-FDG PET in pregnancy and fetal radiation dose estimates. *J Nucl Med*. 2011;52(7):1035–1040.
15. Baker J, Ali A, Groch MW, et al. Bone scanning in pregnant patients with breast carcinoma. *Clin Nucl Med*. 1987;12(7):519–524.
16. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. *Eur J Cancer*. 2010;46(18):3158–3168.
17. Collins JC, Liao S, Wile AG. Surgical management of breast masses in pregnant women. *J Reprod Med*. 1995;40(11):785–788.
18. Oyama T, Koibuchi Y, McKee G. Core needle biopsy (CNB) as a diagnostic method for breast lesions: Comparison with fine needle aspiration cytology (FNA). *Breast Cancer*. 2004;11(4):339–342.
19. Bonnier P, Romain S, Dilhuydy JM, et al. Influence of pregnancy on the outcome of breast cancer: A case-control study. Societe Francaise de Senologie et de Pathologie Mammaire Study Group. *Int J Cancer*. 1997;72(5):720–727.
20. Middleton LP, Amin M, Gwyn K, et al. Breast carcinoma in pregnant women: Assessment of clinicopathologic and immunohistochemical features. *Cancer*. 2003;98(5):1055–1060.
21. Clark RM, Chua T. Breast cancer and pregnancy: The ultimate challenge. *Clin Oncol (R Coll Radiol)*. 1989;1(1):11–18.
22. Kuerer HM, Gwyn K, Ames FC, et al. Conservative surgery and chemotherapy for breast carcinoma during pregnancy. *Surgery*. 2002;131(1): 108–110.
23. Han SN, Amant F, Cardonick EH, et al. Axillary staging for breast cancer during pregnancy: Feasibility and safety of sentinel lymph node biopsy. *Breast Cancer Res Treat*. 2018;168(2):551–557.
24. Loibl S, Schmidt A, Gentilini O, et al. Breast cancer diagnosed during pregnancy: Adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncol*. 2015;1(8):1145–1153.
25. Kal HB, Struikmans H. Radiotherapy during pregnancy: Fact and fiction. *Lancet Oncol*. 2005;6(5):328–333.
26. Greskovich JF, Jr., Macklis RM. Radiation therapy in pregnancy: Risk calculation and risk minimization. *Semin Oncol*. 2000;27(6):633–645.
27. Mazonakis M, Varveris H, Damilakis J, et al. Radiation dose to conceptus resulting from tangential breast irradiation. *Int J Radiat Oncol Biol Phys*. 2003;55(2):386–391.
28. Hebert-Croteau N, Freeman CR, Latreille J, et al. Delay in adjuvant radiation treatment and outcomes of breast cancer--A review. *Breast Cancer Res Treat*. 2002;74(1):77–94.
29. Toesca A, Gentilini O, Peccatori F, et al. Locoregional treatment of breast cancer during pregnancy. *Gynecol Surg*. 2014;11(4):279–284.
30. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol*. 2004;5(5):283–291.
31. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. *Semin Oncol*. 1989;16(5):337–346.
32. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: Embryo-fetal outcome in 160 patients. *Ann Oncol*. 2004;15(1):146–150.
33. Murthy RK, Theriault RL, Barnett CM, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. *Breast Cancer Res*. 2014;16(6):500.
34. Mir O, Berveiller P, Ropert S, et al. Use of platinum derivatives during pregnancy. *Cancer*. 2008;113(11):3069–3074.
35. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther*. 1997;74(2):207–220.
36. National Toxicology P. NTP monograph: Developmental effects and

pregnancy outcomes associated with cancer chemotherapy use during pregnancy. *NTP Monogr*. 2013;(2):i–214.
37. Zagouri F, Sergentanis TN, Chrysikos D, et al. Trastuzumab administration during pregnancy: A systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;137(2):349–357.
38. Kelly H, Graham M, Humes E, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer.* 2006; 7(4):339–341.
39. 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.
40. Hilliard J, Pang CN, Sawyer CH. Effects of luteinizing hormone-releasing hormone on fetal survival in pregnant rabbits. *Fertil Steril*. 1976;27(4): 421–425.
41. Gohar J, Mazor M, Leiberman JR. GnRH in pregnancy. *Arch Gynecol Obstet*. 1996;259(1):1–6.
42. Amant F, Van Calsteren K, Halaska MJ, et al. Gynecologic cancers in pregnancy: Guidelines of an international consensus meeting. *Int J Gynecol Cancer.* 2009;19 Suppl 1:S1–12.
43. Bilgin K, Yaramis A, Haspolat K, et al. A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. *Pediatrics*. 2001;107(1):36–41.
44. Dale DC, Cottle TE, Fier CJ, et al. Severe chronic neutropenia: Treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol*. 2003;72(2):82–93.
45. Scarpellini F, Sbracia M. Use of granulocyte colony-stimulating factor for the treatment of unexplained recurrent miscarriage: A randomised controlled trial. *Hum Reprod*. 2009;24(11):2703–2708.
46. 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(20):2532–2539.
47. Litton JK, Warneke CL, Hahn KM, 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(4):369–376.
48. Amant F, Vandenbroucke T, Verheecke M, et al. Pediatric outcome after maternal cancer diagnosed during pregnancy. *N Engl J Med*. 2015; 373(19):1824–1834.
49. Moran MS, Colasanto JM, Haffty BG, et al. Effects of breast-conserving therapy on lactation after pregnancy. *Cancer J*. 2005;11(5):399–403.
50. Azim HA, Jr., Bellettini G, Liptrott SJ, et al. Breastfeeding in breast cancer survivors: Pattern, behaviour and effect on breast cancer outcome. *Breast*. 2010;19(6):527–531.
51. Briggs GG, Freeman RK, SJ. Y. *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. 8th ed: Lippincott Williams & Wilkins; 2008 Apr 1.
52. Kroman N, Jensen MB, Wohlfahrt J, et al. Pregnancy after treatment of breast cancer--A population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol*. 2008;47(4):545–549.
53. de Bree E, Makrigiannakis A, Askoxylakis J, et al. Pregnancy after breast cancer. A comprehensive review. *J Surg Oncol*. 2010;101(6):534–542.
54. Azim HA, Jr., Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies. *Eur J Cancer.* 2011;47(1):74–83.
55. Largillier R, Savignoni A, Gligorov J, et al. Prognostic role of pregnancy occurring before or after treatment of early breast cancer patients aged < 35 years: A GET(N)A Working Group analysis. *Cancer.* 2009;115(22): 5155–5165.