Review Article

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Breast cancer and pregnancy

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Abstract:
Background: In the past decades the incidence of pregnancy-associated breast cancer (PABC) increased. Possible explanations are the trend to postpone childbearing and the general increase in the incidence of breast cancer.
Materials and methods: A sytematic review of the literature was performed with the aim to report on incidence, diagnosis, treatment and prognosis of breast cancer during pregnancy. We also cover the issue of pregnancy following a diagnosis of breast cancer including fertility preservation and prognosis.
Results: Ultrasound is the imaging method of choice in pregnancy, but mammography can also be performed as the fetal irradiation dose is low. To avoid a delay in diagnosis every sonographic mass in pregnant women which does not clearly correspond to a cyst needs further investigation by biopsy. Treatment should follow as close as possible the guidelines for non-pregnant patients. Administration of chemotherapy is possible after the first trimester. There is a large body of evidence for the use of anthracyclines. In contrast radiotherapy, trastuzumab and antihormonal treatment by tamoxifen are contraindicated during pregnancy. Pregnancy does not seem to influence prognosis. Most adverse obstetric outcomes are related to preterm delivery, which should therefore, whenever possible, be avoided. Young patients with breast cancer and incomplete family planning should be referred for counseling about fertility preservation options before the initiation of adjuvant treatment. A pregnancy following breast cancer does not have a negative impact on prognosis.
Conclusion: Multidisciplinary management of women with breast cancer in pregnancy is mandatory and data should be collected to allow further improvement in management.

Keywords: breast cancer, fertility, obstetrical outcome, pregnancy, pregnancy-associated breast cancer
DOI: 10.1515/hmbci-2017-0026
Received: May 2, 2017; **Accepted:** July 17, 2017

Introduction

The majority of studies reporting on the incidence of breast cancer during pregnancy include also cases of pregnancy-associated breast cancer (PABC). This term implies breast cancer diagnosed during pregnancy and 12 months postpartum.

A swedish population-based cohort study analyzing cancer and multi-generation register estimates the incidence of PABC at 28/100,000 live births [1]. Most cases were diagnosed after delivery. Breast cancer and melanoma were the two most common malignancies during pregnancy and the postpartum period [2].

Fortunately to-date the incidence of PABC is low. But the authors found a clear increase during the last 20 years. Possible explanations are the overall increase in the incidence of breast cancer and the trend of postponing childbearing. In fact, in Switzerland in 2013 in more than one third of the live births the mother was aged >34 years [3].

Thus, PABC is actually still a rare but complex entity which demands multidisciplinary management. In this review of the literature we want to give an overview about actual recommendations. Eligible articles were identified by a search of MEDLINE® electronic database for the period up to march 2017 using the keywords "breast cancer" and "pregnancy", "PABC", "breast cancer and fertility" or "breast cancer and obstetrical outcome". We also checked all references of relevant articles. Search was limited to publications in English, French and German.

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Body of review

Breast cancer during pregnancy

Diagnosis

Delay in diagnosis of PABC remains an important concern with impact on prognosis. Bonnier et al. [4] found a median delay to diagnosis of 2.2 months in pregnant patients compared to 1.2 months in non-pregnant women.

Most patients present with a lump detected through breast self-examination [5]. Ultrasound is the imaging modality of choice because of a high sensitivity and absence of X-rays. As breast cancer in young women often presents with benign features in ultrasound every sonographic mass which does not clearly correspond to a cyst needs further investigation by biopsy. Milk fistula as described in case reports are extremly rare [6].

In case of malignancy a mammography must be performed to exclude multicentric or bilateral disease. The fetal irradiation dose is estimated at 0.004 μGy and thereby largely under the critical threshold of 0.1 Gy.

Data about the value of breast magnetic resonance imaging (MRI) in pregnancy is poor. Sensitivity and specificity can actually not be defined. Moreover the contrast agent gadolinium is known to pass the placental barrier and animal experiences showed teratogenic effects.

Staging procedures for distant metastasis should be delayed until after pregnancy if possible.

Tumor charcteristics of PABC are similar to those of breast carcinoma in young women in general; Middleton et al. evaluated 39 specimens of breast carcinoma which occured during pregnancy. They found a majority of hormone-receptor negative carcinoma (72% ER neg., 76% PR neg.) with a high proliferation rate in 60% and poor differentiation in 84% [7].

Treatment

Surgery

Surgery does not differ from non-pregnant patients and choice of treatment (mastectomy versus breast conserving surgery) should be made according to the usual criteria.

Despite the hypervascularization of the breasts during pregnancy and lactation current studies do not show a higher complication rate [8]. Reconstruction should be differed from the postpartum period. A small case series described the immediate breast reconstruction with an expander in 13 pregnant patients without complications [9].

Dependent on the term of the pregnancy intraoperative fetal monitoring can be discussed.

Sentinel node biopsy during pregnancy has been widely disucussed. Main concerns were radiation exposure of the fetus and a potential modification of lymphatic drainage during pregnancy.

In several studies the measured average radiation dose to the uterus was 1.1 μGy [10]. Therefore the radiotracer should be injected at the day of surgery to reduce time and dose of radiation exposure.

The utilization of blue dye is contraindicated due to a possible teratogenicity. In the 1980s methylen blue was used for intra-amniotic injections as a diagnostic tool. Subsequently an accumulation of fetal intestinal atresia has been observed.

Intratumoral injection of blue dye results in a low dose to the fetus. Some authors described sentinel node biopsy in pregnant patients using blue dye without any complications. But the relatively high rate of allergic reactions (2%) must also be considered.

Gropper et al. [11] published the largest series of patients who underwent sentinel node biopsy during pregnancy. In all 25 patients (seven with blue dye) the intervention was performed without complications. Twenty-five live-births were observed. One fetus was born with a cleft palate, but the mother presented additional risk factors.

Systemic therapy

Most patients with a PABC will need chemotherapy due to their young age and tumor biology. Table 1 shows the most important studies dealing with women who received chemotherapy for breast cancer during pregnancy [12], [13], [14], [15], [16].

Table 1: Summary of studies dealing with chemotherapy for breast cancer during pregnancy.

Authors	Design	n	Agents	Malformations	Follow-up
Berry et al. [12]	Prospective	24	FAC	0	–
Ring et al. [13]	Retrospective	28	16 AC/EC 12 CMF	0	–
Hahn et al. [14]	Prospective	57	FAC	5 (3.2%)	2–157 months
Cardonick et al. [15]	Retro/prospective	104	74 AC/EC 17 FAC/FEC 11 TAC	4 (3.8%)	42 months
Loibl et al. [16]	Retro/prospective	197	178 Anthrazyclines 15 CMF 14 Taxanes	8 (4.1%)	Partial

In conclusion there is sufficient data to support the administration of anthracyclines after the first trimester. The data show a rate of fetal malformations within the range of the general population and a normal development of the children.

Less evidence exists for the application of taxanes during pregnancy. Zagouri published in 2013 a review of the literature with data of 16 studies including 50 women who received taxanes during pregnancy [17]. The most frequent complications were an oligo-/anhydramnios (16.6%), mainly attributed to the co-administration of trastuzumab, and intrauterin growth retardation (12.5%). Malformations were found in two children and 90% of the children were healthy after a follow-up of 16 months.

Nevertheless the regimen of choice for pregnant patients with breast cancer, composed of anthracyclines, cyclophoasphamid and taxanes, is actually the same as in non-pregnant patients.

Poor data exist about pharmacokinetics of chemotherapy agents in pregnant patients. Hence the dosing should be based on the actual weight of the patient [18].

Table 2 summarizes the actual recommendations for the application of chemotherapy for breast cancer during pregnancy as defined in an international expert meeting.

Table 2: Recommendations [18].

- Chemotherapy is contraindicated during the first trimester
- First choice: AC oder EC followed by paclitaxel
- Dose-dense chemotherapy is an option
- Dosing based on the current patient weight
- Interval of 3 weeks between last chemotherapy and delivery is recommended

The use of trastuzumab is contraindicated during pregnancy. The most frequent adverse event is a reversible oligohydramnios caused by a blockade of receptors in the fetal kidneys.

Interestingly trastuzumab causes less complications during the first trimester as the large molecular size of trastuzumab requires active transport to cross the placental barrier and this mechanism is not developed before the 2nd trimester. Thus adminstration during the first trimester in high-risk situations could be discussed [19].

A subanalysis of data from the HERA trial showed an increasesd rate of spontaneous abortion in patients who received trastuzumab in the first trimester. However, in patients who completed their pregnancy to term, fetal outcome was not affected [20]. The authors conclude that accidental fetal exposure to trastuzumab in the first trimester is not a reason for interruption of the pregnancy. No data regarding the administration of pertuzumab during pregnancy exist.

The adjuvant antihormonal treatment by tamoxifen is contraindicated during pregnancy due to the teratogenic effect observed in animal studies. Several case reports on humans showed major congenital anomalies like Goldenhar's syndrome or ambiguous genitalia [21], [22]. It is therefore recommended to respect an interval of 2 months after stopping tamoxifen before attempting pregnancy.

Radiotherapy

The American Association of Physicists in Medicine published, in the 1990s, a report on the effects of irradiation during pregnancy [23]. Most data are derived from observations made on survivors of Hiroshima and Nagasaki.

The impact of irradiation on the fetus depends on the stage of pregnancy. In the periconceptional period a dose of 0.1 Gy can cause abortion. During organogenesis irradiation can induce malformations especially of the the central nervous system (e.g. microcephaly).

After the first trimester the consequences consist mainly of growth restriction, mental retardation and sterility. The critical threshold for teratogenic effects is fixed at 0.1 Gy.

Carcinogenic effects are stochastic and the risk increases with the dose.

There are some reports in the literature about women who received radiotherapy during pregnancy. Luis et al. reviewed the existing data in 2009. Twenty-three women received radiotherapy because of breast cancer between 2 and 24 weeks of pregnancy. Fetal dose was evaluated at max. 0.16 Gy. Two perinatal deaths were reported. The other women delivered healthy babies but no long-term follow-up of the children is available [24]. In general, radiotherapy should be postponed until after delivery. In special cases after weighing the risk of delaying radiotherapy against potential harm to the fetus, radiotherapy with effective shielding might be considered in early pregnancy when the uterus is inside the pelvis distant from the irradiation field.

Prognosis

Information on the prognosis of PABC is crucial when counseling patients whether to continue pregnancy or not.

Since the 1990s 16 studies analyzing the prognosis of patients with PABC were published. Table 3 shows an overview of the most important studies [25]. Ten studies found no difference in survival of women with PABC compared to non-pregnant patients and six authors concluded that prognosis was worse for PABC. However, studies were very heterogenous in number of patients, follow-up and study populations. Reasons for poorer survival might be a delay in diagnosis and treatment but pregnancy at time of diagnosis does not seem to be an independent prognostic factor.

Table 3: Prognosis of PABC (Modified according to [25]).

Study	Patients (n)			Follow-up	Conclusion
	Pregnant	Postpartum	Controls		
Ibrahim 2000	72		216	47.5 months	No difference in DFS or OS
Bladström 2003	94		7779	10 years	Worse DFS and OS for PABC
Mathelin 2008	18	22	61	10 years	Worse DFS and OS for PABC
Stensheim 2008	59	46	13,106	4.9 years	No difference in OS
Beadle 2009	51	53	668	91 months	No difference in OS
Halaska 2009	16	16	32	142 months	No difference in DFS or OS
Azim 2012	65		130	5 years	Poorer DFS for PABC, no difference in OS
Amant 2013	311		865	5 years	No difference in DFS or OS
Genin 2015	16	71	174	113 months	No difference in DFS or OS

One of the most recent and largest studies published by Amant et al. analyzed the outcome of 311 patients with PABC compared to 865 non-pregnant controls. After adjusting for age, tumor characteristics and therapy no effect on disease-free survival (DFS) and OS was found [25].

Obstetrical outcome

Two important multicentric studies analyzed obstetrical outcome in patients with PABC [16], [26]. Both showed an increased prevalence of preterm labor in patients who received chemotherapy. Birthweight was also lower after intra-uterine exposure to chemotherapy.

Fifty percent of women with breast cancer delivered preterm and in the majority of cases (90%) labor was induced [16]. Most neonatal complications were related to preterm birth. The authors conclude that preterm delivery should be avoided whenever possible.

The choice of delivery mode should be done following the usual obstetrical criteria.

Histological examination of the placenta is recommended as case reports of placental metastasis exist.

Pregnancy after breast cancer

Women with a desire for a child after the diagnosis of breast cancer have two main concerns: the impact of treatment on fertility and an eventual negative effect of the pregnancy on prognosis.

In a recent study the authors questioned women between 18 and 45 years with newly diagnosed breast cancer about their family planning [27]. Fifty percent had not completed their family planning yet, but only 9% had been informed about the possibilities of fertility preservation. Knowing about the effects of chemotherapy and antihormonal therapy on fertility proper information of patients should be mandatory.

Up to 40% of women receiving chemotherapy for breast cancer experience a chemotherapy-induced amenorrhea (CIA) [28]. Incidence depends on age and treatment regimen. In general younger patients are less likely to suffer from CIA. A treatment by CMF (cyclophosphamide, methotrexate, 5-fluoruracil) seems to induce more amenorrhea than a regimen with ACT (doxorubicin, cyclophosphamid, paclitaxel) or AC (doxorubicin, cyclophosphamid).

It has also been shown that the anti-Müllerian hormone level decreases significantlly during chemotherapy [29]. Nevertheless it is actually impossible to predict individual fertility after chemotherapy.

For this reason all women who did not complete child bearing at diagnosis should be informed about the different possibilities of fertility preservation including GnRH analogues, cryoconservation of oocytes or ovarian cortex.

For the choice of the method for fertility preservation the individual prognosis, impact of therapy on ovarian function and delay of treatment should be considered.

The approriate interval between cancer and pregnancy remains unclear. The main concerns are the fear of recurrence and the interruption of antihormonal treatment. Patients should be counselled individually regarding tumor biology and prognosis. In patients with hormone-receptor negative breast cancer a delay of 2–3 years according to prognosis should be respected. In hormone-receptor positive breast cancer an interruption of the antihormonal treatment can be discussed after 3 years, but the patient must be informed about the lack of data [30].

A big meta-analysis of 14 studies by Azim et al. [31] found no negative impact of pregnancy following breast cancer on OS. Women who became pregnant after breast cancer even had improved survival compared to patients with breast cancer who did not. This may be explained by the "healthy mother effect". This term describes the fact that women with a pregnancy after breast cancer may have been selected to some extent because of a better prognosis.

Data about breast-feeding after breast cancer are poor. Patients report frequently about insufficient milk production by the treated breast. Lactation does not seem to influence prognosis [32]. Limitation of the duration can be discussed to permit adequate evaluation in imaging for cancer follow-up.

Expert opinion

This article provides a comprehensive review of the actual available evidence on PABC with a focus on treatment.

PABC is actually still a rare entity but the incidence is increasing. Thus gynecologists, obstetricians and oncologists may be confronted with this complex situation more often and should be familiar with the management possibilities.

To avoid delay in diagnosis physicians must be aware of the potential benign features of PABC in imaging and should perform further investigations by biopsy in every sonographic mass which does not clearly correspond to a cyst.

Treatment of pregnant women with breast cancer should follow as closely as possible guidelines for non-pregnant patients. However, whereas a relatively large body of evidence exists concerning the administration of anthracylines during pregnancy data about taxanes are still poor. Systematic data collection by means of international collaborations is crucial to improve our knowledge about PABC.

In recent studies it has been shown that pregnancy does not have a negative impact on prognosis. Women can therefore be reassured and in general interruption of pregnancy is not indicated.

Women who intend to get pregnant after a diagnosis of breast cancer also need special advice. Knowledge about the different options of fertility preservation is expanding. The relatively new technique of cryoconservation of ovarian cortex shows promising results but data of long-term follow-up remain necessary.

Furthermore the appropriate interval between cancer and a following pregnancy needs to be defined.

Outlook

The ongoing international trials will permit an update of the actual recommendations for the management of pregnant women with breast cancer and thereby hopefully allow an individualized counseling of our patients in the future.

Highlights

– The incidence of PABC is increasing
– Treatment should follow as closely as possible the guidelines for non-pregnant patients
– Multidisciplinary management is mandatory
– Systematic data collection is crucial to allow further improvement of treatment recommendations in pregnant patients with breast cancer
– Early referral of patients with breast cancer and incomplete family planning to a specialist to discuss fertility preservation options is needed
– Appropriate interval between cancer and pregnancy thereafter needs to be defined

Author Statement

Research funding: Authors state no funding involved.

Conflict of interest: Authors state no conflict of interest.

Informed consent: Informed consent is not applicable.

Ethical approval: The conducted research is not related to either human or animals use.

References

[1]Andersson TM, Johansson AL, Hsieh CC, Cnattingius S, Lambe M. Increasing incidence of pregnancy-associated breast cancer in Sweden. ObstetGynecol. 2009;114:568–72.
[2]Andersson TM, Johansson AL, Fredriksson I, Lambe M. Cancer during pregnancy and the postpartum period: a population-based study. Cancer. 2015;121:2072–7.
[3]Csonka Y, Mosimann A. Familien in der Schweiz – Statistischer Bericht 2017. Neuchâtel: Swiss Federal Statistical Office (Bundesamt für Statistik), 2017.
[4]Bonnier P, Romain S, Dilhuydy JM, Bonichon F, Julien JP, Charpin C, Influence of pregnancy on the outcome of breast cancer: a case-control study. Int J Cancer. 1997;72:720–7.
[5]Cordoba O, Llurba E, Saura C, Rubio I, Ferrer Q, Cortés J, Multidisciplinary approach to breast cancer diagnosed during pregnancy: maternal and neonatal outcomes. Breast. 2013;22:515–9.
[6]Taylor D, Lazberger J, Ives A, Wylie E, Saunders C. Reducing delay in the diagnosis of pregnancy-associated breast cancer: how imaging can help us. J Med Imaging Radiat Oncol. 2011;55:33–42.
[7]Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. Cancer. 2003;98:1055–60.
[8]Dominici LS, Kuerer HM, Babiera G, Hahn KM, Perkins G, Middleton L, Wound complications from surgery in pregnancy-associated breast cancer (PABC). Breast Dis. 2010;31:1–5.
[9]Lohsiriwat V, Peccatori FA, Martella S, Azim HA, Sarno MA, Galimberti V, Immediate breast reconstruction with expander in pregnant breast cancer patients. Breast. 2013;22:657–60.
[10]Spanheimer PM, Graham MM, Sugg SL, Scott-Conner CE, Weigel RJ. Measurement of uterine radiation exposure from lymphoscintigraphy indicates safety of sentinel lymph node biopsy during pregnancy. Ann SurgOncol. 2009;16:1143–7.

[11]Gropper AB, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE, Sentinel lymph node biopsy in pregnant women with breast cancer. Ann SurgOncol. 2014;21:2506–11.
[12]Berry DL, Theriault RL, Holmes FA, Parisi VM, Booser DJ, Singletary SE, Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol. 1999;17:855–61.
[13]Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five Londonteaching hospitals. J Clin Oncol. 2005;23:4192–7.
[14]Hahn KM, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M, Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer. 2006;107:1219–26.
[15]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.
[16]Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012;13:887–96.
[17]Zagouri F, Sergentanis TN, Chrysikos D, Dimitrakakis C, Tsigginou A, Zografos CG, Taxanes for breast cancer during pregnancy: a systematic review. Clin Breast Cancer. 2013;13:16–23.
[18]Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. JAMA Oncol. 2015;1:1145–53.
[19]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.
[20]Azim HA, Metzger-Filho O, de Azambuja E, Loibl S, Focant F, Gresko E, 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.
[21]Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. J Am Med Assoc. 1994;271:1905–6.
[22]Tewari K, Bonebrake RG, Asrat T, Shanberg AM. Ambiguous genitalia in infant exposed to tamoxifen in utero. Lancet. 1997;350:183.
[23]Stovall M, Blackwell CR, Cundiff J, Novack DH, Palta JR, Wagner LK, Fetal dose from radiotherapy with photon beams: report of AAPM radiation therapy committee task group no. 36. Med Phys. 1995;22:63–82.
[24]Luis SA, Christie DR, Kaminski A, Kenny L, Peres MH. Pregnancy and radiotherapy: management options for minimising risk, case series and comprehensive literature review. J Med Imaging Radiat Oncol. 2009;53:559–68.
[25]Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J, Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013;31:2532–9.
[26]Van Calsteren K, Heyns L, De Smet F, Van Eycken L, Gziri MM, Van Gemert W, Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol. 2010;28:683–9.
[27]Goldfarb SB, Kamer SA, Oppong BA, Eaton A, Patil S, Junqueira MJ, Fertility preservation for the young breast cancer patient. Ann SurgOncol. 2016;23(5):1530–6.
[28]Sukumvanich P, Case LD, Van Zee K, Singletary SE, Paskett ED, Petrek JA, Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. Cancer. 2010;116:3102–11.
[29]Anderson RA, Themmen AP, Al-Qahtani A, Groome NP, Cameron DA. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. Hum Reprod. 2006;21:2583–92.
[30]Margulies AL, Selleret L, Zilberman S, Nargarra IT, Chopier J, Gligorov J, Pregnancy after cancer: for whom and when?. Bull Cancer. 2015;102:463–9.
[31]Azim HA, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011;47:74–83.
[32]Azim HA, Bellettini G, Liptrott SJ, Armeni ME, Dell'Acqua V, Torti F, Breastfeeding in breast cancer survivors: pattern, behaviour and effect on breast cancer outcome. Breast. 2010;19:527–31.