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REVIEW ARTICLE

Breast cancer and pregnancy; Overview of international bibliography

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Summary

Breast cancer constitutes the first gynaecological malignancy in pregnancy with a frequency of 1 : 3,000 - 10,000 pregnancies. Pregnancy itself does not seem to affect the odds of developing breast cancer or its prognosis.

Breast ultrasonography constitutes the diagnostic method of choice, whereas magnetic resonance imaging (MRI) can be used as adjunct. As main staging tests, thoracic X-ray and abdominal ultrasonography are recommended.

The therapy of choice is modified radical mastectomy for the first two trimesters and lumpectomy or partial mastectomy followed by radiation therapy after childbirth for patients diagnosed in the 3rd trimester of pregnancy. The administration of chemotherapy is deemed acceptable in the 2nd and 3rd trimester, whereas hormonal therapy should be avoided for reasons of safety of the foetus.

Key words: *adjuvant, anthracycline, breast cancer, docetaxel, node positive*

Introduction

Breast cancer during pregnancy (BRCA/PREG) is considered the condition including not only the time of pregnancy but also the period during within the first year from delivery [1]. The diagnostic approach and the therapeutic management of BRCA/PREG requires delicate approach as it concerns both the life and mental balance of the mother and the integrity, viability, and also the future of the foetus.

The increased number of pregnancies in advanced reproductive age is expected to increase the cases of BRCA/PREG.

Epidemiology

Breast cancer constitutes the first gynaecological malignancy in pregnancy with a frequency of 1 : 3,000 - 10,000 pregnancies. The average age of women affected is 33 years (range 23-47) [2].

Pregnancy itself does not seem to influence the odds of developing breast cancer or its prognosis. When comparing survival rates according to age, grade and histological type of breast cancer in women with BRCA/PREG and in women who suffered from breast cancer, survival rates show no statistically significant differences. However, it seems that during pregnancy, cancer is diagnosed at a more advanced stage compared with women developing breast cancer without pregnancy. It is also estimated that the percentage of cases with axillary lymph node metastases is about double in BRCA/PREG cases than in all other cases.

Family history of breast cancer constitutes the most important aggravating factor for BRCA/PREG. In a study, the frequency of appearance of this condition in women with a positive family history was 3-fold higher as opposed to a control population (12.4 vs 4.2) [3]. Over the last few years, research at molecular biology level has shown an increased frequency of inherited mutations of BRCA1 gene in breast cancer diagnosed during pregnancy, a fact which may be associated with poor prognosis [4,5].

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Diagnostic approach

Physical examination

The clinical diagnosis of BRCA/PREG becomes more difficult due to the increased size and the increased density of the mammary gland. The hard texture and the intense hypertrophy of the mammary gland may conceal solid masses. Thus, a delay in diagnosing BRCA/PREG seems to be the rule. [7,8] (Table 1) Characteristically, it has been estimated that a delay in diagnosing of 1 month is translated in an increase in the odds of lymph node metastases by 0.9% [9].

Imaging tests

The increased hyperaemia and density of the breast during pregnancy reduces the diagnostic accuracy of mammography. The high radiological density of the breasts during pregnancy alters the typical characteristics of malignancy, which results in high rates of false negative results and in delayed diagnosis [10,11]. As far as the safety of the foetus is concerned, mammography is marginally harmful, as it exposes the foetus to a radiation dose of 0.4 mrad (0.004 Gy) [12].

Ultrasonography of the breast is the imaging test of choice for the differential diagnosis of palpable masses during pregnancy. Its advantages are the safety for the mother and foetus, the low cost, the high sensitivity and the possibility of repetition. While the sensitivity of mammography for diagnosing malignant alterations in the breast is 68%, that of ultrasonography can reach 93% [13].

MRI can be used as adjunct if there is strong clinical suspicion and breast ultrasound proves unable to give clear diagnostic information. MRI does not emmit ionizing radiation [14,15]. A limitation to the use of MRI is a contraindication for administering the paramagnetic contrast agent gadolinium during the first trimester of pregnancy due to gadolinium's property to penetrate the placenta and to its property to cause anomalies in the development of foetuses in laboratory animals [16].

Biopsy

Fine needle aspiration (FNA) should be performed in suspicious masses of the breasts during pregnancy. Through FNA, cysts can be differentially diagnosed from solid masses. In solid lesions FNA often gives false positive results due to the atypia caused by the pregnancy's hormonal effects. Hence, an open biopsy should be performed if a solid lesion is observed during pregnancy [17]. It should be underlined that no dangers /complications have been reported from local anaesthesia to the foetus or to the mother, and thus biopsy can be performed with substantial safety.

Staging

The staging of breast cancer has to follow the rule of the least possible effect on the foetus. A breast and axillary region ultrasound are recommended as the main imaging tests for staging [12] . Additional diagnostic questions can be explored using MRI. Bone scan is contraindicated, as it exposes the foetus to a radiation dose which is potentially foetotoxic [18].

Treatment

Surgical treatment

Modified radical mastectomy constitutes the treatment of choice in patients with stage I or II disease who are in their 1st or 2nd trimester of pregnancy [19]. The risk of spontaneous abortion during mastectomy is particularly low and thus pregnancy is not a contraindication for surgical management. Delaying surgical management is just as catastrophic for the pregnant patient as it is for a non-pregnant patient (Table 2).
In patients diagnosed in the 3rd trimester of preg-

Table 1. Delay in breast cancer diagnosis from the first signs - symptoms in pregnant and in non-pregnant women

	Pregnant		*Non-pregnant*	
Reference	*No. of patients*	*Delay in diagnosis (months median)*	*No. of patients*	*Delay in diagnosis (months median)*
Applewhite et al., 1973 [53]	48	13.2	2689	5.1
Ishida et al., 1992 [3]	72	6.2	191	5.4
Liberman et al., 1994 [10]	12	8.2	11	1.9
Bonnier et al., 1997 [54]	114	2.2	280	1.2

nancy, partial mastectomy or lumpectomy with lymph node dissection, as well as radiation therapy of the breast after childbirth constitutes an acceptable therapeutic strategy [20,21]. The optimal treatment approach includes termination of pregnancy with the least danger for the mother and foetus, whereas it allows administration of adjuvant radiation therapy after childbirth [20].

Radiation therapy

Radiation therapy should be avoided throughout the pregnancy due to the risk of teratogenic effects to the foetus [18,22]. Exposure to radiation in the first 14 days from conception brings about death and miscarriage of the foetus, in 15-45 days it is associated with congenital dysplasias, and from 45-60 days suspension of development, mental retardation, and lifetime risk of cancer development [18,23]. Indications of radiation therapy include cases with high risk for local and axillary recurrence after lymph node dissection. It is generally accepted that no dose of radiation is tolerable by the foetus, so that local radiation therapy after surgical treatment is administered after childbirth [20].

Hormonal therapy

Adjuvant hormonal therapy should not be administered during pregnancy because it can cause development of female characteristics to boys and also because it has been found to exert teratogenic action in laboratory animals [24]. Tamoxifen can cause congenital anomalies to the foetus, whereas it is accompanied by an increased risk of carcinogenesis [25]. Additional hormonal manipulations during pregnancy are accompanied with increased risk of developing breast cancer in daughters [26], as well as disorders such as increased weight in newborns, neonatal jaundice and twin pregnancy [27].

Chemotherapy

Administration of chemotherapy to a pregnant patient is a tough decision. The expected benefits for the mother should be weighed against all possible dangers for the foetus. Administration of adjuvant chemotherapy is the treatment of choice for pre-menopausal women with breast cancer, metastases to the axillary lymph nodes, as well as in patients with tumours > 1 cm regardless of lymph node status [20].

Chemotherapy should not be administered during the 1st trimester of pregnancy, due to increased risks for the foetus such as spontaneous abortion, reduced viability and congenital abnormalities of organs such as heart and brain [28]. In a NCI study , 210 cases of chemotherapy administration during pregnancy have been recorded, in 52 of which newborn congenital anomalies were reported. These congenital anomalies were related to the administration of chemotherapy during the 1st trimester of pregnancy [29]. In retrospective studies of such cases, genetic abnormalities were observed in about 12% of the foetuses. The abnormalities were mainly connected with the administration of antimetabolites or alkylating agents [28,30,31].

More specifically, among antimetabolites, 5-fluorouracil penetrates the placenta and causes bone marrow suppression of the foetus [32]. Cyclophosphamide and other alkylating agents cause congenital anomalies, especially when combined with radiation therapy [33]. Adriamycin and vincristine have been administered during the 1st trimester of pregnancy without recognisable damages to the foetus [34,35], but the administration of adriamycin in the 3rd trimester can cause myocardial necrosis [36]. The administration of platinum compounds is accompanied with significant concentration in the foetus [37]. Data on taxanes is sparse; it seems, however, that they can be administered with relative safety [38,39]. In addition, there is data on teratogenic action of methotrexate from the experience of its use for the interruption of premature ectopic pregnancy [40-43]. It seems that methotrexate dose more

Table 2. Treatment options of breast cancer during pregnancy

Treatment modality	*Administration*
Modified radical mastectomy	Stage I and II or 1st and 2nd trimester of pregnacy
Partial mastectomy or lumpectomy with lymph node dissection and radiation after childbirth	3rd trimester of pregnancy
Hormonal therapy	Should not be administered during pregnancy
Radiation	Should be avoided in the 1st trimester of pregnancy
Chemotherapy	Should be avoided in the 1st trimester of pregnancy

than 10 mg per week administered in the 1st trimester of pregnancy can lead to foetal dysplasias which characterize the aminopterin syndrome (cranial dysostosis characterized by micrognathia and dysmorphic nose and ears) [43].

The administration of chemotherapy is considered relatively safer during the 2nd and 3rd trimester of pregnancy [44]. Its administration during this period can cause genetic abnormalities as well as non teratogenic complications such as low weight at birth, retarded endometrial development, spontaneous miscarriage, premature labour and myocardial toxicity [45]. Acceptable chemotherapy combinations are AC (adriamycin and cyclophosphamide) and CAF (cyclophosphamide, adriamycin, fluorouracil) whereas CMV (cyclophosphamide, methotrexate, vincristine) and CMF (cyclophosphamide, methotrexate, fluorouracil) have now been abandoned due to the high toxicity of methotrexate [46]. Chemotherapy should be interrupted at least 1 month before labour, whereas lactation is contraindicated throughout its duration [29].

As far as the monoclonal antibody trastuzumab is concerned, there is no clinical data on safety, whereas the finding that overexpression of the HER-2/neu protein is found in the epithelial cells of the foetus, of the placenta, but also in the serum of pregnant women renders its use in pregnancy prohibitive [46].

There is no clinical experience on the use of biphosphonates during pregnancy. These agents do not exert teratogenic action on the foetus but it is recommended to avoid them during pregnancy due to their ability to penetrate the placenta and to their negative effect on the skeleton of the foetuses of laboratory animals [47,48].

Therapeutic termination of pregnancy

In the 1950s and 1960s, therapeutic abortion had an absolute indication due to the possible hormone dependence and to the lack of effective treatment. In the 1980s and 1990s, the therapeutic termination of pregnancy failed to improve the survival rates of patients [49], whereas at the same time it was found that pregnancy has no effect on the course of breast cancer [11]. In addition, it was observed that 80% of breast cancers diagnosed during pregnancy do not express oestrogen and progesterone receptors [50]. This finding abolished the reservations for oestrogen dependence and disease progression during pregnancy. Currently, the choice of therapeutic abortion during the 1st and 2nd trimester of pregnancy in patients with aggressive primary breast cancer or advanced disease does constitute an alternative solution when immediate therapy is deemed necessary [51-54].

Conclusion

The frequency of developing breast cancer during pregnancy is increased along with the increase of the age of childbearing women. Delay in the diagnosis constitutes the main cause of poor prognosis for these patients. The treatment of choice is modified radical mastectomy for the first 2 trimesters, and lumpectomy or partial mastectomy with radiation therapy after childbirth for patients diagnosed in the 3rd trimester of pregnancy. The administration of chemotherapy is deemed acceptable in the 2nd and 3rd trimester, whereas hormonal therapy and the monoclonal antibody trastuzumab should be avoided for reasons of safety of the foetus.

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