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Diagnosis and Therapy of Gestational Breast Cancer: A Review

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ABSTRACT

Purpose: In spite of the general consensus on the issue, to point to major dilemmas which appear in this matter of multidisciplinary interest, and to review current concepts on how to achieve optimal diagnostic and therapeutic outcome.

Results: Recent literature data show that the rate of gestational breast cancer, according to most protocols, range from 0.2% to 3.8%. By definition, the clinical manifestation of this type of carcinoma is expected to occur during pregnancy or within one year after delivery. The mode of treatment and prognosis is identical to those of women with breast carcinoma beyond pregnancy, except for radiotherapy that is not indicated during pregnancy and selective use of cytostatics in polychemotherapy during the first trimester. The only exceptions to this practice are women with any advanced stage of the disease due to delayed diagnosis. Results of large studies indicate that the therapy for breast cancer has no adversarial effect on the prognosis of subsequent pregnancy.

Conclusion: The evaluation and management of women with gestational breast cancer requires a multidisciplinary approach. A chemotherapeutic regimen should be individualised to a maximum reduction of risk, if applied in the second and third trimester. Surgical therapy may include mastectomy and sparing operative procedures. Sentinel node biopsy should be considered in node negative patients. Radiotherapy should be postponed to the postpartum period.

Key words: breast cancer, pregnancy, diagnosis, management

INTRODUCTION

Although gestational breast cancer (GBC) is a rare phenomenon, by definition, it occurs during pregnancy or within one year after delivery. An increasing rate of GBC is expected in delayed pregnancies until the late fertile age [1-4]. Nowadays, an ever increasing number of women tend to plan pregnancy in their late thirties, for occupational, family or some other reasons, which will probably cause corrections in the reported rate of GBC, ranging from 0.2% to 3.8% during pregnancy and lactation, depending on the source of data [5]. Parity at a young age seems to have a protective effect for estrogen receptor positive breast cancer [6]. Yet, GBC is the most common malignant neoplasm during pregnancy, secondary only to cervical carcinoma, with the incidence of 1:3000 to 1:10,000 pregnancies, i.e. involving 6.3% of premenopausal women. It can be estimated that 30,000 new cases of GBC is going to be diagnosed *per* year in the world [1].

Historically, GBC had for a long period a very poor prognosis, because it was considered as incurable by the greatest authorities of the time, e.g., Gross in 1880, Haagensen and Stout in 1943 [7,8]. Operative treatment of GBC, in particular, had been considered as ineffective, due in part to the belief that GBC was mostly an inflammatory breast carcinoma, which was not eligible for surgical therapy. The diagnostic and therapeutic concepts of the disease have now substantially changed, with the management leitmotif being as to preserve pregnancy while treating breast cancer [9,10]. The overall therapeutic concept basically depends on the stage of labour and the stage of the underlying disease, both dictating the choice of specific diagnostic, treatment mode, i.e. surgical therapy, radiotherapy and cytostatic therapy,

as described recently [11,12]. In addition, the legal, ethical, medical, religious and psychosocial principles, which are closely inter-related and quite frequently neglected, should also be considered in the diagnostic-therapeutic approach to GBC [13]. What are the most common dilemmas in GBC?

Aggressiveness of gestational breast cancer

During pregnancy, breasts undergo anatomical changes including edema, water retention, hypervascularization, lobular hyperplasia and glandular hyperplasia, which may considerably hamper the detection of the tumor and discourage clinician to pursue in diagnostics. Many studies point to the existence of axillary metastases at the time of primary tumor detection [14-16], opening an additional dilemma: Is GBC a more aggressive disease itself or should diagnostic delay be considered responsible for its development?

In literature, there are three theories on the "increased aggressiveness" of GBC: vascular theory (circulatory and lymphatic hypervascularization) [17-19]; hormonal theory [20]; and immune theory (elevated cortisol and decreased T lymphocyte and immunoglobulin levels) [20,21]. Recent studies point out that the increased hormone exposure accounts for the poor prognosis; furthermore, after pregnancy, the remodelling of the mammary gland might be tumor promoting [22]. Since there is no exact explanation of the phenomenon, the theory of immunosuppression caused by the enhanced corticosteroid activity in pregnancy appears to be most acceptable. On the other hand, there is an increasing means of evidence that GBC development relies on its intrinsic tumor biology, considerably affecting its clinical manifestation, with pregnancy as a higher coincidence. Steroid receptors determined in age-matched patients by the method of immunohistochemistry were positive in both pregnant and non-pregnant women [23]. Literature reports describe a variable rate of BRCA 1 and BRCA 2 tumor-suppressor gene mutations in GBC *versus* sporadic carcinoma [24-26]. This dilemma appears to be a great challenge for molecular biology to discover genetic mutations and identify patients who are at a high risk of breast cancer.

Many authors consider that delay in reaching the diagnosis is of crucial importance for the clinical manifestation and appropriate treatment of GBC [18,23,28]. Finally, comparative studies of pregnant and non-pregnant women matched according to age and stage of disease, and treated by the same physicians show that GBC is not more aggressive than the carcinoma in non-pregnant patients [17].

Diagnosis and Preoperative Staging

Any palpable tumor in a pregnant woman, persisting for more than 2-4 weeks, should be evaluated by the "triple assessment" procedure [3]. Ultrasound (US) diagnosis, followed by US guided biopsy is the procedure of choice, since changes of the breasts during pregnancy make mammography less sensitive towards GBC [28]. Cytology, through the fine needle aspiration biopsy may also be quite difficult to interpret due to the breast changes in pregnancy, whereas core biopsy can induce fistula formation [5,29,30]. In spite of technical advances in image quality and dose reduction by multi-detector computerised tomography (MDCT) technology, CT scanning should be avoided by the reason of fetal exposure to ionizing radiation [31].

Disease staging, which is of paramount importance in GBC, is difficult to assess, because most hemic and biochemical parameters, e.g., alkaline phosphatase, some liver function tests, and tumor markers like CEA and CA15-3, are elevated in pregnancy and therefore of little analytical value, in contrast to non-pregnant women. Therefore, US guided biopsy is the method of choice in the diagnosis of GBC, even considering the anatomical and physiological changes of the breast in pregnancy, which may hamper the diagnosis and staging of the disease.

Therapeutic Dilemmas in GBC

This complex disease requires multidisciplinary treatment, which should be carried out at specialised centres where all therapeutic options and pregnancy management, in all its specific conditions, are available [3,32]. The dilemma of giving preference to pregnancy or to cancer therapy has now been completely abandoned; instead, pregnancy should be preserved whenever possible, while treating the underlying malignancy according to the latest concepts. In women with GBC, the therapeutic aim is the same as in non-pregnant women with breast cancer: local disease control and prevention of systemic metastases [33].

Operative treatment is the first and very important step in the management of breast cancer. Mastectomy is a widely used procedure; however, sparing surgical procedures (BCS) are now generally used in the early stages of GBC [4,28,33, 34]. Any type of operative treatment for GBC is followed by postoperative radiotherapy. In patients with clinically negative axillae, sentinel node biopsy (SNB) should be considered to prevent excessive axillary lymphadenectomies [33,34].

Surgical biopsy during pregnancy and lactation may lead to the occurrence of hematomas (increased breast perfusion) and persistent lactic fistulae, respectively; therefore, many surgeons are unwilling to use this procedure. The issue of anesthesia in GBC is less frequently tackled in the literature, which might suggest that there is no dilemma about the choice of this procedure. Yet, Barnavon and Wallack [35] recommend the operation to be performed in local anesthesia, especially if the term of delivery is near.

Chemotherapy implies a serious fetal risk in early pregnancy, indicating that this mode of treatment depends directly on the gestational age. There is no doubt that cytostatics, used during the first trimester, have the most harmful impact on the fetus [36-38]. The role of placental barrier has not yet been fully clarified. While representing a strong biological barrier to some antineoplastic agents, most of these drugs can pass it and exert their detrimental effects upon the embryo [39]. The use of chemotherapy during the second and third trimester (anthracyclines or FAC protocol) is relatively safe

[28,33,34,40]; however, its administration in the first trimester is associated with an increased risk of spontaneous abortion, fetal death and major fetal malformations. Still, there are literature reports on selective administration of cytostatics in the first trimester, which resulted in spontaneous abortion [40]. Andreadis *et al.* describe the successful use of the FEC protocol for metastatic breast cancer in the first trimester, with a review of other reports on anthracycline therapy [41]. Other authors reported on 6 courses of neoadjuvant chemotherapy (FEC protocol) in the second trimester [42]. Germann *et al.* report on a recent series of 160 women treated with anthracycline during pregnancy, 31 (19%) of them during the first trimester of pregnancy. They also note a significantly higher rate of anthracycline toxicity during the first trimester than later during pregnancy [43]. A recent review studied children with in utero exposure to chemotherapy and revealed no evidence for the development of infertility or late malignancy in children exposed to intrauterine chemotherapy [11] but, for incidence, indicated subclinical cardiotoxicity and heart failure after anthracycline-containing agents [44,45].

Radiotherapy of the breast and axillary lymph nodes is discouraged during pregnancy. When irradiation is used postpartum as adjuvant therapy, breastfeeding from the irradiated breast is also discouraged [46]. However, an appropriate approach to the issue and assessment of the fetal risk of radiation requires a thorough understanding of the variable effects upon the developing embryo. Radiation exposure during the preimplantation stage (days 0-10), i.e. from fertilisation until embryo implantation, has the most detrimental effects on the embryo. Another high-risk period for the fetus is the period of organogenesis (until the end of the 8th week), when exposure to radiation may entail cardiotoxic and neurotoxic sequels as well as growth retardation. Upon completion of organogenesis, the fetus is more resistant to ionising radiation and the associated lesions are less common.

Justification of Therapeutic Abortion

In contrast to historical opinion, when abortion was a rule, since 1963 the concept has been thoroughly changed; predominated by the belief that therapeutic abortion is not associated with any prognostic benefit for the patient [47]. It should be noted that therapeutic abortion has been a controversial issue in the management of GBC for decades, along with the possibility of pregnancy followed by a therapy for breast carcinoma. This dilemma may be emphasised by the patient's attitude, if insisting on preserving pregnancy or on abortion.

In spite of these dissonant views on therapeutic abortion, it is considered to be indicated only when progressive development of the malignant disease is expected or fetal lesions due to continued intensive adjuvant therapy (first trimester) are likely to occur. Therapeutic abortion definitely does not improve the patient's outcome but allows her to continue with an aggressive adjuvant therapy. Accordingly, routine abortion is only indicated following thorough consideration of the relevant criteria [48].

Pregnancy after Breast Cancer Treatment (Subsequent Pregnancy)

While there is an increasing number of those supporting the theory that the first pregnancy carried out in early mature fertile age provides the most efficient natural protection from breast cancer in women through "glandular maturation during pregnancy and protective effect of progesterone" [49], there still remains the question of the justifiability and prognosis of pregnancy in women treated for breast cancer [50]. It is known that only some 7% of mastectomized women of fertile age decide for pregnancy [51], and 70% of these pregnancies occur within the first five years of the treatment for breast cancer [52]. After Harrington in 1973 [53], other authors have also confirmed the hypothesis that pregnancy following treatment for breast cancer does not increase the risk of disease recurrence [54] but even improves survival in comparison with other stage-matched tumors [16,26,53-55]. Also, two recently published population-based studies from Denmark and Australia reported no negative influence on the prognosis of pregnancy after breast cancer treatment [56], as even better survival at five and ten years in the subsequent conception group compared to similar cohorts [57]. In spite of some dilemmas, it appears quite reasonable to accept the consensus opinion on the need of control testing in two (N0 tumors) or five years (N1-2 tumors) of treatment. Such a strategy provides valuable data on the locoregional state of the disease. In women treated for breast cancer, fertility is evaluated for two main risk factors: the harmful effects of cytostatics and tamoxifen, and the adverse effects of radiotherapy [5]. In spite of the controversial experiences reported in the literature, chemotherapy frequently leads to menopause [58], with special reference to alkylating agents and their detrimental effect on fertility. In patients treated with tamoxifen, fertility seems to depend exclusively on the type and length of therapy. The effect of tamoxifen on the human fetus is less well known [11]. A review of tamoxifen during pregnancy revealed at least 100 pregnancies while under tamoxifen or the use during pregnancy. Few congenital defects were observed, but without a typical pattern appearing [59]. Thus, the question of whether all modes of adjuvant therapy for GBC have an impact on subsequent fertility of the patient would best be answered "yes" in some cases which cannot be anticipated and specified.

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