Breast cancer in pregnant women: report of two cases and review of the literature

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Abstract

Malignant tumours in pregnant women are rare. The terms 'gestational breast cancer (GBC)' and 'pregnancy-associated breast cancer' are given to breast cancer cases diagnosed during pregnancy and up to one year post-partum. Treatment methods, as well as treatment onset and time of pregnancy termination, remain controversial. We describe two fatal cases of GBC in multiparous women over 35 years of age. The first patient was a thirty-seven year old woman with breast cancer diagnosed in the 26th week of gestation treated with surgery and postoperative chemotherapy. The second case was a thirty-nine year old pregnant woman with primary inoperable breast cancer treated with chemotherapy since the 24th week of gestation. We conclude that breast cancer during pregnancy requires a multidisciplinary approach to ensure optimal care for both the mother and the baby. Prognosis in GBC similarly to breast cancer in non-pregnant women depends mainly on the stage of the disease at the time of diagnosis.

Key words: breast cancer, pregnancy, treatment, prognosis.

Introduction

Malignant tumours in pregnant women are rare. Leukaemias and lymphomas are the most common malignant neoplasms in pregnant women under 25 years of age [1, 2]. In older patients breast cancer occurs predominantly and it is diagnosed in 1/100 000 pregnancies [3]. Incidence of breast cancer increases with age of pregnant woman [2, 4]. Breast cancer diagnosed during pregnancy and up to one year post-partum is known as gestational breast cancer (GBC) [1, 5]. According to Jassem [5] and Wong et al. [6] GBC is diagnosed in 10-40/100 000 women, which means 2-3% of all breast cancers. Similar frequency of this cancer, e.g. 0.2-3.8%, was described by Ring et al. [4].

Because of physiological changes in pregnant women, including morphological and functional changes in the mammary gland, detection

of breast tumours is difficult [6]. A multidisciplinary approach is needed involving a gynaecologist, a medical oncologist and a surgeon. Treatment methods, as well as treatment onset and time of pregnancy termination (if necessary), remain controversial [1].

The aim of the study was to analyze two cases of gestational breast cancer and to review the literature related to management and prognosis in such cases.

Case reports

Case I

Two cases of pregnant women with breast cancer diagnosed during pregnancy were analyzed. Patients were treated in the Centre of Oncology, Medical University of Lodz during 2002-2004. Clinical signs and symptoms in patients, diagnostics, treatment and its outcome were analyzed.

Thirty-seven year old multipara, with a negative family history of malignancies, previously not diagnosed with breast diseases, detected a painless lump in her left breast during self examination in February, 2002. The gynaecologist did not confirm any diagnosis of breast tumour. Two months later the patient became pregnant with twins. Her pregnancy was confirmed in the 25th week of gestation. At the same time a tumour in her left breast was diagnosed. Ultrasound breast scan, performed in the 26th week of gestation, revealed a tumour 2 cm in diameter in the upper external quadrant of the left breast, 6 cm from the nipple; axillary revealed cancer cells. The patient was qualified for Madden type modified radical mastectomy and she was operated on in the 27th week of gestation. The histological examination disclosed infiltrating ductal carcinoma G3, pT1N1Mx. One metastatic lymph node was found with infiltration of its capsule out of 3 axillary nodes resected. Oestrogen receptors [ER], progesterone receptors [PR] and HER2 receptors were absent. The pregnancy was terminated by caesarean section in the 32nd week of gestation. She delivered healthy twins – a female newborn of 1550 g and a male of 2200 g. Seven days after delivery adjuvant chemotherapy was administered. Clinical and additional examination revealed no distant metastases. The patient was treated with 6 cycles of doxorubicin (adriblastin) and cyclophosphamide. After 14 months abdominal ultrasound revealed numerous liver metastases. The patient underwent further treatment with cytostatics – 5 cycles of Taxotere and methotrexate – but the clinical state deteriorated, which led to chemotherapy withdrawal. Unfortunately, after 1 cycle of methotrexate and fluorouracil (second line treatment) progression of the disease was observed, and the patient died.

Case II

A 39-year old multipara, with a negative family history of malignancies, in the 16th week of gestation during vaginal examination was diagnosed, and the diagnosis was confirmed by ultrasound examination. Tumour in the right breast was detected by the same physician during the first visit. Tumour with ulceration and decay encompassed almost the whole breast (diameter about 10 cm). The patient was sent to the oncology centre for further evaluation and treatment. The histopathological examination of a surgical biopsy specimen confirmed breast cancer (infiltrating ductal cancer, ER/-/, PR/-/, HER2/3+/). Because of the primary inoperable status of the disease the patient was qualified for chemotherapy. Taking into consideration the advanced stage of pregnancy (24th week), the decision to continue it was made. The patient received doxorubicin monotherapy. After 2 cycles chest radiography showed lung metastases. After informed written consent, termination of the pregnancy by caesarean section was recommended (an additional indication for caesarean delivery was transverse fetus presentation). The caesarean section was performed in the 34th week of gestation. A male newborn of 53 cm, 1900 g, 8 Apgar score was delivered. During laparotomy bilateral ovariectomy was performed. No peritoneal involvement or visceral metastases were noted. Neither ovary was macroscopically suspected but histopathological investigation revealed foci of breast cancer metastases. After a two-week postpartum period, the patient received cyclophosphamide, methotrexate, and 5-fluorouracil regimen in the Department of Oncology. No remission after chemotherapy was achieved and the patient died one year later.

Discussion

There is disagreement in worldwide literature concerning the influence of pregnancy on the incidence and course of breast cancer. According to Kroman et al. [7] high oestrogen concentration during pregnancy can increase the growth of breast cancer [7]. However, other studies did not show that in breast cancer patients pregnancy and lactation have a significant impact on poor outcome, and prognosis is similar for pregnant and non-pregnant women depending on the stage of disease [3, 5, 6]. Many studies have shown that in pregnant breast cancer patients the percentage of advanced stages of disease at the time of diagnosis is higher than in the remaining group of breast cancer patients [1, 6]. It has also been shown that early breast cancer is 2.5 times more rarely diagnosed in pregnant patients compared to other women. These differences can be explained by physiological

changes in the breast during pregnancy (enlargement, angiogenesis), which make physical examination less sensitive, and by complete lack of self-examinations of pregnant women as well as low attention to proper breast examination given by gynaecologists [2].

Regular self-examination performed by women has a significant influence on early detection of breast tumours. Additionally, gynaecologists are required to conduct the breast examination in pregnant women [5]. When a breast tumour is detected in pregnant or post-partum women, the diagnostic tools should be applied as in non-pregnant patients [2-4, 6, 8]. Ultrasonography, mammography (during breast feeding) and biopsy should be done to establish precise diagnosis and stage of disease [1-3, 9]. According to the German Breast Group (GBG-29), sensitivity of mammography in such cases is about 68%, while sensitivity of ultrasonography is 93% [2]. Additionally, excluding computer tomography (CT), the remaining radiological investigations, e.g. chest X-ray with abdominal shielding, liver ultrasound and non-contrast magnetic resonance imaging (MRI) (especially after the first trimester), should also be done [6].

The optimal treatment of GBC patients is still a dilemma for the gynaecologist, surgeon and oncologist [1, 2, 4, 8, 10, 11]. Proper standards of treatment of such patients are needed. According to MD Anderson Cancer Center protocols, if early breast cancer is diagnosed in the first trimester of pregnancy (by the 16th week of gestation) abortion should be considered [8]. If pregnancy is continued, the risk of poor outcome is higher, because adjuvant chemotherapy cannot be administrated in the early phase of gestation [4, 12]. If abortion is performed, chemotherapy should be given according to general standards for non-pregnant women with breast cancer (MD Cancer Center and GBG-29 recommendations) [2, 8, 12]. If pregnancy is continued, radical modified mastectomy should be performed in the first trimester as a treatment of choice [6, 13, 14]. Most cancer centres do not perform breast conserving surgery, because it should be followed by radiotherapy, which is contraindicated during pregnancy irrespective of its phase [6, 13, 14]. However, surgical treatment is connected with the risk of complications such as wound infection, cellulitis or erysipelas, which is similar for pregnant and non-pregnant women [15]. Radiotherapy should be postponed to the second or third trimester of pregnancy because of its teratogenic potential [11, 13].

To avoid axillary node dissection and reduce postoperative complications such as arm oedema, a sentinel node biopsy (SNB) can be performed to assess the nodal staging in early breast cancer patients. The sentinel node is the first lymph node on the way of lymphatic flow from the primary tumour. SNB is usually performed using a radiotracer. To improve the identification rate, this technique is often combined with blue dye mapping. Previously pregnancy was a contraindication to performing SNB. Taking into consideration the low risk of fetus irradiation, several studies have described the use of radiotracer technique of SNB in pregnant breast cancer patients [16-18]. Further prospective studies have already been launched to assess the safety and utility of SNB in these patients [18]. However, blue dye technique is still contraindicated in pregnant patients [16-18]. Breast cancer prognostic factors for pregnant and non-pregnant women are similar and include: clinical staging (according to TNM system), age, grading (G), the number of metastatic nodes, expression of oestrogen (ER) and progesterone (PgR) receptors, and expression of human epidermal growth factor receptor (HER-2) [6, 14, 16].

It was also observed that chemotherapy given during pregnancy may cause spontaneous abortion and increased risk of congenital malformations in 7.5-17% of neonates. Adjuvant and neoadjuvant chemotherapy is not likely to influence normal development of the fetus [1, 6, 11, 12, 19]. According to Gwyn et al. [8], Hahn et al. [11], and Bodner-Adler et al. [1], patients with GBC in the 2nd and 3rd trimester of pregnancy can be treated with doxorubicin (50 mg/m^2 per 72 hours), cyclophosphamide (500 mg/m^2 per 1 hour) and 5-fluorouracile (500 mg/m^2 within 1-4 days). Ring et al. [4] also describe a group of patients treated with CMF regimen. In the French National Survey conducted by Giacalone et al., docetaxel, paclitaxel and vinorelbine chemotherapy was also administrated to pregnant women [10].

Time and mode of delivery are a compromise between the risk of less aggressive treatment of cancerous disease and the risk of preterm delivery with its complications [4]. There are some reports demonstrating an increased number of peripartum complications such as pre-eclampsia or fetal hypotrophy in breast cancer pregnancies [4], but not all studies confirmed these data [8, 11, 13]. In pregnant women with breast cancer treated in the MD Anderson Cancer Center, the number of caesarean sections and of vaginal deliveries were similar [8]. We share the opinion that pregnancy with GBC should be terminated after the 33rd week of gestation. However, Epstein et al. [12] recommend termination in the 36th week of gestation. In the presented cases children were born by caesarean section in the 32nd and 34th week of gestation respectively. Maternal and neonatal sepsis and haemorrhage are potential complications of myelosuppression resulting from chemotherapy administrated in the last trimester, which should be taken into consideration [5].

Indications for adjuvant treatment during pregnancy and after delivery are established after

surgery and histopathological findings. After delivery chemotherapy as well as radiotherapy should be provided. Hormonal therapy should be provided only if oestrogen and progesterone receptors are present [2, 6, 8, 12, 14, 19]. Breast feeding is contraindicated for women with GBC treated with radiotherapy and hormonal therapy, since many cytotoxic drugs can enter the breast milk [6, 9]. Therefore these patients should be given delactating agents [6, 9].

After GBC treatment, regular check-ups in the oncology centre for early detection of recurrence or metastatic diseases is essential. Lambe demonstrated that for a few years after GBC and delivery there is a transient increase in the risk of breast cancer recurrence, compared to non-pregnant patients [20]. Ring et al. [4] and Wong et al. [6] showed the necessity of regular check-ups in children born by GBC mothers because of late side effects of exposure to chemotherapy *in utero* such as: gonadal malfunction, developmental and neurological disorders or carcinogenic mutations. Children of mothers treated with anthracycline can experience cardiotoxic side effects [4]. However, all distant side effects of chemotherapy in the 2nd and 3rd trimester are extremely rare [11-13].

It is important to mention those patients after gestational breast cancer treatment who are currently contemplating future pregnancies or who are already pregnant. There is a unanimous opinion that pregnancy after GBC treatment has no influence on course of disease and that history of breast cancer has no impact on course or outcome of future pregnancies [5, 9].

On the basis of our observations and review of the literature we suggest that:

1. Detection of any breast tumour during pregnancy should lead to immediate diagnostic procedures and treatment. Fine needle aspiration biopsy should be safety performed in this group of patients.
2. Prognosis depends mainly on the stage of the disease at the time of diagnosis.
3. The mode of treatment should be discussed in a multidisciplinary team including a surgeon, clinical oncologist and gynaecologist and should be accepted by the patient. The main concern of obstetricians and oncologists is the decision of continuation vs. termination of pregnancy if breast cancer is diagnosed in the second trimester of pregnancy. Decisions regarding abortion should be based on the patient's will and on therapeutic necessities.
4. The treatment of choice is surgery. Radiation therapy should be avoided because of its toxic impact on the fetus. Chemotherapy in the treatment of GBC is possible after the first trimester of pregnancy. It should be administrated according to the same principles as applied in non-pregnant patients.

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