

MANAGEMENT OF BREAST CANCER DURING PREGNANCY

Diaa M. El-Mowafi, MD

Professor, Obstetrics and Gynecology Department
Benha Faculty of Medicine, Egypt
Educator & Researcher, Wayne State University, Detroit, MI USA
Fellow, Geneva University, Switzerland
Consultant & Head of Obstetrics and Gynecology Department,
King Khalid General Hospital, Hafr El-Batin, Saudi Arabia

Introduction

Pregnancy and cancer result in two diametrically opposing emotional reactions in young women. The first leads usually to a joyous elation, whilst the other to dismay and horror. When the two occur together, the patient is inevitably distraught and terrified, whilst her obstetrician and medical advisers are faced with a therapeutic dilemma involving surgical, perinatal, obstetric, psychological and moral issues.

Breast cancer occurring during pregnancy or within the first year after delivery is considered to be pregnancy-associated breast cancer (PABC).¹ Some researchers have distinguished between malignancy occurring during pregnancy and during lactation. Because of the variability in the length of lactation, cancer occurring up to one year after delivery has been accepted as standard definition in most articles.^{2,3}

Breast cancer is the most common cancer encountered in pregnant women occurring in about 1 in 3,000 pregnancies. This incidence is expected to increase as more women choose childbearing at a later age. It is estimated that the obstetrician attending 250 deliveries per year would need to accumulate 40 years of clinical experience to encounter 2-3 cases of PABC.⁴ This may lead to erroneous perception that PABC is rare. If the probable latent or preclinical time period of breast cancer is considered, it becomes likely that larger numbers of women with breast cancer have been pregnant at sometime during the course of the disease, despite the fact that they do not meet the criteria for PABC. When women delay their first pregnancy until the age of 35 years or more, the risk of breast cancer increases by three times compared to those women who initially conceive prior to the age of twenty.⁵ Diagnosis and treatment of breast cancer during pregnancy encompasses many diagnostic and therapeutic dilemmas. The engorgement of the breasts in this period may hinder detection of masses and delays in diagnosis are common. This delay in addition to the young age can explain that overall survival of pregnant women generally worse than in nonpregnant women.⁶ Mamography has a limited value in diagnosis due to increased breast density during pregnancy. Chemotherapy and radiotherapy are contraindicated. Still there are two questions have

to be answered: Should pregnancy terminated when breast cancer is diagnosed? Can and when this lady get pregnant again?

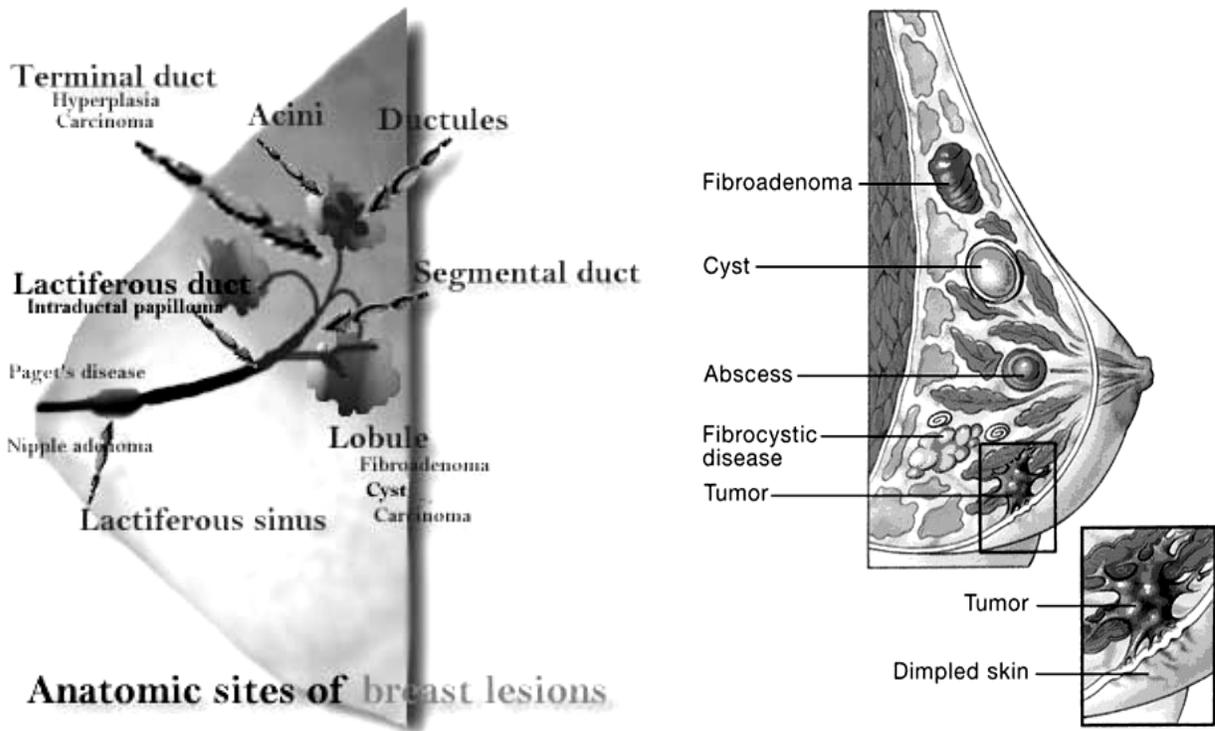
Anatomy

The paired hemispheres of breast tissue are attached on their planoconcave surface against the fascia of the ventral chest wall from the parasternal to the anterior axillary line covering the second through the seventh ribs. The adult female breast has two components. These are the epithelial elements responsible for milk formation and transport, namely the acini and ducts, and the supporting tissues, muscle, fascia and fat. The epithelial elements consist of twenty or more lobes. Each lobe drains into a mammary duct, each of which ends separately at the nipple. The lobe consists of lobules, the number of which is very variable. Each lobule is a collection of between ten and hundred acini grouped around, and converging on a collecting duct (Fig.1).

The breast is contained in a fascia envelope, its superficial layer being subcutaneous and its deep layer adjacent to the fascia of the chest wall muscles. Fascial septa separate each lactiferous lobe into a separate entity. These fascial partitions extend from the deep to the superficial fascial envelope. In the superior aspect of the breast, these fascial supports are thickest, presumably because of gravity traction, and are called Cooper's ligament.

The fat of the breast composes a significant proportion of the breast volume. It occurs as a 1-3 cm layer between the skin and the superficial fascia. The fatty tissue in the most dependent portion of the breast often becomes edematous and indurated as a function of gravity and dependency. This indurated area is known as inframammary ridge. Vascular supply is from the axillary vessels through the upper outer quadrants and through perforating internal mammary vessels via the parasternal and intercostal spaces.

The lymphatics of the breast drain mostly to the axilla and then medially along the axillary vein. Most of these lymphatics drain around and under the pectoral muscles, although some pathways do exist through and between the musculature (Rotter's nodes). The medial and centromedial areas of the breast contain lymphatics that course toward the sternum, perforate the intercostal spaces, and drain into the internal mammary chain inside the thorax. Lesser pathways of drainage include epigastric, supraclavicular, and anterior cervical lymphatics.



Physiologic Changes in the Breast during Pregnancy

Pregnancy induces both proliferation and differentiation of the mammary epithelium. Both lobular and alveolar growth occur. Differentiation of the alveoli into mature milk-producing cells requires the stimulus of cortisol, insulin, and prolactin.⁷ Prolactin is the major stimulus for galactopoiesis, and prolactin levels are markedly elevated during the later trimesters of pregnancy and lactation. The weight of the breasts approximately doubles with a 180% increase in blood flow. The increase in size, weight, vascularity, and density makes detection of mass lesions difficult both clinically and mammographically.

Genetic Factor in Breast Cancer

The occurrence of breast cancer early in life, bilaterally or with tumors of other organs (particularly the ovary) suggests an underlying genetic susceptibility. In women with hereditary breast cancer both mutated P53 and the BRCA1 gene have been identified. The BRCA1 gene, located on chromosomal region 17q12-q23, has previously been associated with early-onset breast cancer. This gene is estimated to account for about 45% of families with several cases of breast cancer and up to 67% of such families where the age at onset of the cancers is less than 45.⁸ Almost all families with epithelial ovarian cancer in addition to several cases of breast cancer carry the BRCA1 gene.⁹ However, it has to be said that only a small proportion of breast cancers (5%) are caused by dominant genes.⁸

Differential Diagnosis of Breast Carcinoma

I. Benign Lesions Unique to Pregnancy and Lactation

Conditions that present as a dominant lump in the breast include carcinoma, fibrocystic disease, fibroadenomas, sarcomas, fat necrosis, and other uncommon breast lesions. These include galactoceles, sebaceous cysts, histiocytomas, leiomyomas, lipomas, adenolipomas, granular cell tumors, neurofibromas, sarcoidosis, and tuberculosis (Fig.1).

Although most of the benign lesions seen in pregnancy are the same as those seen in the nonpregnant state (e.g., fibroadenomas, lipomas, papillomas), they may be altered in size or consistency as well as histologic appearance by the hormonal stimulation of pregnancy and lactation. Approximately 30% of breast masses are lesions unique to pregnancy, such as lactating adenomas, galactoceles, mastitis, and infarcts.¹⁰

The lactating adenoma (nodular lactational hyperplasia or lactating nodule) is a benign breast lesion unique to pregnancy and lactation. Histologically, it is characterized by florid lactational changes with a tubuloalveolar appearance to the glands. There is considerable variability in size.¹¹

Infarction of a fibroadenoma, lactating adenoma, or hypertrophied breast tissue can occur during pregnancy. The typical lesion presents with increase in size and tenderness of a preexisting mass or as a new tender mass. Histologic examination may reveal extensive necrosis with few or no residual glandular elements.¹⁵

Galactoceles are single or multiple nodules that contain retained milk. Anything that obstructs the ductal system during lactation may cause a galactocele. Most commonly, these lesions occur with the cessation of lactation when milk is allowed to stagnate in the ducts. The presentation may be delayed for months after the cessation of nursing. These palpable lesions are usually located peripherally in the breast. Sometimes fluctuance is elicited upon palpation, and firm pressure on the mass may express milk. Aspiration can be both diagnostic and curative if the lesion does not recur. The findings on mammography are highly suggestive of this lesion owing to the mixed water and fat densities. Mammography is usually not necessary, as the clinical presentation is usually characteristic. Occasionally, a benign or malignant tumor is the cause of obstruction. Excision is advised if the lesion recurs after aspiration or if a mass persists.

Lactational mastitis may rarely progress to breast abscess. Although inflammatory carcinoma of the breast is no more common in PABC than in the nonpregnant state, its incidence is high enough to recommend biopsy of the abscess wall when a breast abscess is drained.¹²

II. Bloody Nipple Discharge during Pregnancy and Lactation

Bloody nipple discharge is a relatively common occurrence during pregnancy and lactation. This finding per se does not necessarily portend serious consequences. Although bloody nipple discharge may occur with malignancy, it is usually associated with a palpable mass. Cytologically, bloody nipple secretions commonly demonstrate desquamated epithelial cells similar to those seen in intraductal papillomas. Pregnancy induces changes in the ducts, which lead to the formation of delicate intraductal epithelial spurs that are easily traumatized and shed, thus resulting in a bloody discharge.¹² Although cytologic study of the bloody discharge is indicated, it may be

difficult to interpret because the proliferative changes associated with pregnancy may confound the diagnosis of a malignant process.¹⁴

If a bloody discharge is not accompanied by a palpable mass and if the cytology is not suggestive of malignancy, it is appropriate to observe the patient clinically for several months postpartum. If the bloody discharge persists for more than 2 months after delivery, is localized to one duct, or is associated with a palpable mass, mammography and biopsy may be indicated. The presence of blood is not a contraindication to breast-feeding. Bloody discharges may commonly be associated with the initiation of breast-feeding and usually cease after breast-feeding.¹⁵

Clinical Presentation of Breast Cancer in Pregnancy

Carcinoma usually presents as a painless, firm, deep-seated mass. Ninety percent of these masses are detected by self-breast examination.¹⁵ Any breast mass warrants prompt attention, and every effort must be made to reduce the delay between signs, symptoms, and diagnosis in PABC. Local infiltration may cause fixation of the tumor to the chest wall. This is elicited by adduction of the arm to set the pectoralis muscle and fascia. Fixation or edema of the skin are other signs of advancing malignancy, altered vascularity and increased metabolism of the tumor produce increased heat as measured by thermography or skin erythema after alcohol application. Although a thorough breast examination must be an integral part of the initial prenatal examination, this examination ideally should be performed prior to the development of physiologic breast changes (Fig.2). An enlarging mass that persists without regression and other primary or secondary signs malignancy such as nipple retraction, fixation of a mass to skin, skin thickening, dimpling, or development of axillary adenopathy should be considered indications of possible malignancy, and a diagnostic work-up should be initiated.

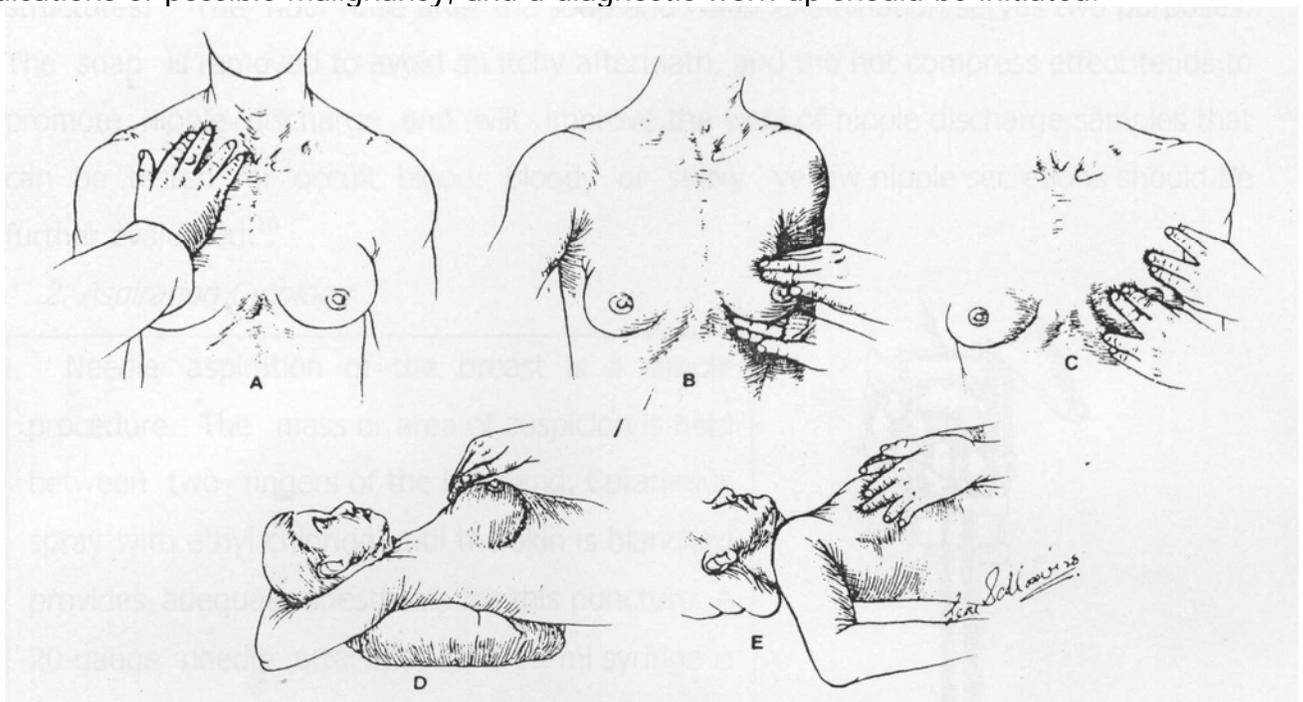


Fig. 2

Delay in Diagnosis of Breast Cancer in Pregnancy

Diagnosis of breast cancer in pregnancy usually delayed 5-7 months due to physiological changes that take place with pregnancy.¹⁷ This will lead to discovering of the breast cancer in a relatively advanced stage. The increased vascularity and lymphatic drainage from the gravid or lactating breast is another factor that aids metastatic spread. Difficulty in evaluating the mass lesions in the pregnant and lactating breast, a reluctance to perform biopsy, false diagnosis as an inflammatory mass that fails to respond to treatment can be established, and inadequate flow up by patient and physician have all been reported. Physical examination may be difficult because the breasts are hypervascular, engorged, and nodular. A discreet mass is often difficult to palpate during lactation and malignancy may be mistaken with mastitis.

Over 75% of pregnant women diagnosed with breast cancer have nodal metastases, far more than the general population. Nettleton and colleagues¹⁸ created a mathematical model to infer the risk of nodal metastases with PABC. If the tumor doubling time is assumed to be 65 days, a delay of 6 months in diagnosis raises the probability of nodal metastases by more than 10%.

Techniques of Evaluating Breast Lumps

1. Friction-Free Examination

The breast skin can be rendered friction free by the use of powder, thin lubricating jelly, or warm soap and water, thus improving an appreciation of breast structures by palpation. Subareolar prominences can be distinguished as a circular ring of uniform structures. The hot rinse after the soap and water examination serves two purposes. The soap is removed to avoid an itchy aftermath, and the hot compress effect tends to promote nipple discharge and will improve the yield of nipple discharge samples that can be tested for occult blood. Bloody or sticky yellow nipple secretions should be further evaluated.¹⁹

2. Mammography

The increase in size, vascularity and glandular density of the breasts during pregnancy is characterized by an increase in radiographic density, thus limiting the sensitivity of mammography. Mammography, therefore, should be used as a screening test during pregnancy or lactation. However, mammography should not be avoided, if indicated, because with abdominal shielding the radiation exposure to the fetus is negligible.²⁰ There are no reports of untoward effects of mammography on the mother and fetus.

Ultrasound may be a useful diagnostic modality, and several series have shown increased accuracy in confirming the presence of palpable masses in PABC.³

Ultrasonography accurately depicts the difference between solid and cystic masses and is being subjected to extensive trials of its accuracy in diagnosing early malignant disease in the breast. It is used as an adjunct to mammography since combinations of the two modalities have been shown in some reports to be better than either alone.²¹ Calcification, asymmetric density, axillary lymphadenopathy, skin and trabecular thickening were helpful for diagnosis of PABC. Sonographic findings of a solid mass with posterior acoustic enhancement and a marked cystic component were somewhat

different from the appearance of breast cancer in nonpregnant women, possibly because of the physiologic changes of pregnancy and lactation. Magnetic resonance imaging (MRI) is of great help to delineate the soft tissue lesions in the breast nowadays.

3. *Aspiration Cytology*

Needle aspiration of the breast is a simple procedure. The mass or area of suspicion is held between two fingers of the left hand. Cutaneous spray with ethyl chloride until the skin is blanched provides adequate anesthesia for this puncture. A 20-gauge needle attached to a 10-ml syringe is quickly thrust into the center of the area. This syringe and needle are previously prepared by aspirating a small amount of Ringer's lactate into the dead space of the syringe and needle lumen. After insertion of the needle, vigorous suction is applied to the syringe while multiple small tracts are made in the breast tissue (Fig.3).

Aspirated cyst fluid is spread thinly on an albumin-coated or totally frosted slide and sprayed with cytologic fixative and submitted as a Papanicolaou smear.

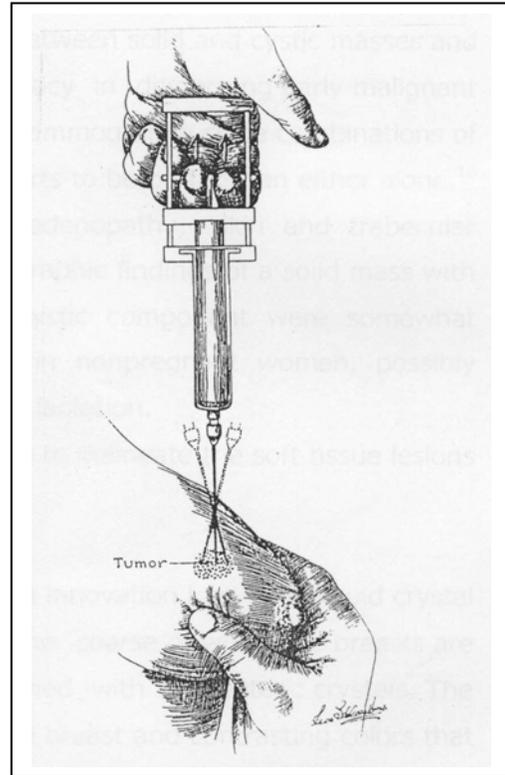


Fig.3

4. *Thermography*

Most of the thermographers have resorted to an innovation known as liquid crystal thermography, a type of brachthermometry, in the course of which the breasts are pressed directly against a thermosensitive plate lined with cholesteric crystals. The resulting thermographic film depicts the skin of the breast and contrasting colors that represent the underlying thermal pattern. The equipment with which this is accomplished is relatively less expensive and has been widely advertised for use in free-standing breast clinics and private offices. Although some authors recommended thermography as a helpful tool in diagnosis of breast cancer,²² other stated that it is seldom employed for that purpose.²³

5. *Breast biopsy*

A complete evaluation of any lump in the breast only by excisional biopsy and histologic examination of the tissue. In women over the age of 50 years, any dominant breast lump is an indication for immediate excision. In younger patients, especially if menstruation is still occurring, reexamination should be scheduled after the next menstrual period and excision performed if the mass remains or becomes larger.

Abnormal biopsy material should be submitted in ice for determination of estrogen and progesterone-binding protein of the tumor.

Diagnostic work-up of the pregnant or lactating woman with a palpable mass

Masses discovered during routine examination or detected by the patient required evaluation. Significant physician delay has been noted in virtually all series of PABC. Mammography is of limited value. Ultrasound may be of help in differentiating cystic versus solid masses and may confirm the presence of a mass when physical examination equivocal and the woman complains of pain or tenderness. The decision to observe the mass in the pregnant woman is fraught with hazard as physical examination becomes progressively more difficult with increasing breast enlargement and vascularity as pregnancy progresses. A mass may seem to disappear when, in fact, it is enlarging and simply has become buried in the surrounding breast tissues. Since at least 25% of mammograms in pregnancy may be negative in the presence of cancer, a biopsy is essential for the diagnosis of any palpable mass. Diagnosis may be safely accomplished with a fine-needle aspiration or excisional biopsy under local anesthesia. Fine-needle aspiration cytology is the initial procedure of choice for evaluating breast masses detected during pregnancy and lactation. The cytopathologist must be informed that the patient is pregnant or lactating because the physiologic changes of pregnancy and lactation induce proliferation in the normal breast that can be confused with malignant change. Fine-needle aspiration cytology is useful in distinguishing benign breast masses of pregnancy from those with marked cytologic atypia requiring surgical biopsy and minimize the delay in diagnosis of carcinoma associated with pregnancy.²⁴

Although breast biopsy is one of the most common surgical procedures performed during pregnancy, it is reserved for masses in which fine-needle aspiration cytology is nondiagnostic. Because most breast masses associated with pregnancy and lactation are benign and with the more extensive use of fine-needle aspiration cytology, the number of open breast biopsies performed during pregnancy will be small. Breast biopsy may be performed under local or general anesthesia. Procedures using local anesthesia are usually without risk to the fetus.

The nursing mother should be advised to stop breast-feeding and to allow milk production to cease prior to biopsy. The cessation of lactation will decrease the risk of milk fistula and vascularity of the breast. Milk fistulas are more likely to occur when central lesions are excised. If milk fistula occurs, meticulous attention to local cleanliness and dressing changes is important to decrease the incidence of secondary infection and possible abscess formation. The fistula will generally close spontaneously when breast-feeding is stopped. The development of breast infection with or without an abscess following biopsy is more common in lactating women because of nutrient medium the represents.

Although inflammatory breast carcinoma is not more common in PABC than in the general population with breast cancer, an incidence ranging from 1.4%-4% is reported.¹² For this reason, all abscesses that are surgically drained should have a biopsy of the wall and any suspicious area.

If the patient insists on continuing breast-feeding, she must be informed of the risks of milk fistula and the increased incidence of postoperative infection and abscess. The breast-feeding woman should express as much milk as possible prior to surgery.

Pathology of Breast Cancer²⁵

Carcinoma of the breast is either spheroidal cell or adenocarcinoma.

(A) Spheroidal cell carcinoma (90%)

It consists of groups of spheroidal cells embedded in a fibrous stroma.

1. Atrophic scirrhous carcinoma:

The amount of fibrous tissue exceeds much the number of cells. It grows slowly, affecting postmenopausal women with atrophic breasts. The tumor is small and very hard.

2. Scirrhous carcinoma:

It is the commonest variety (65%), affecting the middle aged females. The tumor is small hard, and fixed. When cut with a knife, gritty sensation is felt, it retracts when cut and the cut surface becomes concave. The tumor is grayish in color with areas of degeneration, necrosis and hemorrhage. It has no capsule and infiltrates surrounding structures.

3. Encephaloid carcinoma:

It occurs in well developed breasts in young females. It may reach a large size, grows rapidly and disseminates early, cut section is brain like with areas of hemorrhage and necrosis. Histologically, it appears as masses of highly malignant cells with minimal delicate vascular stroma.

4. Mastitis Carcinomatosa:

It occurs during pregnancy and lactation. The breast becomes swollen and painful with dilated veins, red hot edematous skin; the picture similar to acute mastitis. The differentiation can be by clinical test using antibiotics. Histologically, it is a rapidly proliferating anaplastic cells with very little fibrous tissue stroma.

(B) Adenocarcinoma:

1. Duct carcinoma arises in the larger milk ducts either on top of duct papilloma or de novo. It occurs in elderly females and spreads less rapidly than spheroidal cell carcinoma.

2. Intracystic papilliferous carcinoma is rare.

(C) Paget's Diseases of the Nipple

It is rare, affecting middle aged and elderly females. It is a malignant eczema eroding the nipple and spreading peripherally. It is usually followed after 2 years by the appearance of scirrhous carcinoma within the breast. Histologically, there is hyperplasia of all layers of epidermis with the appearance of vacuolated Paget cells among the basal cells.

Staging System for Breast Cancer

- T Primary tumor measurement
- T0 No tumor

- TIS Preinvasive carcinoma (CIS), noninfiltrating intraductal carcinoma or Paget's disease of nipple and no demonstrable tumor
- T1 Tumor size 2 cm
 - T1a No fixation to pectoral fascia and/or muscle
 - T1b Fixation to pectoralis fascia and/or muscle
- T2 Tumor size 2-5 cm
 - T2a No fixation to pectoralis fascia and/or muscle
 - T2b Fixation to pectoralis fascia and/or muscle
- T3 Tumor size more than 5 cm
 - T3a No fixation to pectoralis fascia and/or muscle
 - T3b Fixation to pectoralis fascia and/or muscle
- T4 Tumor of any size with direct extension to chest wall or skin (not including skin dimpling or nipple retraction)
 - T4a Fixation to chest wall
 - T4b Edema, infiltration or ulceration of the skin (including peau d'orange), or satellite nodules confined to the same breast
 - T4c Both (T4a and T4b)
- N Regional lymph nodes
 - N0 No palpable homolateral axillary nodes
 - N1 Movable homolateral axillary nodes
 - N1a Metastasis not suspected
 - N1b Metastasis suspected
 - N2 Fixed homolateral axillary nodes
 - N3 Homolateral supraclavicular or infraclavicular nodes or edema of the arm
- M Distant metastases
 - M0 No evidence of distant metastasis
 - M1 Distant metastases present, including skin involvement beyond the breast area

Stage-Grouping

TIS	Carcinoma in situ			
Invasive carcinoma				
Stage I	T1a	N0	or N1a	M0
	T1b	N0	or N1a	M0
Stage II	T0	N1b		
	T1a	N1b		
	T1b	N1b		
	T2a	N0	or N1a	M0
	T2b	N0	or N1a	
	T2a	N1b		
Stage III	T2b	N1b		
	Any T3		with any N	
	Any T4		with any N	M0
	Any T		with N2	
	Any T		with N3	

Stage IV Any T Any N with M1

Should Termination of Pregnancy be Considered in Cancer Breast?

Hormonal factors appear to play an important role early on in development of breast cancer; however, pregnancy itself does not look clearly to influence the outcome of an established breast cancer.¹⁷

Through the 1950s and 1960s, concerns regarding the hormonal stimulation tumor growth, poor survival, and the lack of effective systemic therapy for breast cancer led many clinicians to advocate therapeutic abortions when breast cancer was diagnosed during pregnancy. Subsequent series demonstrated that therapeutic abortion not only failed to improve survival but might be detrimental.^{16,26} The finding of a high percentage of estrogen receptors (ER)- and progesterone receptors (PR)-negative tumors in most series of PABC give little theoretical grounds for pregnancy termination. Most series of PABC reporting on receptor status indicate that as many as 80% of lesions are ER-and PR-negative.³ Studying of histopathological parameters and immunoreactivity for estrogen and progesterone receptors, c-erbB-2 and c-erbB-4 showed low frequency of hormone receptors, BRCA1, p27, cyclin E, D1 and high expression of c-erbB-2.^{25,26} These findings gave the impression that PABC is an aggressive tumor.

The sole advantage of pregnancy termination is that full and complete treatment of aggressive or advanced disease with chemotherapy, radiotherapy, and surgery may be instituted without consideration of the effects on the fetus.

It is difficult to interpret some of the data indicating a worse prognosis associated with pregnancy termination because there may be considerable selection bias (abortions were performed only in women with more advanced or more aggressive tumors).²⁹

The medical recommendation to terminate a pregnancy should be based on whether pregnancy will present a significant obstacle to effective therapy and whether the fetus will sustain harm as a result of therapy. Because pregnancy has no effect upon the course of disease, the termination of pregnancy does not ameliorate disease. Spontaneous abortions and prematurity are not increased in pregnant women with malignancy. As chemotherapy can not be given before 14-15 weeks of pregnancy, therapeutic abortions may be considered in the first or second trimester so that metastatic disease can be treated promptly, particularly if the patient is ER-positive.³⁰

Treatment of Pregnancy-associated Breast Cancer

Perhaps no aspect of breast cancer care is more challenging than the treatment of the pregnant patient. In addition to the usual complexities of treatment decisions, one must add the incalculable factors related to the importance of childbearing, and the potential for side effects upon the fetus or child through exposure to chemotherapy or radiotherapy. It is very difficult to make general comments about treating such patients. Each individual will weigh the potential risks and benefits differently, and may reach different decisions. Patients are invariably best served by multimodality team

approaches, with coordinated efforts of surgeons, medical oncologists, and obstetricians trained in high-risk maternal-fetal medicine.

Breast conservation requires radiation therapy. Generally, this is not administered during pregnancy because of the potential for radiation exposure to the fetus. Surgery can usually be performed safely during pregnancy with minimal risk to the fetus and mother, particularly in the second and third trimesters. When compared with radiation therapy and chemotherapy, surgery is least likely to affect the pregnancy. Thus the usual treatment for technically operable breast cancer is modified radical mastectomy. This operation entails the preservation of the pectoralis major and minor muscles, providing better arm motion and thoracic outline and reducing the incidence of postoperative lymphedema of the arm. It is probably the procedure most frequently used today for breast cancer.²⁰ Following modified radical mastectomy, radiotherapy to the chest wall, internal mammary lymph nodes, and the dissected axilla was customary for patients whose final pathologic report indicated the presence of lymph node metastases. This approach has been superseded because radiotherapy has not been effective in controlling lymph node metastases or hematogenous spread. Staging studies are performed selectively, and individualized decision regarding subsequent chemotherapy is made. Women with advanced or technically inoperable disease may require palliative chemotherapy or radiotherapy.

In general, the metastatic work-up should be limited to those patients in whom there is a high clinical suspicion of metastatic disease and in whom documentation of disease would alter management. The fetal radiation exposure from a chest radiograph obtaining with abdominal shielding is minimal. The alkaline phosphatase level is normally elevated during pregnancy and is therefore an unreliable indicator of metastatic disease. Ultrasound of the liver is preferable to CT scanning. MRI may be indicated if ultrasound is nondiagnostic. Radiography of the long bones and skull can be performed in a symptomatic woman, but a complete skeletal survey exposes the fetus to an unnecessary large dose of radiation. A general bone scan is avoided because of low yield. However, if bony metastases are strongly suspected, a bone scan with technetium 99m is preferable to a skeletal survey. Because this agent was used for placental scanning before the availability of ultrasound, there is a sufficient experience with its use in the second and third trimesters. Adequate hydration prior to and during the scan facilitates rapid washout of the isotope from the blood. Draining the bladder with Foley catheter during the procedure and for 8-12 hours after the scan avoids an accumulation of the isotope within the pelvis.³¹

Radiotherapy of Breast Cancer

In General, radiation therapy is contraindicated during pregnancy. An external irradiation dose of 5000 cGy to the breast exposes the fetus to at least 10 to 15 cGy. The part of the fetus located immediately below the diaphragm late in pregnancy is exposed to several hundred centigrays.³² Because much of this dose comes from internal scatter of radiation within the body of the mother, abdominal shielding is only partially effective. The fetal dose depends on the total dose administered, the distance from the fetus to the field source, the field size, and the energy source. The fetal dose

varies and must be calculated for each case. A general guideline is to limit the total fetal dose to 5 cGy.³³ Radiation therapy is rarely used if other alternatives exist.

Breast-Conserving Surgery during Pregnancy

Because breast-conserving surgery (lumpectomy or quadrantectomy) generally employs postoperative radiotherapy, this modality is discouraged. Although this surgery can be performed during pregnancy, the radiation therapy required to complete local therapy for the breast must be delayed until after delivery. This is most suitable when PABC is diagnosed during the late third trimester.³⁴

It has been suggested that delays of as much as 8 weeks from diagnosis to definitive therapy may allow safe delivery of the infant.³⁵ However; delaying radiation therapy may result in an increased incidence of local failure. Evidence suggests that selected patients who undergo breast-conservation therapy may benefit from chemotherapy prior to radiation therapy.³⁶ Based on that, it is prudent to limit breast-conserving therapy to those women who desire breast preservation, are otherwise suitable candidates, and are diagnosed late in pregnancy.

Mitchell (1993)²² described the operation to be done by placing self-retaining retractor in the wound and grasping the tissue immediately overlying the lesion with an Allis clamp or tooth forceps. Minor bleeding, which can obscure the field, must be controlled at each step by cautery. Although it is possible to perform the operation alone, an assistant is very helpful in keeping the field clear and providing countertraction. Maintaining traction on the tissue to be resected, the surgeon enucleates it with small curved scissors.

Blunt dissection is of little help, since there are no well-defined tissue planes. Frequent pauses are necessary to evaluate the scope of the dissection and to avoid cutting into the lesion or removing too much normal lobular tissue. The instrument elevating the lesion is shifted around its periphery as the dissection progresses to provide better exposure of the underside.

After removal of the tumor, the defect is closed with fine absorbable suture material, taking care that these sutures do not cause retraction or dimpling of the overlying skin. Some surgeons prefer to drain the area, and some don't. All bleeding must be controlled before closure. When there is a large residual defect, as after segmental resection, a plastic type of closure for a satisfactory cosmetic result, and suction drainage may be used to avoid the postoperative accumulation of fluid. The skin is closed with either subcuticular stitch of fine absorbable suture material or interrupted 5/0 nylon. A pressure dressing for the first 24 hours is desirable but may not be necessary in relatively minor cases. The sutures should be removed in not more than 6 days to prevent scarring, and steristrips are applied as necessary.

When a bloody nipple discharge suggests the likelihood of an intraductal papilloma, sharp dissection is carried medially from a circumareolar incision placed in the breast quadrant that pressure tests have indicated in most likely to be the source of bleeding. Directly beneath the nipple, the main ducts are encountered and placed on traction with a small hook. The ducts are followed downward until the lesion is found, usually not more than 3 to 4 cm from the surface.

Papillomas are dark red and soft and may be multiple. Generous portion of the duct system around the diseased area is resected and the severed ends are ligated (Fig. 5). Usually there is a relatively small defect that need not be closed, and care must be taken not to cause retraction of the nipple by suturing. Inverting the nipple and scraping all ductal tissue from the under surface has been advocated but seems unnecessary in most cases.

Chemotherapy

Generally speaking, all chemotherapeutic agents are theoretically teratogenic and mutagenic. Their use may result in fetal growth restriction, fetal malformation, spontaneous abortion, or fetal death. It is important to differentiate teratogenic and mutagenic effects from those related to a suboptimal uterine environment or to maternal toxicity, such as neutropenia, infection, thrombocytopenia, or myocardial toxicity. Chemotherapy should be given only after 14-15 weeks gestational age. The first trimester is the most critical time period with respect to exposure to chemotherapy. The blastocyst is resistant to teratogens in the first 2 weeks of life. If it is not destroyed, a surviving blastocyst exposed during the first 2 weeks will not manifest any abnormalities from a chemotherapeutic agent. The third to the eighth week of development, 5 to 10 weeks gestational age, is the period of maximal susceptibility to teratogenic agents. With the exception of brain and gonadal tissue, organogenesis is complete by 13 weeks' gestation.

If chemotherapy induces severe damage early in gestation, spontaneous abortion results. If, however, sublethal damage occurs between the second and the tenth week of gestation, teratogenesis may occur. After organogenesis is complete, the risk for birth defects induced by chemotherapy is decreased, and intrauterine growth restriction becomes the dominant effect. Approximately, 10% to 20% of infants exposed to cytotoxic agents during the first trimester have major malformations as compared with a rate of 3% in the general population. The underline rates of spontaneous abortion and birth defects in the general population are large enough to confound the data from small series. In general, chemotherapy should be delayed whenever possible until after the first trimester.

Most series of PABC that report the ER and PR status indicate that as many as 80% of patients are ER- and PR-negative.³ During the first trimester the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) should not be used owing to the toxicity of folate antagonists. If chemotherapy must be administered during the first trimester the combination of cyclophosphamide, doxorubicin (Adriamycin), and 5-fluorouracil (CAF) should be considered. CMF can be used safely during the second and third trimesters.³⁴

Chemotherapy is contraindicated in lactating women as many chemotherapeutic agents including cyclophosphamide, doxorubicin, methotrexate, hydroxyurea, and cisplatin are secreted in breast milk. Otherwise, breast-feeding should be stopped before initiating the chemotherapy. Still all other modalities of treatment are available during lactation. If surgery is planned, breast-feeding should be stopped to reduce size and vascularity.

Anti-estrogen and oophorectomy

Tamoxifen has been considered inappropriate due to concerns over possible teratogenesis and lack of efficacy. In a case report, Isaacs et al., in 2001 reported that the use of tamoxifen in pregnancy is complex, but is not necessarily associated with fetal harm and may be considered a therapeutic option in selected cases.³⁷ Theoretically, advanced disease may be helped by oophorectomy, but as if this is not proven and the patient still in the child bearing period, hormonal manipulation by anti-estrogens is more practical depending on receptor status of the tumor.

General Plan for Treatment of Breast Cancer with Pregnancy

Generally speaking, the treatment is individualized according to each case circumstances that include: the gestational age in which the cancer was discovered, surgical staging, pathology of the tumor, hormonal receptors status, involvement of lymph nodes, number of children the lady has. Stage I and II are operable and are treated by modified radical mastectomy with or without postoperative irradiation, hormone therapy or chemotherapy. Stage III and IV are inoperable and are treated by simple mastectomy as palliative measure for pain and fungation followed by palliative chemotherapy, hormone therapy or irradiation.

I. First and second trimester: Termination of pregnancy could be the choice to allow free hand dealing with the cancer especially in late stages and positive lymph nodes sampling. Those cases will need post operative radiation and/or chemotherapy. Both of them are contraindicated in that period of pregnancy.

II. Third trimester: Surgical treatment should be applied without delay; pregnancy should be terminated once the fetal maturity allows that. Postpartum radiotherapy and chemotherapy can be given with prevention of lactation in case of chemotherapy.

Metastasis of Breast Cancer to Conception

Metastatic spread to the placenta has been reported but is extremely rare.³⁸ Placental metastasis has generally been reported in association with widespread metastatic disease. Spread to the fetus has never been reported, although such spread has been reported for melanoma, hematopoietic malignancies, hepatoma, and choriocarcinoma. Careful histologic examination of the placenta is required even if the placenta is grossly normal. The fear that breast cancer may spread to the fetus is a major concern of patients.

Prognosis

Breast cancer is generally believed to carry a worse prognosis during pregnancy because of the potential adverse effects of anticancer treatment on the fetus and of pregnancy related hormonal and immunological modifications on the disease.³⁸ Also, most studies indicate that PABC tends to be more advanced at initial presentation because pregnancy-related changes in the breasts obscure clinical and radiological manifestations. Actually, breast cancer has equivalent prognosis in pregnant and nonpregnant women when matched by age and stage at diagnosis at the same institution during the same time period.^{3,4,35,39}

Does Pregnancy Protect from Breast Cancer?

Interruption of the first pregnancy will remove the protective effect of that first full term pregnancy, and subject the woman to a small but real increased risk of developing breast cancer in the future compared to the risk she would have if she carried the pregnancy. According to the United States National Cancer Institute an overall 50% increase in the subsequent risk of breast cancer, following an induced abortion. If a woman has a mother, sister, aunt or grandmother with breast cancer, she will increase her chance of getting breast cancer by 80%, if she is under 18, she will double her chance of getting breast cancer, and if both conditions pertain, her risk is much higher.⁴⁰

Pregnancy after Treatment of Breast Cancer

Chemotherapeutic agents significantly affect the subsequent fertility. The risk of premature ovarian failure induced by chemotherapy can be estimated from the women's age, the agent used, and the total dose.⁴¹ Alkylating agents such as cyclophosphamide cause amenorrhea through direct ovarian depression. The severity of the depression seems to be a function of the number and activity of the follicles present at the initiation of the chemotherapy. Prepubertal ovaries, not yet under cyclic hormonal control, seem protected against destruction from chemotherapy. The younger the patient, the larger the reserve of oocytes that can be recruited after chemotherapy. Although cyclophosphamide is a major cause of ovarian failure, methotrexate and 5-fluorouracil are not. Approximately 50% of women less than 35 years of age resume menses after a full course of adjuvant chemotherapy.

As a general rule, cancer identified prior to conception should be adequately treated with appropriate follow-up before pregnancy is attempted. Once successfully treated, few malignant diseases absolutely preclude future pregnancy. There are no prospective studies evaluating the effects of subsequent pregnancy on breast cancer. Although most recurrences are seen within 2 years, many women have later recurrences. No studies have shown an adverse effect of subsequent pregnancy even in patients with positive axillary nodes and in those in whom the pregnancy occurs earlier than 2 years after treatment.³⁷ Several studies have suggested that women who become pregnant after treatment for breast cancer demonstrate a trend toward improved prognosis when compared with women not subsequently pregnant.^{42,43} Abortion does not improve survival, and termination of pregnancy is considered only in women with recurrent disease. It is recommended that patients wait two or three years after diagnosis before attempting to conceive.

Summary

Breast cancer is the most common cancer in pregnant and postpartum women, occurring in about 1 in 3,000 pregnancies. The average patient is between 32 to 38 years of age and, with many women choosing to delay childbearing, it is likely that the incidence of breast cancer during pregnancy will increase. There is no evidence to implicate pregnancy or lactation in either the etiology or the progression of breast

cancer. The increase in size, weight, vascularity, and density of the breasts in pregnancy hinder the early detection of the breast masses either clinically or by mammography. Most of the benign lesions seen in pregnancy are the same ones in the nonpregnant state. Most of Pregnancy associated breast cancer (PABC) present as painless masses, and as many as 90% of these masses are detected by breast self-examination. Women with PABC generally have more advanced disease with larger tumors, a higher percentage of inoperable lesions, and a higher percentage of nodal involvement. As most PABC presents with a palpable mass, the role of imaging modalities in the evaluation of these patients remains limited. Fine-needle aspiration cytology is the initial procedure of choice for evaluating breast masses during pregnancy and lactation. Induction of abortion does not improve survival. Operable disease in the first 6 to 7 months of pregnancy should be treated by modified radical mastectomy, as irradiation is contraindicated. Late in pregnancy, a lumpectomy and axillary dissection can be done, with irradiation being delayed until after delivery. General anesthesia is safe if the usual precautions are taken to compensate for the physiologic changes induced by pregnancy. Adjuvant chemotherapy can be considered in the second and third trimesters but better to be delayed until after delivery. In patients with locally advanced or metastatic cancer diagnosed early in pregnancy, for whom both chemotherapy and radiation therapy would be indicated, consideration must be given to termination of pregnancy. Unfortunately, delay in diagnosis is common and 70-89% of patients with operable primary lesions have positive axillary lymph nodes. Late stage appears to be the only reason for the generally worse prognosis in these patients. As stage for stage, they have a course similar to that of nonpregnant patients. No studies have shown an adverse effect of a subsequent pregnancy even in patients with positive axillary nodes and patients get pregnant earlier than 2 years after treatment. In spite of that it is advised to postpone pregnancy for 2 years to allow proper diagnosis and management of recurrences. In addition, recurrences may influence the decision to be a mother.

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