Benign Diseases of the Breast; Female Athlete Triad Syndrome

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I. INTRODUCTION

Breast complaints are among the most common reasons that women seek medical attention. Patients may present with a palpable mass, a mammographic abnormality, nipple discharge, pain, or any combination of these problems. Fortunately, most complaints prove to be benign in origin; however, physicians still need to assess for potentially serious conditions. The physician’s role in evaluating a patient presenting with a breast problem includes assessing and screening for breast cancer, providing a diagnosis, and treating the condition. This review will address the evaluation and management of common benign breast conditions seen in clinical practice (Table 1). Ten case patients are presented to highlight essential features of benign breast diseases.

II. MANAGEMENT OF A PALPABLE BREAST MASS

GENERAL PRINCIPLES

Palpable breast masses and abnormalities are among the most common breast problems for which a patient seeks clinical evaluation. Although breast masses and abnormalities are predominately benign conditions, especially in premenopausal women, the possibility of breast carcinoma should always be assessed. Complete evaluation includes patient history, a thorough risk assessment, physical examination, radiologic studies, and usually some form of needle aspiration or tissue biopsy of the mass.

Imaging Studies

The patient’s age influences the choice of diagnostic imaging of breast masses. For women older than 30 years, a bilateral mammogram is performed to evaluate the mass for possible signs of malignancy. Mammography also will determine if any other lesions exist and require evaluation. In addition, a directed breast ultrasound of the palpable breast mass will determine whether the mass is solid or cystic. For women younger than 30 years, generally it is not necessary to perform a bilateral mammogram; a directed breast ultrasound to determine the consistency of the mass is the initial imaging study of choice. However, a mammogram should be obtained in patients younger than 30 years who have an abnormal needle biopsy or sonogram and who also have a first-degree relative diagnosed with breast cancer prior to the age of 40 years.
Fine Needle Aspiration

At the time of initial presentation, the clinician should perform a fine needle aspiration (FNA) of the palpable breast mass. FNA is an accurate, cost-efficient, relatively simple office procedure that is performed with a 22-gauge needle and a 10-mL syringe. This procedure provides rapid cytologic results and immediate information on whether the mass is cystic or solid, and it can be used in place of sonogram or to clarify indeterminate sonographic findings. For solid lesions, slides are prepared and sent to cytopathology for evaluation. The false-negative rate should be less than 5% in experienced hands,1 and the incidence of false-positive findings is generally less than 0.5%.2 Alternatively, in the office setting, the physician can perform a core biopsy of the palpable breast mass under local anesthesia with a 14-gauge Tru-Cut needle.

Indications for Excision of a Palpable Breast Mass

When physical examination, imaging, and FNA (the so-called “triple test”) are used to evaluate a dominant breast mass (ie, a lesion clearly differentiated from the rest of the breast), the false-negative rate for malignancy is 0.2% to 2%.3 Strictly speaking, excisional biopsy is the gold standard for providing a definitive diagnosis; however, it need only be performed if: (1) the results of the FNA are inconclusive or discordant with the clinical examination or radiologic appearance of the mass; (2) the FNA or core biopsy reveals atypia; or (3) the patient desires surgical excision as an alternative to FNA or core biopsy for definitive diagnosis as well as alleviation of symptoms or concern regarding the palpable mass.1

### III. CASE PRESENTATIONS OF PALPABLE LESIONS

#### CASE PATIENT 1

Patient 1 is a healthy 19-year-old woman presenting for evaluation of a self-detected mass that has been in the upper outer section of her left breast for 2 months. A left breast ultrasound reveals a 1.2-cm solid, well-circumscribed mass in the upper outer quadrant of the breast. The mammogram and sonogram are normal. The lesion is tender on palpation. A repeat mammogram and ultrasound are scheduled. Given the patient’s age and the benign appearance of the lesion, the clinician recommends observation and periodic follow-up.
breast. The physician performs FNA of the mass at the initial clinical evaluation; cytopathologist’s report reveals no evidence of malignancy.

**Fibroadenoma**

The most likely clinical diagnosis is a fibroadenoma. Fibroadenoma is a benign, solid breast tumor composed of epithelial and stromal elements. It is the most common breast tumor found in adolescents and young women but also may occur in older women. Fibroadenomas often express estrogen receptors and can fluctuate in size with the menstrual cycle. Palpation of a fibroadenoma typically reveals a well-circumscribed round or oval, firm, rubbery, mobile mass (Table 1). If the work-up reveals findings consistent with a presumed fibroadenoma, the mass can be followed clinically. It should be excised if it enlarges or changes in consistency, outside of normal fluctuations with the menstrual cycle. Fibroadenomas larger than 5 cm are called giant fibroadenomas and need to be differentiated from phyllodes tumors. Cytology results, however, cannot always distinguish phyllodes tumors from giant fibroadenomas; fibroadenomas can fluctuate with the menstrual cycle, whereas phyllodes tumors do not (see “Case Presentations of Palpable Lesions, Patient 4”). The treatment for giant fibroadenomas is complete surgical excision.

**Patient 1 Follow-up**

The mass is diagnosed as a fibroadenoma, and the patient is told that it will not require surgical excision. She is advised to continue with breast self-examinations and to report any changes in the mass to her physician because these changes may indicate the need for excision. Additionally, breast sonograms are obtained every 6-months. After 2 years of follow-up sonography, the stability of the lesion is documented.

**CASE PATIENT 2**

Patient 2 is a 42-year-old woman who has no family or personal history of breast cancer. She presents for evaluation of a palpable right breast mass that she has had for 3 months. A bilateral mammogram reveals a benign-appearing, well-circumscribed nodule in the right breast corresponding to the palpable mass. A directed right breast ultrasound reveals a simple cyst.

**Breast Cysts**

A breast cyst is a fluid-filled structure that derives from the terminal duct lobular unit. Breast cysts are a relatively common entity in premenopausal women and are more common in women approaching menopause. Patients often present with a palpable breast mass, which may be painful. Physical examination typically reveals a smooth, round, mobile mass (Table 1). Symptomatic cysts can be aspirated to provide relief. Management of a breast cyst is shown in Figure 1.

If FNA yields fluid and results in complete resolution of the breast mass, then these results are diagnostic of a simple cyst. If the mass completely resolves, then adjuvant breast imaging is not necessary. The aspirated fluid will be either non-bloody (ie, clear, yellow, brown, orange, green, black) or bloody. If grossly bloody fluid is obtained, then the fluid should be sent for cytologic analysis to rule out malignancy. As long as other indications for surgical excision are not present, all non-bloody cyst aspiration fluid may be discarded because it has been shown in multiple studies that this non-bloody fluid is benign. Indications for definitive surgical excision of a breast cyst to rule out associated malignancy include incomplete resolution of the breast mass after cyst aspiration, discovery of an associated solid component of the cyst by breast ultrasound, bloody fluid that is atypical by cytologic analysis, or recurrence of the cyst after 2 complete aspirations. However, some clinicians elect to send all cyst fluid for cytologic analysis. Follow-up is essential. If any change is noted in size or consistency of the breast cyst on examination or on follow-up ultrasound, further evaluation is warranted.


![Flowchart](image-url)
Chapter 1—Benign Diseases of the Breast

Patient 2 Follow-up

Patient 2 reports pain at the site of the palpable cyst and undergoes aspiration, which completely resolves the palpable finding. Cytology of the fluid is normal, and the patient continues with routine breast examinations and annual mammography.

CASE PATIENT 3

Patient 3 is a 57-year-old woman who presents 2 weeks after a car accident with a large, firm fixed mass in the upper outer quadrant of her right breast.

Fat Necrosis

The most likely diagnosis is fat necrosis associated with the trauma of the car accident. However, a very careful history needs to be taken because fat necrosis is a benign condition that can mimic breast carcinoma. A diagnosis of fat necrosis requires a recent, related history of trauma significant enough to cause ecchymosis. For example, fat necrosis can develop after breast surgery, especially after autologous tissue breast reconstruction for carcinoma. Patients reporting a history of minor trauma 3 years before the development of the lump, however, are unlikely to have fat necrosis.

Patients may report that the affected breast initially appeared to be bruised with black/blue discoloration and that a large, hard, and usually tender mass developed over the course of the next few days to weeks. On physical examination, a firm, discrete, poorly circumscribed mass is palpated (Table 1). Unlike carcinoma, the mass is often painful. If the patient presents early, ecchymosis or resolving ecchymosis can be seen in the skin, which lends more credence to the diagnosis of fat necrosis rather than carcinoma. These masses do not fluctuate with the menstrual cycle. The mammographic and sonographic appearances of fat necrosis—a spiculated, irregular, solid mass—are virtually identical to those of carcinoma.

Patients presenting with this type of mass should be biopsied. If the clinical threshold is high for fat necrosis and if the cytology is reliable, then FNA is sufficient. If the FNA is consistent with fat necrosis, then the patient needs to be followed through to resolution of the mass. If the mass persists beyond 3 to 4 months with no change in size, then surgical excision is warranted. If FNA is nondiagnostic, then a core biopsy or surgical excision is warranted. Fat necrosis is self-limiting and tends to resolve spontaneously. As long as carcinoma is ruled out, it is safe to observe these patients. If patients present during the acute phase after trauma, nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to relieve symptoms of discomfort.

Patient 3 Follow-up

Patient 3’s mammogram and sonogram reveal an irregularly shaped mass. She undergoes FNA biopsy of the mass; cytology reveals cells consistent with fat necrosis. Follow-up examination in the office 4 weeks later shows a significant decrease in the size of the nodule. After an additional 3 months, the nodule resolves.

CASE PATIENT 4

Patient 4 is a 35-year-old woman who presents with a 6-cm nontender, mobile mass in the upper outer quadrant of her right breast.

Phyllodes Tumor

The differential diagnosis for this mass includes cyst, fibroadenoma, cancer, and, because of the large size, a phyllodes tumor, a rare fibroepithelial tumor that occurs only in the breast. These lesions are also known as cystosarcoma phyllodes and can be classified as benign, malignant, or borderline. Whether the lesion is benign depends on histologic factors, which are determined by cellular atypia, mitotic activity, tumor margins, and stromal overgrowth. The typical clinical presentation of a phyllodes tumor is a large, palpable, painless mass that is smooth, round, and multinodular (Table 1); it does not fluctuate in size with the menstrual cycle. The size of these tumors ranges from 1 to 40 cm; phyllodes tumors often are greater than 3 cm at the time of presentation. Sometimes, these tumors present as a rapid enlargement of a previously stable, long-standing nodule. mammographic and sonographic appearances of phyllodes tumors are similar to that of a fibroadenoma—a smooth, multi-lobulated mass. Sonogram reveals a large, well-circumscribed, smooth lesion. Occasionally, a cystic area may be seen within the solid mass.

Benign lesions have approximately a 20% chance of local recurrence; hence, wide local excision with a 2-cm margin is the method of treatment for these tumors. A locally recurrent tumor is not an indication of malignancy. Because of their similarity to fibroadenomas, phyllodes tumors are often enucleated at the time of surgery. If permanent pathologic analysis reveals a phyllodes tumor, then re-excision with a 2-cm margin is recommended.

Patient 4 Follow-up

The patient undergoes surgical excision of the 6-cm mass. Frozen section at the time of surgery confirms a phyllodes tumor, and wide surgical margins are taken. Two years later, she does not have any signs of recurrence. Patient 4, based on her age, continues to receive mammography at her annual examination.
CASE PATIENT 5

Patient 5 is a 36-year-old woman who presents with a tender, hard “cord” in the outer aspect of her right breast.

Mondor’s Superficial Thrombophlebitis

Mondor’s superficial thrombophlebitis is a benign and rare condition of the breast. The pathogenesis is thrombosis of the lateral thoracic or superior thoracicoepigastric veins. Events that predispose patients to this condition include trauma to the breast, infection, recent biopsy (including surgical and core biopsies), and excessive physical strain such as weight lifting. Rheumatoid arthritis also is associated with Mondor’s disease. Associated carcinomas have been reported in 5% to 10% of cases; therefore, mammography should be obtained to rule out a malignancy.

On physical examination, a tender cord is usually palpable in the lateral or mid-breast (Table 1). If the patient recently had a breast biopsy, the cord can be found adjacent to the biopsy site. The cord is superficial and can cause dimpling of the skin, which is most pronounced when the patient raises her arms above her head. The process is self-limiting and treatment consists of warm soaks and NSAIDs until resolution of the cord.

Patient 5 Follow-up

Based on her symptoms, the patient is treated for thrombophlebitis with NSAIDs and warm soaks for 6 weeks. Follow-up examination in the office demonstrates resolution of the cord.

IV. SIGNS AND SYMPTOMS

BREAST PAIN

Breast pain without an associated mass is one of the most common reasons patients seek medical attention. Etiologies of breast pain include cysts, mastitis, and fibrocystic changes (Table 1). Treatable causes of breast pain include cysts and mastitis. In most cases, however, the cause of pain in either or both breasts is idiopathic and most likely related to hormonal changes of the menstrual cycle.

Fibrocystic Changes

When taking a history for breast pain, the physician should ascertain whether signs and symptoms of infection (eg, redness, increased pain, warmth) are present. If these symptoms are present, then the most likely diagnosis is infection-related and can be appropriately treated. Patients reporting the presence of a tender mass may have a cyst or, more unlikely, a fibroadenoma (see Section III, “Case Presentations of Palpable Lesions, Case Patient 1”). If these symptoms are not present, then the most likely diagnosis is related to fibrocystic changes. Pain caused by hormonal and fibrocystic changes tends to be cyclical and is most prominent during the week before and the week of menstruation. The pain usually subsides or disappears about 7 to 10 days after the onset of menstruation. Patients with prominent fibrocystic changes may detect a palpable mass, usually in the upper quadrants, associated with the tenderness. The physical examination for idiopathic breast pain is typically unremarkable with no discrete palpable masses. However, depending on the timing of the menstrual cycle, a thickening may be palpated in the area of tenderness. A follow-up examination 7 to 10 days after the onset of the menstrual cycle usually demonstrates resolution of the thickening.

A mammogram (in patients who are candidates for mammography) and/or directed sonogram should be obtained to evaluate for a nonpalpable lesion. Solid lesions should be biopsied by FNA, core needle, or surgical excision. If a cyst is seen corresponding to the location of the patient’s tenderness, then a sonogram-guided aspiration can be performed to alleviate symptoms of breast pain.

In many cases, the pain from fibrocystic changes is tolerable and patients are mostly concerned that the pain could represent a carcinoma. If the physical and radiologic examinations are normal, then patients can be reassured that they do not have a carcinoma. Steps that patients can take to decrease breast pain include wearing a good support bra (sports bra), reducing caffeine intake, and taking an NSAID such as ibuprofen. Gately and colleagues have reported on the effective use of linolenic acid (evening primrose oil) at a dose of 3 g daily in treating cyclical breast pain. Other reports, however, indicate that evening primrose does not help with breast pain.

If a postmenopausal woman presents with new onset of breast pain after taking HRT, the physician should consider stopping the HRT if the pain is intolerable. Withdrawal of the medication often produces dramatic relief. If patients present with tenderness in the medial aspect of the breast, then a musculoskeletal origin (eg, costochondritis) should be considered; this condition can be effectively treated with NSAIDs.

In summary, the initial step in the evaluation of breast pain is a careful review of the patient’s history to characterize the pain, followed by physical and radiologic
examinations to exclude the presence of a mass. For most women without a dominant mass, reassurance is sufficient therapy. Usually the symptoms can be successfully treated with a good support bra, NSAIDs, and caffeine intake reduction.

**BREAST INFECTIONS**

**Case Patient 6**

Patient 6 is a 23-year-old woman 10 weeks postpartum and breast feeding who presents with severe right breast pain and fever (her temperature is up to 102°F).

**Mastitis**

The differential diagnosis includes mastitis and possible abscess formation. Mastitis during breast feeding is common and can produce significant systemic symptoms such as shaking, chills, malaise, leukocytosis, and elevated temperature up to 102.5°F. Mastitis without an associated abscess presents with induration, erythema, warmth, and diffuse tenderness. The presence of a fluctuant area with localized tenderness should raise the possibility of an underlying abscess. If the physical examination is equivocal for an abscess, then an ultrasound should be obtained. Often, palpable axillary adenopathy may be appreciated.

The treatment for uncomplicated mastitis is antibiotic coverage, warm soaks, and continued decompression of the breast. Mothers can and should continue to nurse to decompress the breast and to prevent stasis of milk. The infant does not require antibiotic therapy and will not be adversely affected by continued breast feeding. Antibiotic coverage should include the most common organism, *Staphylococcus aureus*, which can be covered by cephalaxin (Keflex) or dicloxacillin. Warm soaks and manual pressure are crucial components of treatment. If a discrete indurated or fluctuant area is apparent in the breast, then FNA and/or ultrasound is warranted to evaluate for an underlying mass or abscess cavity.

Many breast abscesses can be successfully treated with percutaneous aspiration, antibiotics, and warm soaks. However, if conservative therapy fails and the patient’s symptoms/fever persist and progress, then surgical incision and drainage of the abscess are warranted. The wound should be irrigated with large volumes of antibiotics, packed open, and allowed to granulate secondarily. Close clinical follow-up is essential. In patients with unresolved or recurrent mastitis, inflammatory breast cancer should be considered. A full thickness skin biopsy can be used to determine whether cancer is present.

**Patient 6 Follow-up**

The patient is diagnosed with mastitis related to lactation. She is treated with a 10-day course of cephalaxin and warm soaks, with prompt resolution of her fever and symptoms.

**Case Patient 7**

Patient 7 is a 45-year-old woman who presents with a 2-day history of sensitivity around the right nipple; she does not have a fever. The day before presenting, she notices swelling, redness, and a hard lump under the right nipple.

**Abscess**

The leading diagnosis is a subareolar abscess, which is an infection of the terminal ducts. Often patients first report exquisite nipple sensitivity. Other presenting symptoms (eg, localized tenderness, erythema, induration and a mass) develop 24 to 48 hours later, usually around the nipple areolar complex. Patients may develop a fever or leukocytosis.

If patients present early and if no discrete abscess has formed yet, then treatment consists of warm soaks and a 7 to 10 day course of an oral antibiotic such as cephalaxin or dicloxacillin. Pain can be managed with acetaminophen. If a discrete mass is palpated, then an FNA biopsy should be performed to confirm that an infection is present and to rule out a malignancy. Because of the tenderness associated with the infectious process, patients typically are unable to tolerate mammography. If a mass is palpated, sonography is useful to evaluate the presence of an abscess or a solid lesion.

If patients present with a fluctuant area initially or subsequently, then the abscess cavity needs to be incised and drained (I&I) and the wall of the cavity should be biopsied to rule out carcinoma. The wound should be left open and allowed to granulate secondarily. Some studies have reported a 38% chance of recurrence with I&D only. Therefore, many clinicians advocate surgical excision of the terminal ducts once the acute inflammatory response has resolved. Occasionally, a fistula may develop after surgical treatment of the abscess. Then, the fistula needs to be probed at the time of the surgery and the tract surgically excised.

In most cases, if patients present early and if they are treated appropriately with antibiotics and warm soaks, they do not need surgical intervention. Although the acute inflammatory process usually resolves within 7 to 10 days, the induration and firmness under the nipple may take as long as 4 to 6 weeks to resolve. Patients should be seen in follow-up to ensure that the firmness, if present, completely resolves.
**Patient 7 Follow-up**

In the office, the patient undergoes FNA biopsy of the palpable lump under the right nipple. Cytology reveals acute inflammatory cells. She is started on a 10-day course of cephalexin and warm soaks. Follow-up examination in the office 2 weeks later reveals the resolution of the lump and pain.

**NIPPLE DISCHARGE**

**Case Patient 8**

Patient 8 is a 42-year-old woman who presents with a history of 2 episodes of spontaneous bloody discharge from her right nipple.

**Intraductal Papilloma**

Evaluation of patients with nipple discharge begins with a very careful history. It is important to differentiate between spontaneous discharge and discharge that can only be elicited with manipulation. Another important feature is whether the discharge is unilateral or bilateral. Discharge that is serous, serosanguinous, bloody, or watery is more likely to be secondary to an underlying growth. Discharge that is brown, green, gray, or milky is usually physiologic. Milky discharge associated with amenorrhea, infertility, and visual field disturbances should raise the suspicion of a pituitary adenoma. Medications—such as antihypertensives, oral contraceptives, phenothiazines, and tranquilizers—may also cause nipple discharge. The clinical features that indicate the need for surgical evaluation include spontaneous discharge; unilateral localization; confinement to 1 duct; association with a mass; bloody, serous, serosanguinous, or watery discharge; and older age.10

The most common cause of spontaneous bloody nipple discharge is an intraductal papilloma, which is a wart-like growth arising from a single major collecting duct in the subareolar region.33 Patients often report seeing blood on their bra or nightgown. The second most common presentation of an intraductal papilloma is spontaneous, clear, serous discharge from a single duct.

In patients with intraductal papilloma, bloody nipple discharge is elicited from a single duct. The papilloma cannot be palpated in most cases. If the papilloma is palpated, it typically feels like a pea-sized nodule at the areolar ridge. When evaluating a patient with nipple discharge, the physician should try to find the trigger point, which is the location of the breast where compression causes nipple discharge.34 In many cases, the physical examination is otherwise normal. If nipple discharge can be elicited, the fluid should be sent for cytologic analysis.

Radiologic work-up should include a mammogram, sonogram, and possible ductogram. In most cases, the mammogram of the retroareolar region will be normal. On a sonogram, a dilated duct with an intraluminal lesion may occasionally be seen, which is very suggestive of an intraductal papilloma (Table 1). However, a normal sonogram does not rule out the presence of an intraductal papilloma. If the sonogram/cytology fluid results are inconclusive and a dilated duct is present, then a ductogram may be performed.35 A filling defect within the duct is diagnostic of an intraductal papilloma.

If a papillary lesion is suspected based on history, physical examination, radiologic examination, or cytologic analysis, then the treatment is surgical excision.36,37 All intraductal lesions need to be excised because they cannot be classified as benign or malignant before pathologic assessment. The surgical procedure of choice is complete excision of the terminal ducts if the patient is not interested in breast feeding at a later time. Selective duct excision may be accomplished with the use of ductography localization for the patient interested in future breast feeding.35 If patients have selective duct excision, they are at greater risk for additional intraductal papillomas (ie, the lesions can recur).

**Patient 8 Follow-up**

In this patient, cytology of the right nipple discharge reveals cells consistent with a papillary lesion. Mammogram and sonogram are normal. She undergoes surgical excision of the terminal ducts in her right nipple. Pathology reveals a benign intraductal papilloma. No further treatment is indicated.

**V. RADIOLOGIC AND PATHOLOGIC FINDINGS**

**CASE PATIENT 9**

Patient 9 is a 47-year-old woman who undergoes a routine annual mammogram. The radiology report indicates that a radial scar is visible in the central aspect of her left breast.

**Radial Scar**

Radial scars are asymptomatic; they do not cause a palpable lump or pain. Radial scars are diagnosed by mammography or pathologic analysis. When diagnosed by pathologic analysis only, radial scars are incidental findings seen in breast tissue that was excised because of another abnormality. On mammography, radial scars appear as soft tissue densities with irregular serrated edges or spiculated margins, similar in appearance to carcinomas.38 Microscopically, radial scars have a stellate
configuration, similar to the spokes of a bicycle wheel. The lesion has a sclerotic center with a central core containing obliterated ducts and elastin deposits. The center is surrounded by contracted ducts and lobules that may contain proliferative lesions. All the elements of the pathologic findings are benign.

The association of radial scars with the subsequent development of carcinomas is controversial. In a retrospective case-control study, Jacobs and colleagues found that radial scars were an independent histologic risk factor for breast cancer. Other studies have indicated a relationship of radial scars to the subsequent development of carcinomas, commonly tubular carcinomas, therefore, surgical excision is the most prudent management as a preventative measure.

When seen on mammography, radial scars should be biopsied by surgical excision rather than by percutaneous core sampling for several reasons. Even when totally excised, radial scars can present a difficult histologic diagnosis. Therefore, complete excision, rather than core samples, is needed to evaluate the entire architectural pattern. Finally, core biopsies are not ideal for radial scars because patients need surgical biopsy regardless of the results. In other words, if a core biopsy confirms the presence of a benign radial scar, the patient will still need surgical excision; scarring usually does not recur after excision.

In summary, radial scars are asymptomatic. They do not cause a palpable lump or pain. Radial scars are usually found on routine mammographic screening or as incidental findings in a pathologic specimen. Radiologically, they mimic carcinomas and may be associated with tubular carcinomas. Local excision is the treatment of choice.

**Patient 9 Follow-up**

Surgical excision of the radial scar is performed on patient 9. Final pathology reveals no evidence of carcinoma. She continues with routine annual mammography and monthly self-examination of her breasts.

**CASE PATIENT 10**

Patient 10 is a 54-year-old woman who undergoes a right breast biopsy for indeterminate microcalcification that was discovered on her annual mammogram. Pathology reveals proliferative fibrocystic changes with lobular carcinoma in situ (LCIS).

**Lobular Carcinoma in Situ**

LCIS, also known as lobular neoplasia, is not a pre-malignant condition. Unlike ductal carcinoma in situ (DCIS), LCIS is a benign process, and the 2 conditions are unrelated. However, LCIS is a risk factor for the development of bilateral breast cancer. LCIS is always an incidental microscopic finding in breast tissue removed for another reason. LCIS does not produce a mass and is not associated with any typical radiologic findings.

The major issue in the management of patients with LCIS is the subsequent risk of developing an invasive cancer. Patients with LCIS have an increased risk of carcinoma that is equivalent to a patient whose mother had bilateral premenopausal breast cancer or a risk that is 7 to 10 times greater than the risk for the general population. The most common form of breast cancer that these patients are at risk for is infiltrating ductal carcinoma. Both breasts are at equal risk of developing carcinoma, not just the side on which the LCIS was diagnosed. Traditionally, management options for women at increased risk have included close surveillance or, uncommonly, bilateral prophylactic mastectomy. Unilateral mastectomy with mirror-image biopsy of the contralateral side has no clinical basis given the natural history of LCIS and is no longer considered a sound medical option.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 and the Italian Tamoxifen Prevention study assessed tamoxifen treatment for 5 years in high-risk patients (ie, all patients with LCIS). Data from these chemoprevention trials have shown a 30% to 50% risk reduction of developing both invasive and noninvasive breast cancer in patients with LCIS who receive tamoxifen treatment. Thus, the current management of LCIS includes chemoprevention with tamoxifen for 5 years. Patients may also be enrolled in the STAR (Study of Tamoxifen and Raloxifene) trial, which compares raloxifene and tamoxifen for the prevention of breast cancer. At the current time, raloxifene (Evista) is the only FDA-approved drug treatment for osteoporosis. However, it is being investigated as a chemopreventive agent. Patients with LCIS may be referred to the STAR trial for chemoprevention.

In many ways, LCIS differs from DCIS. LCIS is a marker of increased risk and not a malignant condition; therefore, no radiation or chemotherapy treatment is required. Also, it is not necessary to completely excise LCIS because it is always an incidental finding and a benign process. DCIS is a pre-malignant condition that, if untreated, will most likely progress to an invasive carcinoma in the exact location where it was diagnosed. DCIS leads to infiltrating carcinoma and therefore needs to be excised with clear margins.

To summarize, LCIS is a risk factor for the development of bilateral breast cancer. It lacks clinical or mammographic signs and is always an incidental finding at
the time of biopsy. Current management for risk reduction includes tamoxifen therapy for 5 years or bilateral prophylactic mastectomy, usually with reconstruction. However, mastectomy is being used less frequently given the availability of chemoprevention. LCIS patients do not require excision to negative margins, radiation therapy, or systemic chemotherapy.9

Patient 10 Follow-up

After the diagnosis of LCIS, the patient is referred to a medical oncologist. She is started on 5 years of tamoxifen therapy for chemoprevention. In addition, she receives bilateral biannual mammography and has continued to be without signs of cancer.

VI. SUMMARY POINTS

• Palpable lesions should be evaluated by needle biopsy (fine needle or core), mammography, and sonography if age appropriate.
• Infections (eg, mastitis) should be treated with antibiotics and warm soaks with follow-up examination to demonstrate resolution of the process. Patients with recurrent or resistant infections should undergo biopsy to rule out inflammatory carcinoma.
• Bloody nipple discharge most likely represents an intraductal papilloma but requires surgical excision to rule out a papillary carcinoma.
• A radial scar seen on mammography should be surgically excised.
• LCIS is a marker of increased risk for developing a subsequent invasive carcinoma. Therefore, patients with LCIS should receive either chemoprevention or mastectomy and should be closely monitored.

REFERENCES


Chapter 2—Female Athlete Triad Syndrome: A Case Study

Samantha M. Pfeifer, MD

I. INTRODUCTION

Female participation in sports has increased significantly since the Title IX Legislation/Educational Assistance Act passed in 1972. This law mandates nondiscrimination in all educational programs (including athletics) offered by institutions receiving federal funding. As a result, female participation in organized sports at the high school, college, and Olympic level has increased from less than 18% in 1972 to approximately 40% in 1996.1 With more competitive female athletes, several trends have emerged. From a gynecologic perspective, the most significant of these has been disruption of the normal menstrual cycle, which can manifest as delayed puberty, oligomenorrhea, and/or amenorrhea. In 1980, this menstrual dysfunction in female athletes was associated with eating disorders and weight suppression.2,3 Amenorrhea was subsequently associated with stress, decreased bone density, and osteoporosis.4,5 In 1992, the American College of Sports Medicine coined the phrase “female athlete triad,” referring to the interrelated problems of disordered eating, amenorrhea, and osteoporosis seen in female athletes.

II. CASE PATIENT 11 PRESENTATION

Patient 11 is a 21-year-old college senior who is referred for evaluation of secondary amenorrhea. She reports that menarche occurred at age 16 years, which followed breast development at age 14. Menses have always been irregular. For the first 2 years after menarche, she had only 1 or 2 periods a year. She has not had any bleeding for the past 3 years. She is not sexually active. She denies any abdominal pain, cramping, hot flashes, night sweats, galactorrhea, visual changes, hirsutism, or acne. Her gynecologic history is unremarkable, and she has never had a pelvic examination. Her medical history is notable only for stress fractures in her right leg that occurred 1 year ago. She denies weight loss or fatigue. She reports eating a healthy low-fat diet. She has been a competitive runner since she was in seventh grade. Currently, she competes on the cross-country team in the fall and on the track team in the spring. She runs and lifts weights 2 hours daily.

CHARACTERISTICS OF NORMAL MENSTRUATION

Regular menstrual cycling requires normally functioning anatomy and an intact central nervous system (CNS). The anatomic structures are the vagina, uterus, and ovaries located in the pelvis. The central endocrine control involves the hypothalamus and pituitary glands. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile pattern (every 60 to 90 minutes) from the ventromedial neurons, which in turn stimulates the pituitary gland to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH promote ovulation and production of estrogen/progesterone. Estrogen stimulates development of the endometrial lining of the uterus. Withdrawal of estrogen and progesterone initiates menses. The hypothalamus also is responsible for initiating puberty and subsequent estrogen production, leading to the development of secondary sexual characteristics.

Timing of puberty depends on geographic area, family history, nutritional status, and body fat percentage.6 The average age of menarche in the United States is 12.8 years. Onset of puberty is marked by the release of GnRH from the hypothalamus in a pulsatile fashion, initially only at night. FSH and LH stimulate the granulosa cells in the ovary to produce small amounts of estrogen. Gradually, the GnRH pulses occur throughout the day and mature to a normal adult pattern. Estrogen causes proliferation of endometrial tissue in the uterus. Menarche occurs with shedding of the endometrial tissue, but initial shedding does not usually reflect ovulation. After menarche, menstruation may be irregular because the hypothalamic-pituitary axis has not matured and ovulation has not necessarily occurred. By 2 years after menarche, ovulation should be occurring in a cyclic pattern and menstruation should be regular. A normal menstrual cycle is 24 to 35 days long and is marked by a predictable menstrual cycle.

Chapter 2—Female Athlete Triad Syndrome: A Case Study

Samantha M. Pfeifer, MD
flow of 3 to 7 days. The cycle is divided into 3 stages: follicular phase, ovulation, and luteal phase.

**DIAGNOSIS OF AMENORRHEA**

Patient 11’s history reveals that she is a competitive athlete. Athletes (as well as parents or guardians of athletes) need to understand that amenorrhea is not a normal result of involvement in athletics. Athletic amenorrhea is a diagnosis of exclusion. Most menstrual irregularities in highly trained female athletes are caused by a disruption in the normal function of the hypothalamic-pituitary axis. Menstrual disturbances seen in this population range from delay in pubertal development to complete amenorrhea (no menses); oligomenorrhea (fewer than 9 menstrual cycles per year); or irregular, erratic menstruation. Abnormal or absent menstruation is seen more commonly in athletes with very low body fat, such as ballet dancers, endurance athletes, and gymnasts.

Patient 11 has secondary amenorrhea, which is defined as no menses for more than 6 months in those with a history of prior menstruation. At this point, all causes of secondary amenorrhea should be considered. Pregnancy should be excluded by serum or urine pregnancy test. It is useful to know whether the ovaries are producing estrogen, which can be assessed by obtaining a vaginal smear and determining the vaginal wall cell type. Parabasal cells are associated with a hypoestrogenic state, whereas superficial cells are seen with an estrogenic environment. The progestin withdraw (or progestin challenge) test involves giving progestin, typically medroxyprogesterone acetate 10 mg daily for 5 to 10 days. If vaginal bleeding occurs after administration of the progestin, then it implies enough estrogen production is occurring to result in proliferation of the endometrium. The progestin challenge test does not, however, guarantee that enough estrogen is present for normal metabolic functioning (eg, maintenance of secondary sexual characteristics and promotion or maintenance of bone density).

In the absence of estrogen production, amenorrhea can be classified into either (1) hypergonadotropic (high FSH), or (2) eugonadotropic or hypogonadotropic (normal to low FSH) categories. The hypergonadotropic group includes gonadal dysgenesis and premature ovarian failure. The eugonadotropic or hypogonadotropic group includes hypothalamic conditions, such as stress, weight change, eating disorders, competitive athletic endeavors, phenoxytoxin use, and substance abuse. Other etiologies include chronic diseases, CNS tumor (eg, pituitary adenoma or craniopharyngioma), pituitary infarction (Sheehan’s syndrome, sickle cell anemia), or Asherman’s syndrome. If estrogen production is evident, causes of amenorrhea include chronic anovulation (as seen with polycystic ovary syndrome, thyroid disease, early stages of ovarian failure) and, rarely, ovarian tumor. However, hypothalamic amenorrhea also can occur in this setting.

**III. CASE PATIENT 11 EXAMINATION**

Patient 11 is a well-developed woman 5 ft 6 in tall weighing 110 lb with a blood pressure of 110/70 mm Hg. She has normal thyroid, cardiac, and pulmonary examinations. Breast examination is normal with no expressed breast discharge. Pelvic examination reveals normal female external genitalia, a poorly rugated vagina, normal uterus, and adnexa that can be palpated. Extremities reveal yellowish appearance of palms and soles.

**LABORATORY EXAMINATION**

The following tests are ordered; the results are shown along with the normal values.

- FSH is 3.8 mIU/mL (normal premenopausal follicular phase, 5.0 to 20.0 mIU/mL).
- LH is 0.5 mIU/mL (normal premenopausal follicular phase, 5.0 to 20.0 mIU/mL).
- Estradiol is < 30 pg/mL (normal > 30 pg/mL).
- Thyroid stimulating hormone (TSH) is 2.3 µU/mL (normal, 0.5 to 4.2 µU/mL).
- Prolactin is 16 ng/mL (normal, 3 to 20 ng/mL).
- Human chorionic gonadotropin (hCG) is < 5 IU/L (negative < 5 IU/L).

Patient 11 is given a progestin challenge test using medroxyprogesterone acetate 10 mg for 10 days. She does not bleed within 3 weeks of completing the medication.

**HYPOTHALAMIC AMENORRHEA**

Hypothalamic amenorrhea occurs with malfunction or hypofunction of the hypothalamus leading to low production of estrogen. The mechanism is suppression of pulsatile GnRH secretion below its critical range. Inadequate functioning of the hypothalamus is reflected in low-to-normal gonadotropin (FSH, LH) secretion from the anterior pituitary and in insufficient estradiol production from the ovaries. Hypothalamic amenorrhea is a diagnosis of exclusion because, although probable causes can be identified, confirmation of the diagnosis is not possible.
Patient 11’s history reveals late onset of menarche at age 16 years, 2 years after thelarche, followed by irregular menses and subsequent amenorrhea. The history of delayed menarche, oligomenorrhea, subsequent amenorrhea, competitive athletic participation since before puberty, stress fracture, and low fat diet along with physical findings of low weight for height, lack of vaginal rugae, and carotenemia all suggest hypothalamic amenorrhea and hypoestrogenism, probably caused by intense athletic participation. Laboratory evaluation confirms low gonadotropins and hypoestrogenemia. Progesterin challenge does not result in bleeding, suggesting inadequate estrogen production. Based on these findings, patient 11 is diagnosed with hypothalamic amenorrhea. Other causes of amenorrhea are excluded such as hyperprolactinemia (because of the absence of galactorrhea and normal prolactin level), thyroid disorder, premature ovarian failure, and pregnancy. Chronic anovulation is not likely given lack of evidence of clinical hyperandrogenism or estrogen production. Hypothalamic amenorrhea can be caused by CNS tumors such as craniopharyngioma, which can be assessed by a flat plate radiograph because these tumors are calcified.

IV. PATHOGENESIS OF AMENORRHEA IN THE FEMALE ATHLETE

GENERAL PRINCIPLES

The pathogenesis of athletic amenorrhea is complex and multifactorial (Figure 2). Amenorrhea, standardized by the International Olympic Committee, is defined as 1 or fewer menstrual periods per year. The prevalence of amenorrhea in the general population ranges from 2% to 5%. Among athletes, amenorrhea is much more prevalent, ranging from 3.4% to 66%. The incidence of amenorrhea varies in different sports and is seen more commonly in runners and ballet dancers (40% to 50%) than in swimmers (12%), which may reflect differences in the physique of the athlete rather than differences in training intensity.

Factors predisposing females to exercise-induced amenorrhea include history of menstrual dysfunction, younger age at intense training, increased training intensity, weight loss, and low percentage of body fat. Although each risk factor is important, they are interrelated and it is difficult to determine which is more significant. Drinkwater and colleagues showed that training intensity was greater in amenorrheic compared to eumenorrheic runners. However, 2 other studies found no difference in training intensity measured as distance run weekly in amenorrheic versus eumenorrheic runners. Training intensity is positively correlated to frequency of amenorrhea among runners; however, this is not true among swimmers and cyclists. At the same level of intensity of training, 26% of runners and 12% of swimmers and cyclists will experience amenorrhea. However, lower body weight in runners was associated with more intense training, whereas body weight remained stable as intensity increased among cyclists and swimmers. This observation suggests that training intensity and weight are both important predictors of amenorrhea.

Concern about weight in female athletes and its effect on amenorrhea is embodied in the female athlete triad syndrome: disordered eating, amenorrhea, and resulting osteoporosis. The triad develops in girls who are driven to excel in sports at all costs. These athletes often are pressured to maintain a thin physique by coaches, peers, and parents to keep their competitive edge. Consequently, these athletes may develop abnormal eating habits that can approach anorexia or bulimia. Low body weight and strenuous physical exercise then lead to amenorrhea and hypoestrogenism. These problems are more likely to occur in athletes involved in sports favoring a thin physique for performance or aesthetic reasons (eg, ballet, figure skating, gymnastics, synchronized swimming, or endurance running). Eating disorders are more prevalent in athletes than in the general population. Dancers and ice skaters have been reported to have higher dieting and bulimia scores compared to swimmers and controls. In addition, 14% to 75% of female athletes admitted to self-induced vomiting and/or laxative or diuretic use to maintain weight.

Many studies have addressed athletic amenorrhea in the biomedical literature. However, evaluating these studies can be problematic because many define amenorrhea as the number of cycles per year with no attention to the endocrine profile. As a result, hypoestrogenic amenorrhea is not distinguished from anovulatory syndromes with normal estrogen levels, making it hard to evaluate the results and treatment options for these patients.

GONADOTROPIN-RELEASING HORMONE

Menstrual disturbances seen in female athletes range from delay in pubertal development to complete amenorrhea, oligomenorrhea, or irregular, erratic menstruation. The mechanism causing athletic amenorrhea is unclear but seems to involve disruption of the pulsatile secretion of GnRH from the hypothalamus. The consequence of decreased GnRH pulse is decreased secretion of FSH and LH from the pituitary.
with subsequent decrease or absence of estrogen production from the ovary. Amenorrheic athletes have been shown to have decreased LH pulse frequency, reflecting decreased GnRH pulse. Factors causing this suppression include athletic activity and nutritional status. It appears that athletic activity alone is not responsible for the decreased GnRH pulsatility. Rather, it is the combination of athletic activity and dietary intake that affects hypothalamic function and menstrual status. Bullen and colleagues demonstrated that strenuous exercise combined with caloric restriction can suppress luteal function, ovulation, and menstruation.

**CALORIC RESTRICTION**

Athletes often consume fewer total calories than they need to support their activity levels, which is referred to as the “energy drain” hypothesis. Loucks and colleagues compared 3 groups of women: those with normal menstrual cycles who were sedentary (CS), normally cycling athletes (CA), and amenorrheic athletes. The authors reported that LH pulse frequency was decreased in CA compared to CS women. They attribute this difference to the level of athletic training because the athletic women expended an extra 700 kcal daily in exercise while consuming a similar number of calories. However, the diet of the athletes contained less fat and more carbohydrates than that of the sedentary women. In another study, the same author has shown that LH pulse frequency decreases with restricted diet (decreased energy balance). The authors studied 7 women age 19 to 27 years who received either a balanced diet (45 cal/kg lean body mass) or a restricted diet (10 cal/kg lean body mass). LH pulse frequency was significantly decreased in those on the restricted diet and returned to normal on the balanced diet. In a different study, LH pulsatility was suppressed after acute exercise in individuals with reduced calorie intake; however, no effect was observed when exercise occurred with supplemental caloric intake.19

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**Figure 2.** Pathogenesis of athletic amenorrhea. E2 = estradiol; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone. (Reprinted with permission from Rose MZ, Lee CT, Maffulli N, Patrizio P. Special gynecological problems of the young female athlete. In: Maffulli N, Chan KM, Macdonald R, et al, editors. Sports medicine for specific ages and abilities. New York: Churchill Livingstone; 2001:141.)
Several studies have evaluated the effect of training intensity and caloric intake on menstrual status. As previously mentioned, Drinkwater and colleagues\textsuperscript{10} found that the distance run weekly was significantly greater in amenorrheic compared to eumenorrheic runners. However, 2 other studies showed no significant difference in distance per week in the same groups.\textsuperscript{11,12} Studies comparing caloric intake in female athletes have not shown a significant difference in daily intake in amenorrheic compared to eumenorrheic athletes.\textsuperscript{11,12,20} Nutritional breakdown reveals no significant difference in the calories derived from protein and fiber in the 2 groups. However, the amenorrheic runners derived a significantly lower portion of their total calories from fat and higher portion from complex carbohydrates compared with eumenorrheic runners.\textsuperscript{12}

The critical body fat hypothesis proposed that 17% body fat is required for menarche and 22% body fat is required to maintain cyclic menses.\textsuperscript{21} A lower percentage of body fat is associated with amenorrhea but is not causative. Regular menstrual cycles are seen in athletes with less than 17% body fat.\textsuperscript{20} Studies have shown that amenorrheic and eumenorrheic runners have the same percentage of body fat. In addition, ballet dancers demonstrate return of menses during rest intervals despite no change in weight.

**OTHER THEORIES FOR ATHLETIC AMENORRHEA**

Another theory to explain the mechanism of athletic amenorrhea is the estrogen fuel hypothesis, which proposes that increased 2-hydroxylase oxidation is associated with oligomenorrhea during periods of high intensity training and decreased body fat.\textsuperscript{22} Female rowers who experienced menstrual disturbances during high intensity training metabolized a significantly greater fraction of estradiol by 2-hydroxylase oxidation (approximately 48%) than the oarswomen who sustained normal menses throughout the training year (38%). The extent of estradiol metabolized by 2-hydroxylase oxidation did not differ between normal cycling athletes and controls. The authors suggested that the group with menstrual irregularity had a greater fraction of estrogen metabolites that are devoid of peripheral estrogen activity (increased cathecholestrogens and decreased estriol) creating a hypoestrogenic state. Frisch and colleagues\textsuperscript{23} showed a significant trend between increasing 2-hydroxylation of estradiol yielding 2-hydroxyestrogen and decreasing subcutaneous fat/total volume associated with anovulation and amenorrhea among the athletes.

\(\beta\)-Endorphins also have been associated with menstrual irregularities in athletes. Harber and colleagues showed that \(\beta\)-endorphin levels were elevated in amenorrheic and eumenorrheic athletes compared to eumenorrheic sedentary women.\textsuperscript{24} In addition, estradiol and progesterone levels in the luteal phase were lower in eumenorrheic athletes compared to eumenorrheic sedentary women.

The role of circulating nutritional hormones in exercise-associated amenorrhea has been reported in recent scientific literature. Several molecules act primarily as nutritional hormones. Insulin, insulin-like growth factors (IGF) type I and II as well as their binding proteins, and leptins change their concentration in response to stress and vigorous exercise. Hormones of the IGF system are present in brain, pituitary, and ovarian tissue; therefore, they can regulate the reproductive hormones (GnRH, FSH, and LH). Recently, leptins have been identified as humoral signals of nutritional status involved in the feedback to the reproductive axis. Leptin is a protein expressed in adipocytes that is highly correlated with the percentage of body fat because it decreases in response to weight loss. In response to leptins, the hypothalamic areas involved in energy homeostasis increase basal metabolism and decrease appetite.\textsuperscript{25} Studies in athletes have revealed lower levels of leptin in amenorrheic and eumenorrheic athletes compared to sedentary controls who have normal cycles.\textsuperscript{20} Low leptin levels in the athletes were associated with low body fat, low insulin, and elevated cortisol. These findings are consistent with a link between adipocyte function, nutritional status, and integrity of the reproductive axis in humans.

Psychological stress plays an important compounding role. Prospective studies have shown that women who had regular menses at the onset of training continued to be regular even with increased training intensity. However, when psychological stress (eg, an approaching competition) is added to the training, the regularity of the menstrual cycle may be affected.

Other hormone conditions that are not associated with lack of estrogen can lead to oligomenorrhea in young women and athletes. Constantinou and Warren\textsuperscript{26} examined the hormonal profile of 69 competitive swimmers and compared them to 279 age-matched controls. Menstrual irregularities were reported by 82% of swimmers compared to 40% of controls. Age at menarche was significantly delayed among swimmers. The authors concluded that swimmers are prone to delayed menarche and menstrual irregularities; however, the associated hormonal profile (higher LH levels and LH/FSH ratios, normal estrogen levels, and higher levels of androgens) differed significantly from the hypothalamic amenorrhea commonly described in ballet dancers and runners. Therefore, reproductive dysfunction in swimmers
is distinct from that of other female athletes; the former is caused by mild hyperandrogenism and polycystic ovary hormonal profile, and the latter is secondary to hypoestrogenism.

The mildest disruption to the menstrual cycle seen in athletes—particularly those training for long-distance endurance events—is luteal phase defect, resulting from inadequate progesterone production in the second half of the menstrual cycle. This defect occurs because of inadequate follicular development before ovulation or inadequate stimulation of progesterone production by the corpus luteum after ovulation. Menstrual cycles may be of normal length with shortened luteal phase.

Delayed menarche also can be seen in female athletes. During puberty, the production of gonadotropins (FSH and LH) stimulates the ovary to produce estrogen, which promotes breast development along with subsequent menstruation and growth spurt. If the GnRH pulse is disrupted, then initiation of pubertal events is delayed. As female sports become more competitive, intense training begins at an earlier age. With greater physical activity in early adolescence, age at menarche is delayed. Girls participating in school sports at any level have menarche later than their more sedentary classmates. Studies also have shown that athletes with abnormal menstrual cycles have a history of menarche occurring at a later age than those with regular menstrual cycles. Warren evaluated exercise level and age of menarche in ballet dancers, music students (who were chosen because of similar goal-oriented life styles), and controls. Ballet dancers experienced menarche at age 15.4 years, which was significantly delayed compared with the musicians and controls, who experienced menarche at 12.6 and 12.5 years, respectively ($P < 0.01$). The dancers’ mean weight and calculated body fat percentage were significantly lower than the controls.

## V. LONG-TERM CONSEQUENCES OF ATHLETIC AMENORRHEA

Decreased bone mineral density, deleterious lipid changes, and infertility are the outcomes of greatest concern in women with athletic amenorrhea.

### REDUCED BONE MASS

Bone is comprised of cortical bone and trabecular bone. Cortical bone, or compact bone, makes up the shafts of long bones. Trabecular bone, also known as spongy or cancellous bone, is present in vertebral bodies, flat bones, and the end of long bones. Bone adapts to mechanical stresses, hormonal changes, and nutritional states by forming or losing tissue. This remodeling is performed by independent bone remodeling units comprised of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells). Bone remodeling activity can result in net bone gain or loss. Estrogen deficiency leads to acceleration of bone turnover so that bone resorption is greater than bone formation. This deficiency eventually results in osteoporosis, a disease characterized by extensive bone loss and fractures. Trabecular bone is affected more than cortical bone. The mechanism is unclear, but several factors have been identified. Lack of estrogen leads to increased osteoclastic activity mediated by interleukin-1 (IL-1), IL-6, and tumor necrosis factor. Parathyroid hormone activity increases during states of estrogen deficiency. Estrogen receptors have been identified on osteoblasts, suggesting a direct effect of this hormone in promoting osteoblastic activity.

Bone density is measured in the spine and hip (femoral neck) because these are the most common sites for fracture in those with osteoporosis. Currently, the most widely used technique is dual energy x-ray absorptiometry (DEXA). This technique measures bone content per area, which is expressed as grams per square centimeter ($g/cm^2$). DEXA measurement does not distinguish trabecular from cortical bone. The advantages of DEXA include low radiation exposure (< 5 mrem/scan), more precise measurements, and rapid assessment (ie, it takes very little time to perform the scan). Peripheral DEXA scanning techniques measure density at the calcaneus (heel) and forearm. These units are less expensive to own and operate; thus, they can be useful as a screening tool. However, correlation to bone density at the spine and hip is only moderate. Quantitative CT (QCT) is another technique of bone density measurement. It has the advantage of providing a 3-dimensional measurement, thereby distinguishing trabecular from cortical bone. However, QCT is much more costly, has a higher radiation exposure, and is more time-consuming than DEXA. Older techniques of single and dual photon densitometry are not as reliable as newer techniques and should not be used.

The World Health Organization (WHO) criteria for diagnosing osteoporosis is bone density more than 2.5 standard deviations (SD) below young adult mean bone density. Osteopenia (decreased bone density) is defined as bone density that is more than 1.0 SD below young adult mean bone density. These standards are applied with DEXA measurements; they were obtained in a homogeneous patient population and do not reflect racial and ethnic differences.

Female athletes are at risk for developing low bone density and osteoporosis. Risk factors that have been
identified include lack of estrogen, amenorrhea and duration of amenorrhea, late age at menarche, low body weight, low calcium intake, and hypercortisolism. Peak bone mass, which is achieved in early adulthood, is also a major determinant of osteoporosis risk. Theinz and colleagues showed that the highest rate of bone accumulation occurred by 2 years after menarche, and bone mass failed to increase significantly by ages 17 to 20 years. Therefore, decreased bone accumulation during this critical time results in decreased peak bone mass. The young female athlete is particularly at risk because of hypoestrogenism and delayed puberty.

Numerous studies have confirmed that bone density in amenorrheic athletes is 10% to 20% lower than in normally menstruating athletes (Table 2). However, spine density did not differ in normally menstruating athletes versus non-athlete controls. Although weight-bearing exercise helps prevent osteoporosis, it is not enough to overcome the negative effect of hypoestrogenism on the skeleton of amenorrheic athletes. Young et al evaluated the net effect of exercise, hypogonadism, and body weight on bone density at weight-bearing and non–weight-bearing sites in ballet dancers. They found that bone density at weight-bearing sites (eg, femoral neck, Ward’s triangle, trochanter) was the same as in normal controls. However, bone density at non–weight-bearing sites (eg, ribs, arms, skull) and sites containing predominantly trabecular bone (lumbar spine) was lower than in normal controls. Decreased spinal bone density also has been described in female athletes with luteal phase defects and anovulatory cycles. Drinkwater et al evaluated bone density in athletes with varying menstrual histories; they found a direct correlation between bone mineral density and frequency of menstruation, with the highest bone density seen in the athletes with the highest number of menstrual cycles per year. It also has been shown that amenorrheic athletes who regained menstruation had measurable increases in bone mineral density over time.

Stress fractures also are seen more commonly in amenorrheic compared to eumenorrheic athletes (Table 3). Delayed menarche also has been shown to correlate with increased rates of stress fractures and scoliosis in ballet dancers. It is unclear why athletes get stress fractures. One theory is that stress fractures result from overuse of bones weakened by osteopenia, although a direct correlation between these fractures and low bone density had not been established. It is also unclear why stress fractures occur in weight-bearing cortical bone rather than in trabecular bone, as is seen in osteoporosis.

**OXIDATIVE STRESS AND LIPID CHANGES**

Amenorrheic athletes might be at risk for cardiovascular disease secondary to the lack of estrogen protection. Ayres and colleagues studied plasma and low-density lipoprotein (LDL) oxidation parameters and creatinine kinase activity in 7 eumenorrheic and 7 amenorrheic athletes before and after an acute bout of exercise. The amenorrheic athletes had decreased mean plasma estradiol, higher baseline creatinine kinase, increased oxysterol formation (a measure of LDL peroxidation), and a greater decrease in lag time of diene conjugation (a further measure of LDL oxidation) after exercise. They concluded that amenorrheic female athletes demonstrate an increased potential for lipid peroxidation after exercise, which may put them at risk for cardiovascular disease. However, only 14 athletes were studied, so the risk is still theoretical.

**INFERTILITY**

Females who experience menstrual irregularity or amenorrhea are frequently concerned about risks of future infertility. In these women, the obvious concern is lack of estrogen and ovulation. Assuming no other factors are present that could affect fertility, these women should have an excellent chance of achieving a pregnancy. If cyclic menstruation does not return with modification of diet and exercise, then fertility drugs can be used to induce ovulation. Clomiphene citrate is successful approximately 60% of the time in inducing ovulation in women with oligo-ovulation or anovulation. Hypoestrogenic women require human menopausal

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**Table 2. Difference in Bone Mineral Density Between Amenorrheic and Eumenorrheic Athletes**

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Athlete Type</th>
<th>% Decrease in BMD* (EA versus AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinkwater10</td>
<td>Runners</td>
<td>14</td>
</tr>
<tr>
<td>Drinkwater31</td>
<td>Mixed</td>
<td>17</td>
</tr>
<tr>
<td>Marcus10</td>
<td>Runners</td>
<td>17</td>
</tr>
<tr>
<td>Myerson48</td>
<td>Runners</td>
<td>10</td>
</tr>
<tr>
<td>Warren44</td>
<td>Dancers</td>
<td>13</td>
</tr>
<tr>
<td>Wolman49</td>
<td>Mixed</td>
<td>20</td>
</tr>
</tbody>
</table>

AA = amenorrheic athletes; BMD = bone mineral density; EA = eumenorrheic athletes.

*Percent decreases of BMD are statistically significant.

gonadotropins (FSH and LH) to induce ovulation. This medication directly stimulates the ovaries to produce estrogen and a dominant follicle because it is replacing endogenous FSH and LH. Treatment with human menopausal gonadotropins has a 25% chance of achieving a pregnancy with each cycle, assuming that all other factors are normal.

VI. EATING DISORDERS

CASE PATIENT 11 CONTINUED

Patient 11 is questioned further about her lifestyle. Her daily training schedule involves 2 hours of weight lifting and running either with the team or on her own. She is very careful to eat only low-fat foods, and her diet is predominantly vegetables, although she occasionally eats chicken. She avoids dairy products because of the fat content. She often skips meals. She feels her performance is best at her current weight, a belief shared by her coach.

DISORDERED EATING AND THE FEMALE ATHLETE

Disordered eating, or eating disorder not otherwise specified (EDNOS), is a term used to describe a wide spectrum of abnormal eating patterns. The term helps to diagnose athletes who have an eating problem but fail to meet all the criteria for the strict diagnosis of anorexia nervosa (AN) or bulimia nervosa (BN). AN is characterized by a severe self-imposed weight loss (> 15% of body weight), altered body image, intense fear of becoming fat, and amenorrhea. BN is characterized by concern about body shape and weight, binge eating, and inappropriate behavior to prevent weight gain (eg, self-induced vomiting, laxative and/or diuretic use, fasting, and excessive exercising). Disordered eating is defined in the Diagnostic and Statistical Manual of Mental Disorders–IV by the following: all the criteria of AN but regular menses, all criteria of AN but weight in normal range, all criteria for BN but occurring less often than twice each week for a duration of less than 3 months, inappropriate compensatory behavior, and binge eating disorder. Thus, identification of disordered eating among athletes must include focusing not only on AN and BN behavior but also on pathogenic weight control behaviors that can affect health and performance.

The risk factors for developing an eating disorder include chronic dieting, low self-esteem, family dysfunction, physical or sexual abuse, obsessive compulsive disorder and perfectionism, poor coping skills, and poor nutrition knowledge. Additional risk factors in athletes include participation in sports where the emphasis is on weight for performance or appearance. Also, sports where the athletes wear form-fitting or revealing uniforms or are judged individually provide a risk for disordered eating. Other risk factors include identifying oneself only as an athlete and having the drive to win at any cost. There may be pressure to lose weight for parents, coaches, and peers. Intense training and competition at an early age, as well as overtraining and undernourishing athletes, can place the athlete at risk.

Eating disorders often occur in athletes. In the general population, the incidence of anorexia is 0.5% to 1.0% and the incidence of bulimia is 2% to 5%. In athletes, the incidence of anorexia and bulimia is 4% to 39%. Pathogenic weight control has been reported in 62% of athletes. It is difficult to ascertain an accurate prevalence of disordered eating among female athletes because of the secretive nature of eating disorders. Under-reporting by female athletes is common because disclosure may jeopardize their position on the team.

Eating disorders occur in all types of athletes but are more common in athletes whose performance is judged on an ideal thin physique. A study of dancers, skaters, swimmers, and controls ages 14 to 18 years evaluated prevalence of dieting and bulimia. Dancers and skaters had higher dieting and bulimia scores compared to swimmers and controls. In addition, dancers and skaters wanted to weigh 6 to 7 kg less than what swimmers wanted to weigh. Traditionally, training staff have not been helpful in prevention of eating disorders in young athletes. In a study of 42 collegiate gymnasts, 67% were told they were too heavy by their coaches and 75% admitted to vomiting and laxative and/or diuretic use.

The consequences of eating disorders in athletes are far reaching. Eating disorders are linked to menstrual

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### Table 3. Incidence of Stress Fractures in Amenorrheic and Eumenorrheic Athletes

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Athlete Type</th>
<th>Incidence of Fractures, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindberg et al</td>
<td>Runners</td>
<td>49</td>
</tr>
<tr>
<td>Warren (unpublished)</td>
<td>Dancers</td>
<td>65</td>
</tr>
<tr>
<td>Marcus et al</td>
<td>Runners</td>
<td>55</td>
</tr>
<tr>
<td>Clark et al</td>
<td>Runners</td>
<td>72</td>
</tr>
</tbody>
</table>

AA = amenorrheic athletes; EA = eumenorrheic athletes.

dysfunction, as was shown in a study of female ballet students.\(^{15,43}\) The incidence of eating disorders was 50% in the amenorrheic group but only 13% in the oligomenorrheic or eumenorrheic groups. Poor nutrition also is linked to decreased bone density as discussed earlier. Disordered eating also can impair athletic performance; increase risk of injuries; and decrease endurance, strength, and ability to concentrate.

It is difficult to diagnose and intervene to alter disordered eating among athletes because pathogenic weight control behavior is often not perceived as a problem. Rosen found that 70% of athletes who reported using laxatives and self-induced vomiting to maintain weight believed their behavior was harmless.\(^{42}\) Another problem is that coaches, training staff, and parents often view these behaviors as benign or adaptive and not reflective of a potentially serious health concern.

### VII. PREVENTION OF OSTEOPOROSIS IN THE FEMALE ATHLETE

#### HORMONE THERAPY

The goal of treatment/prevention of osteoporosis in the young female athlete is to build bone and ideally to achieve maximum bone mass. Options include a combined oral contraceptive pill (OCP) containing 30 to 35 µg of ethinyl estradiol or natural estrogen preparations, such as 17\(\beta\)-estradiol or conjugated estrogens. The OCP has the advantage of contraceptive benefits and therefore may be a preferred choice for some athletes.

Unfortunately, there is a lack of good randomized clinical trials to determine the optimal hormone regimen to build bone. Cumming\(^{44}\) performed a retrospective study over 24 to 30 months to evaluate the efficacy of hormone replacement therapy (HRT) using Premarin (conjugated estrogens) 0.625 mg daily and medroxyprogesterone acetate 10 mg for 14 days per month. Sixteen women with exercise-associated amenorrhea had vertebral and femoral neck bone density measurements by DEXA of more than 1.0 SD below the mean. All were counseled on the use of HRT. Eight of these women continued HRT for 2 years. The other 8 subjects refused or quickly discontinued HRT. No significant differences were noted between the 2 groups—even in bone density—before the study. After 2 years, a repeat DEXA scan showed a significant increase in vertebral and femoral neck bone density in the HRT group. The women not taking HRT had a nonsignificant decrease in bone density at these sites.

Other small studies have shown increase in bone density in amenorrheic females using conjugated estrogens or combined oral contraceptives, but no randomized controlled trials have been done in amenorrheic athletes to assess which regimen is optimal to achieve maximal peak bone density.\(^{45,46}\) One concern is that young females may need more estrogen to build and maintain bone mass during adolescence and young adulthood than would traditionally be given to a menopausal woman. Unfortunately, no prospective studies have evaluated this important issue and optimal dosing has yet to be determined. The issue is further complicated by the high incidence of disordered eating in elite female athletes, which limits body weight and caloric/calcium intake, both of which affect osteoporosis.

HRT is often refused by athletes because they are concerned these medications will cause weight gain and poor performance. Mild weight gain is a potential side effect of both HRT and OCPs, but it is not noted to be clinically significant.\(^{46}\) Weight gain, however, is perceived to be a significant side effect by many athletes. For this reason, HRT is often refused, especially by athletes participating in sports that favor a thin physique. Although there is little information available, OCPs do not appear to impair athletic performance.\(^{47}\) Coaches often fuel these concerns; consequently, athletes are reluctant to take these medications for fear of poor performance and loss of their position on the team.

#### OTHER OPTIONS

Alternatives to hormonal therapy for osteoporosis include bisphosphonates, which are derivatives of pyrophosphate that specifically target the skeleton and are potent inhibitors of bone remodeling. Currently, 2 bisphosphonates—alendronate and risedronate—are marketed for osteoporosis. The role of bisphosphonates has not been evaluated in young female athletes. However, it is not advisable to use bisphosphonates in reproductive-age women at the present time because of their long half-life.

Adequate calcium intake is important to achieve and maintain peak bone mass. The recommended daily allowance of calcium is 1200 mg. Increasing calcium intake to 1500 mg daily has been proposed for adolescents and young adults. Calcium intake has been evaluated in amenorrheic and eumenorrheic athletes with conflicting results. Amenorrheic athletes have been shown to consume less or equivalent amounts of daily calcium than eumenorrheic athletes.\(^{20,47}\) Calcium intake, however, is generally below the recommended daily allowance in the general population.
VIII. TREATING THE FEMALE ATHLETE TRIAD SYNDROME

GENERAL PRINCIPLES

Athletic amenorrhea is associated with hypoestrogenism, increased risk of osteoporosis, and disordered eating. The best treatment approach is to address all of these issues and to correct the underlying problem. A team approach involving a physician, nutritionist, counselor, coach, and the athlete’s family is advocated to improve nutrition and de-emphasize weight control; modification of the training schedule may be necessary. Forcing weight gain and eliminating participation in sports are counterproductive because this can affect self-esteem and worsen the problem. Nutritional counseling and eating a diet with adequate calories and calcium are very important. Healthy role models are necessary to encourage the image of the “strong” athlete. If this approach is unsuccessful in achieving return of menses or as primary treatment for amenorrhea, then HRT with a combination of estrogen/progesterone is advised to treat hypoestrogenism and prevent osteoporosis.

Awareness and prevention of disordered eating as well as its consequences for athletes are paramount to decreasing the problem. Fortunately, efforts have been put forth to prevent eating disorders in female athletes. The national governing board for gymnastics has increased the age limit for participation and has begun educating coaches about eating disorders/nutrition to increase awareness of the female athlete triad. Similar efforts have been initiated by the International Olympics Committee and the National Collegiate Athletic Association (NCAA).

CASE PATIENT 11 TREATMENT AND FOLLOW-UP

Her physician decides that patient 11’s bone density should be measured because her history of a stress fracture and secondary amenorrhea suggest that her bone density may be compromised. Results from DEXA are: spine, \( t < -1.35 \); hip, \( t < -1.59 \).

Patient 11’s history reveals significant dietary restrictions including a very low-fat diet (predominantly vegetables) and a lack of dietary calcium. In addition, her training schedule is strenuous. Her laboratory studies are consistent with hypothalamic amenorrhea most likely caused by exercise and disordered eating. Her DEXA scan reveals osteopenia.

Patient 11 is brought in for consultation. On further questioning, she stresses that her success on the sports teams is very important to her and that she does not want to do anything to compromise her performance. The consequences of amenorrhea and osteopenia are reviewed in detail with her. She is not eager to start any type of HRT because she is concerned therapy will affect her performance. A more conservative approach is selected that takes her concerns into consideration. She is referred to a nutritionist for counseling and follow-up regarding diet and calcium supplementation. Weight maintenance is stressed. With her consent, the coach is made aware of the health concerns, and her coach’s cooperation is secured. By the end of the season, patient 11 still has not begun to menstruate; therefore, as previously agreed, she is started on HRT during the “off season.” Combined oral contraceptives are chosen for ease of administration and cycle control. Through the subsequent season, she tolerates the oral contraceptive well and has regular withdrawal bleeding. A DEXA scan is repeated after 1 year of HRT and calcium supplementation. Slight improvement in bone density is apparent.

IX. SUMMARY POINTS

- The female athlete triad syndrome refers to the interrelated problems of disordered eating, amenorrhea, and osteoporosis.
- The mechanism of athletic amenorrhea is unclear. However, it seems to involve disruption of the pulsatile secretion of GnRH from the hypothalamus caused by exercise, inadequate diet for level of activity, and decreased amount of body fat.
- Athletic amenorrhea is a diagnosis of exclusion: all other causes of hypothalamic amenorrhea should be investigated.
- Factors associated with athletic amenorrhea include history of delayed menarche, prior menstrual dysfunction, increased training intensity, younger age at intense training, weight loss and low percentage of body fat, and sports in which a thin physique offers an advantage (eg, running, ballet, figure skating).
- Decreased bone density leading to osteoporosis is the most significant long-term consequence of athletic amenorrhea. Because most bone mass is built up during the teenage years, the adolescent with athletic amenorrhea is additionally compromised because she will not achieve peak bone density.
- Eating disorders are seen more frequently in athletes when compared with the general population. The incidence of disordered eating or EDNOS also is higher in athletes and is associated with sports in which performance is judged based on an “ideal” thin physique.
• The pharmacologic treatment of patients with the female athlete triad syndrome involves HRT with estrogen and progesterone using either natural hormones or a combined OCP. Very few studies have evaluated this treatment, and the most effective regimen has yet to be determined.

• The preferred management of the female athlete triad syndrome is a multidisciplinary approach involving physician, nutritionist, counselor, coach, and the patient’s family to correct hypoestrogenism/disordered eating and to prevent osteoporosis.

REFERENCES


