Nonsurgical Management of Fibroadenoma and Virginal Breast Hypertrophy

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Abstract

Keywords

- ▶ juvenile (virginal) hypertrophy
- ▶ fibroadenoma
- ▶ cryoablation
- ▶ tamoxifen
- ▶ image-guided biopsy

The management and treatment of an adolescent presenting with a fibroadenoma or virginal breast hypertrophy can be challenging as there is a paucity of original research on these conditions. Although surgical therapies are often discussed as first-line therapy in adolescents presenting with a breast mass, it is prudent that nonsurgical interventions and medical therapies be considered as initial therapy with the goal of maintaining an acceptable cosmetic outcome.

Clinicians need to be cognizant when applying experience and knowledge in the management of the mature woman presenting with fibroadenoma or virginal hypertrophy; these breast conditions differ when compared with that of the teenage population.¹ As both fibroadenoma and virginal hypertrophy are benign conditions, options for management that do not include surgical intervention are desirable in the adolescent population. Several nonsurgical interventions and medical therapies are available that may be useful in selected cases. Herein, we provide an overview of these conditions and describe nonsurgical options for the management of fibroadenoma and hormonal options for the management of virginal hypertrophy.

Nonsurgical Management of Breast Fibroadenoma

A fibroadenoma typically presents as a well-circumscribed, rubbery, and firm mass. The natural history of fibroadenomas varies. A majority will grow slowly and can be around 2 to 3 cm in size when detected by the adolescent, then remain static in size or resolve spontaneously.^{2,3} Conservative management includes clinical observation with monitoring over 2 to 3 months. A change in character or growth in the mass requires further evaluation with breast imaging, utilizing primarily directed breast ultrasound in the adolescent population. With a typical sonographic appearance, conservative

management with short-term follow-up exam and ultrasound as indicated, usually at 6-, 12-, and 24-month intervals. Alternatively, a core needle biopsy with ultrasound guidance can be performed for tissue diagnosis.⁴ Indications for surgical referral and surgical excision include a rapidly enlarging breast mass, fibroadenoma or mass > 5 cm, or a breast mass causing distortion of the breast architecture with associated skin changes.² Other factors that may prompt surgical excision include localized discomfort and interval growth. Conservative management of fibroadenomas < 4 cm that are stable in size, single, or multiple, is acceptable to most patients. However, watchful waiting can be a source of anxiety for some adolescents, as well as for their families, and nonsurgical options may be considered.⁵

The goals of nonsurgical management of breast fibroadenomas are to cease growth of the lesion and reduce the palpable mass while maintaining an acceptable cosmetic outcome. A variety of minimally invasive techniques are available or being researched and include ultrasound-guided vacuum-assisted biopsy,⁶ cryoablation (or cryotherapy), and MRI-guided focused ultrasound.^{7,8}

Ultrasound-Guided, Vacuum-Assisted Excisional Biopsy

Image-guided, percutaneous, vacuum-assisted biopsies are routinely performed for diagnostic purposes in adult women.

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The procedure is performed in an outpatient setting with local anesthetic and is less invasive with a better cosmetic outcome than surgical excision.⁹ In addition to diagnostic use, there are multiple reports of the use of ultrasound-guided vacuum-assisted biopsy for excision of a lesion, with the cosmetic outcome following vacuum-assisted excision shown to be preferable to surgery in cases of solitary and multiple breast masses.¹⁰

Reports of complete removal of the lesion at the time of the vacuum-assisted excisional biopsy varies from 75 to 100%.^{6,9-17} Although follow-up is limited, a residual mass can be seen at the time of follow-up imaging in 6 to 45% of cases.^{9,14,18-22} The palpable abnormality can be removed in 77 to 88% of cases, which may often be the indication for intervention in an adolescent.^{11,18} However, although all imaging evidence of a mass may be removed, this does not necessarily indicate a complete histologic excision and recurrence can occur.^{11,19,20}

There are several technical challenges to excising lesions with vacuum-assisted biopsy. The presence of local anesthetic, blood, air, and/or soft tissue edema contributes to loss of visualization of lesions and can limit complete removal. Passing the probe through the immediate subareolar region is generally avoided due to potential ductal injury, as well as patient discomfort. The size of the lesions selected for excision using this technique varies, but good cosmesis and elimination of the lesion can usually be accomplished for lesions < 3 cm.^{10,11} Lesions should not be closely apposed to the skin surface (< 0.5 cm from the skin) due to potential for skin damage. For lesions close to the skin surface or pectoralis major muscle, local anesthetic and/or saline can be injected to increase the distance available for the needle so the procedure can be performed safely.

Adult patients generally tolerate the procedure well. In 94% of patients surveyed immediately following an ultrasound-guided biopsy for removal of a breast mass, pain was not present or was mild; no patients described severe pain.²³ The complication rate of vacuum-assisted biopsy ranges from 1.1 to 10%, with potential complications including hematoma, skin defect, or rarely pneumothorax.^{20,22-24} Most patients experience some bruising in the week following the procedure.²⁵ Breast discomfort is usually controlled with over-the-counter analgesics.¹⁹

Cryoablation

Cryoablation, or the use of extreme cold, is an outpatient procedure performed with local anesthetic that consists of ultrasound-guided placement of a cryoprobe in the center of a targeted lesion. Usually two freeze-thaw cycles are used. During the cycles of freezing, the cells closest to the cryoprobe develop intracellular ice that permanently damages the cell membranes. Cells further from the cryoprobe freeze more slowly, leading to extracellular ice formation and a hypertonic extracellular environment. Osmotic shifts lead to cell damage and eventual lysis. Additional anoxia results from endothelial damage caused by the subfreezing temperatures, completing the process of ablation several days after the procedure.²⁵⁻³⁰

The ice margin generated by the cryoprobe is well-visualized with high-frequency ultrasound transducers and can be used in lesions that are near the skin while generating a uniform distribution of necrosis.^{26,27} Strategies to protect the skin include dripping sterile room-temperature saline on the skin, placement of moist gauze between the probe or sheath and the skin, and ultrasound-guided sterile saline injections between the ice ball and skin surface to keep the advancing ice at least 5 mm from the surface.²⁶ Freezing times depend on the size of the lesion and local vascularity but range from 6 to 30 minutes.^{26,27}

The process of cryoablation results in a rounded area of necrotic tissue that is progressively eliminated by the body.²⁶ Lesions decrease in size over time, and may take at least 12 months to resolve.²² In a long-term study of 37 patients by Kaufman et al with a follow-up averaging 2.6 years, the results showed that 94% of small (≤ 2 cm) and 73% of larger (> 2 cm) fibroadenomas were no longer palpable in a heterogeneous female population aged 13 to 66 years.²⁶ The largest series by Nurko et al consisted of 444 patients, of whom 75% had palpable lesions prior to therapy.²⁹ The number of patients with a palpable finding decreased to 46% at 6 months and 35% at 12 months. It is an encouraging treatment for patients with multiple or growing fibroadenomas.²⁵ An additional benefit is the comparison to vacuum-assisted excision of lesions where residual tumor is viable and can recur; ablated tissue has not been shown to regrow.²⁶

Local ecchymosis and swelling are common after the procedure, and usually resolve within 3 weeks.^{26,27} A hematoma or an infection are less common complications.²⁷ Over-the-counter analgesics adequately control postprocedure breast discomfort in the majority of patients.²⁷ Adult patient satisfaction with the procedure is high, ranging from 88 to 100%.²⁷⁻²⁹

MRI-Guided Focused Ultrasound

Magnetic resonance imaging- (MRI-) guided focused ultrasound is a noninvasive tissue ablation method that utilizes focused ultrasound beams to penetrate through soft tissues and cause localized high temperatures.³⁰ Well-defined areas of ablation are produced while sparing the surrounding tissues. When used in conjunction with MRI, excellent anatomic resolution and temperature sensitivity are achieved. An advantage of focused ultrasound ablation is that the area of the ablation can be tailored to the shape of the lesion, as compared with cryoablation or radiofrequency ablation where the ablation apparatus dictates the shape of the ablation zone.⁸

Patients are imaged in the prone position using a water bath as a coupling agent for the ultrasound transducer.³¹ Local anesthetic and conscious sedation are administered. Although heating during each individual sonication is rapid, cooling is required between sonications which can increase the total procedure time sometimes to an hour or greater.³² Hynynen et al reported 11 fibroadenomas in adult women that were treated with MRI-guided focused ultrasound.³¹ Seventy-three percent of the lesions were partially or

completely treated, with no adverse effects reported. The three cases that were not effectively treated were likely due to patient motion during the ablation.

Juvenile (Virginal) Breast Hypertrophy

Juvenile or virginal hypertrophy is a rare breast condition characterized by diffuse hypertrophy of the breast without the presence of a discrete mass or nodularity. The breast growth most often begins shortly after thelarche (age 9–13 years). Most often, the condition has a bilateral presentation, but unilateral hypertrophy has been described. Affected adolescent girls present with massive and rapid breast growth following normal puberty. The breast weight has been measured up to 23 kg.³³ Associated skin changes can include erythema and inflammation, striae, peau d'orange, thinning, and dilated veins. The massive enlargement can result in tissue necrosis and skin rupture. The weight of the breasts may be associated with neck strain, back pain, and poor posture. Patients often report noncyclical mastalgia, which is attributed to the dense tissue of the breast.³⁴ The embarrassment and unwanted attention from peers can be a source of psychological stress, poor self-esteem, and social adjustment.

The underlying etiology or mechanism for this pathologic overgrowth is unclear, but is speculated to be due to an abnormal response or sensitivity of breast tissue to hormonal influences that occur during puberty.³⁵ Hormones produced by the anterior pituitary (follicle-stimulating hormone, luteinizing hormone, growth hormone, and adrenocorticotrophic hormone) stimulate ductal proliferation, whereas progesterone and prolactin stimulate lobuloalveolar growth.³⁶ No specific endocrine abnormalities have been found to correlate with the development of virginal hypertrophy. Testing for hormonal levels, specifically serum estradiol, progesterone, prolactin, and gonadotrophins, often does not reveal systemic hormonal imbalances, so is not routinely indicated.

Although a hereditary or familial etiology has been suggested in case reports, most often the condition is sporadic. New research evaluating a possible genetic basis for this disease has led to the discovery of the PTEN (phosphatase and tensin homologue) gene that encodes a tumor-suppressing phosphatase. In animal studies, a deletion in this gene has been linked to precocious puberty.³⁷ The histological appearance of the breast stroma reveals gross stromal and epithelial growth with dilated ducts and ductal hyperplasia. Studies evaluating the presence of hormonal receptors have not found an association between an increase in estrogen receptor levels and hypertrophic tissue. In addition, serum hormone profiles are within normal limits.^{38–40} Drug-related induction of virginal hypertrophy has been reported with the use of D-penicillamine. The mechanism of action is postulated to be due to the effect of D-penicillamine on sex hormone-binding globulin, which increases the amount of circulating free estrogen.⁴¹

The workup of new-onset virginal hypertrophy with breast imaging is of limited value primarily due to the dense breast tissue, which can significantly reduce mammographic

sensitivity. Breast ultrasound can be considered for evaluation of a focal area of the palpable abnormality, but whole breast ultrasound is also of limited value. Breast MRI can be considered for evaluation of occult disease if there are other clinical concerns. Mammography is not recommended because of the lack of sensitivity in the dense breast.

Disease-specific guidelines on treatment are lacking given the rarity of the condition. The evidence for treatment options is based primarily on case reports. Several case reports describe various treatment options including surgical treatment alone or surgical treatment followed by some form of antiestrogen therapy. The surgical management options are breast reduction surgery (reduction mammoplasty) or subcutaneous mastectomy with immediate implant reconstruction. Although the option of breast reduction surgery is less invasive compared with subcutaneous mastectomy, the concern has been a higher risk of recurrence of breast growth. Hoppe et al published a meta-analysis of case reports and reported an odds ratio of 7.0 ($p < .01$) for the likelihood of breast growth recurrence following breast reduction surgery as compared with subcutaneous mastectomy.⁴²

Medical therapies that have been used in adult women with breast disorders include dydrogesterone, medroxyprogesterone (Depo-Provera), selective estrogen receptor modulators (SERM), bromocriptine, and danazol. Tamoxifen is the only SERM approved for use in premenopausal women at increased risk for breast cancer. However, the safety and long-term use of tamoxifen in the adolescent population is not known due to the infrequent use and paucity of published data. The mechanism of action involves estrogen blockage of the estrogen receptor with both agonist and antagonist properties. The National Surgical Adjuvant Breast and Bowel Project (NSABP) was a large breast prevention trial in the United States that included healthy premenopausal women 35 years and older as well as postmenopausal women, but there is little data on safety and risks in adolescents.⁴³ This study demonstrated a 49% reduction in estrogen-receptor breast cancer. Life-threatening risks associated with tamoxifen therapy include thromboembolism, stroke, uterine cancer, and decrease in bone density. These risks were more concerning among postmenopausal women except for the decrease in bone density, which was seen in premenopausal women.⁴³ Other side effects commonly described with tamoxifen use were hot flashes, night sweats, vaginal dryness, and vaginal spotting. However, even among high-risk women there is reluctance to use tamoxifen due to the risks and side effects that affect quality of life.⁴⁴

The evidence in the adolescent population on the use of tamoxifen in arresting further breast growth is variable. The tamoxifen dose ranges from 10 to 40 mg per day. The medication can be initiated at 10 mg and then increase to 40 mg if there is no effect at the lower dose. The optimal duration of time after which noticeable slowing of breast growth or completely stopped growth may be seen is 4 to 6 months.^{38,42} One of the challenging aspects for the physician caring for these patients is that the best time to initiate medical therapy is unclear in the literature. It has been suggested that medical therapy with antiestrogens be

Table 1 Medical and surgical management options for virginal hypertrophy

Surgical management	Medical therapy followed by surgery	Surgery followed by medical therapy	Medical therapy
Breast reduction surgery or subcutaneous mastectomy with implant reconstruction	Tamoxifen 10–40 mg/d for 6 mo and no cessation in breast growth Breast reduction surgery or subcutaneous mastectomy with implant reconstruction	Breast reduction surgery or subcutaneous mastectomy with implant reconstruction and recurrent breast growth Tamoxifen 10–40 mg/d for 6 mo	Tamoxifen 10–40 mg/d for 6 mo with clinical improvement or cessation of breast growth Continue tamoxifen for 6 mo and reassess

administered either preoperatively or postoperatively. A review of case reports assessing antiestrogen use concluded that the most successful management sequence is to initiate tamoxifen to control breast growth for at least 6 months. If there is improvement with a decrease in breast size, then continuing tamoxifen for another 6 months could be considered. If there is evidence of poor response with breast regrowth after 6 months of tamoxifen use, then surgery is the definitive therapy.^{38,45} As there are no specific guidelines, several surgical and medical therapy approaches can be considered based on patient and surgeon preference (► **Table 1**). However, at this time, there is inadequate reported experience with medical therapy for adolescents with juvenile breast hypertrophy to predict risks and benefits.

Dydrogesterone, a progesterone analogue that does not have estrogenic or androgenic properties, has also been considered as pharmacologic management in virginal hypertrophy. In a case series, dydrogesterone demonstrated benefit preoperatively and was effective in reducing breast growth recurrence after reduction surgery.⁴⁶ It does not interfere with ovulation and is typically prescribed for treatment of menstrual disorders such as menorrhagia. Case reports again have described the use of this medication in sequence before or after reduction mammoplasty with satisfactory results.⁴⁵ Acute porphyria is a concerning side effect and long-term safety is unknown in the adolescent population.

Other medications described in case reports for the management of virginal hypertrophy include medroxyprogesterone, danazol, bromocriptine, raloxifene, and aromatase inhibitors. The evidence in the literature on the use of these medications is limited. They primarily have been considered for the management of gynecomastia and are less commonly used in the management of virginal hypertrophy.⁴⁷ These medications have not been as successful in suppressing breast growth or preventing recurrent breast growth.³⁵

Conclusion

It is of utmost importance that we tailor the management of benign breast masses presenting in adolescents to the needs of the patient. Nonsurgical options are available or are being researched for the management of benign fibroadenomas and can be considered in patients who do not wish to continue conservative management, but seek to avoid surgical intervention. Juvenile or virginal breast hypertrophy can be a challenging condition to manage for both the patient and physician. Medical therapies may play a role in selected

patients in conjunction with close consultation with surgical colleagues, but data on short- and long-term risks and benefits of use in the adolescent are quite limited.

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