

# American Society for Reproductive Medicine Menopausal MEDICINE

Volume 13, Number 1, Spring 2005

FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

## Testosterone Changes in Women with Age and Menopause



**Henry G. Burger, M.D.**  
Prince Henry's Institute of  
Medical Research  
Monash Medical Centre,  
Clayton, Victoria,  
Australia

### INTRODUCTION

Although there has been interest for many years in the role of testosterone in female sexuality, progress in the field has been slow. Commercial testosterone assays have been directed primarily at use in andrology and have performed poorly in the concentration ranges found in women. Products for testosterone administration were developed for the treatment of male hypogonadism and were unsuitable for adaptation to the 10-fold lower dosage rates likely to be appropriate for women. Recently, substantial changes have occurred, with recognition of the need for assays sufficiently sensitive to measure testosterone reliably in the female range; recognition of the importance of the role of sex hormone binding globulin in the interpretation of testosterone assays; and in its therapeutic use and the emergence of products specifically targeted at female use.<sup>1</sup> An understanding of testosterone physiology in women is an important

### IN THIS ISSUE

Testosterone Changes in Women with Age and Menopause	1
Osteoarthritis and the Postmenopausal Woman	5
Ultrasound in Postmenopausal Women: Ovarian and Endometrial Applications	8

aspect of contemporary endocrinology. The present essay reviews the sources, production rates and serum levels of testosterone and related pro-androgens and androgens in women, discusses testosterone assays and their interpretation; and summarizes the changes which occur with age, emphasising the lack of major change related directly to the menopausal transition and menopause. Causes of androgen deficiency in women are addressed.

### CLASSIFICATION OF THE ANDROGENS, THEIR SOURCES, PRODUCTION RATES AND SERUM LEVELS

Male sex steroids may be divided into pro-androgens and androgens on the basis of their ability to bind specifically to and activate the androgen receptor. The most abundant pro-androgens are dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), while androstenedione is quantitatively much less important. The major biologically active androgen is testosterone, while dihydrotestosterone, its 5 $\alpha$ -reduced metabolite is more potent, but quantitatively of much less significance.

### FROM THE EDITOR

David F. Archer, M.D.

Menopausal women are beset with emerging medical problems. The Women's Health Initiative has left many unanswered questions regarding use of Hormone Therapy in peri- and postmenopausal women. Older women do develop new problems that require medical attention. This issue of *Menopausal Medicine* addresses three of them.

Henry G. Burger, M.D., describes the changes in serum testosterone in aging women. Female Hypoactive Sexual Dysfunction is now a concern that physicians need to address. Serum Testosterone levels do not correlate with reported decline in libido. A knowledge of the normal changes in circulating androgen levels is important in counseling patients with this problem.

Roger W. Lidman, M.D., F.A.C.P., addresses the diagnosis and management of osteoarthritis a major cause of pain and reduced mobility in older women. Current treatments are aimed at preserving function. Exercise is a significant treatment both through reducing weight and increasing muscle strength.

Steven R. Goldstein, M.D., evaluates the uses and potential problems with Ultrasound in postmenopausal women. Ultrasound evaluation of the endometrium and adnexa aid in evaluation of the postmenopausal woman. There are potential problems with the asymptomatic simple ovarian cyst. The simple ovarian cyst is best managed with repeat assessment because of a high incidence of resolution.

# Menopausal Medicine

A Newsletter of the  
American Society for Reproductive Medicine



*President* Robert S. Schenken, M.D.  
*President-Elect* Joseph S. Sanfilippo, M.D.  
*Vice President* Steven J. Ory, M.D.  
*Immediate Past President*  
*Past President* Marian D. Damewood, M.D.  
*Secretary* Sandra A. Carson, M.D.  
*Treasurer* Linda D. Applegarth, Ed.D.  
*Executive Director* Stuart S. Howards, M.D.  
*Dir. of Operations & Strategic Development* Robert W. Rebar, M.D.  
Nancy R. Frankel, B.S., M.B.A.

## DIRECTORS

John E. Buster, M.D.  
William E. Gibbons, M.D.  
Linda C. Giudice, M.D., Ph.D.  
R. Dale McClure, M.D.  
Peter N. Schlegel, M.D.  
Bill Yee, M.D.

## ASRM AFFILIATE SOCIETY PRESIDENTS

Ricardo Azziz, M.D., M.P.H., M.B.A. (SRS)  
Christos Coutifaris, M.D. (SREI)  
Peter N. Schlegel, M.D. (SMRU)  
Eric S. Surrey, M.D. (SART)

## EDITOR

David F. Archer, M.D.  
Professor of Obstetrics and Gynecology,  
Director, Clinical Research Unit, Eastern  
Virginia Medical School, Norfolk, Virginia

## EDITORIAL BOARD

Kurt T. Barnhart, M.D.  
University of Pennsylvania Medical Center  
Penn Fertility Care  
Philadelphia, Pennsylvania

Veronica Ravnkar, M.D.  
Chair of Obstetrics and Gynecology,  
St. Barnabas Medical Center,  
Livingston, New Jersey

John E. Buster, M.D.  
Professor of Obstetrics and Gynecology, Director,  
Division of Reproductive Endocrinology and  
Infertility, Baylor College of Medicine, Houston,  
Texas

## MANAGING EDITOR

Jennifer Price, M.A.

## DIRECTOR, EDUCATION & PUBLICATIONS

Jennifer Kelly, M.A.

*The ASRM is pleased to acknowledge the generous contribution of Wyeth Pharmaceuticals toward the publication of this newsletter.*

# Wyeth

Copyright 2005  
American Society for Reproductive Medicine

1209 Montgomery Hwy., Birmingham, AL 35216  
(205) 978-5000 • [asmr@asmr.org](mailto:asmr@asmr.org) • [www.asrm.org](http://www.asrm.org)

Views and opinions published in *Menopausal Medicine*  
are not necessarily endorsed by the ASRM.

Both the adrenals and the ovaries synthesize pro-androgens and androgens, with testosterone being the immediate precursor for the biosynthesis of estradiol. Adrenal androgen secretion is regulated by corticotropin (ACTH), while LH is the major regulator of ovarian androgen biosynthesis. The liver, adipose tissue, and skin have the enzymes which catalyze the conversion of pro-androgens to androgens and also contain aromatase, which catalyzes androgen conversion to estrogen. It is recognized that circulating DHEAS is a major precursor of the biosynthesis of more potent androgens in target tissues.

DHEAS is a unique secretory product of the adrenal zona reticularis. Its production rate is between 3.5 mg and 20 mg daily during reproductive life and its circulating concentration is in the range of 100 µg/dL to 400µg/dL (3 µmol/l to 12 µmol/l). Dehydroepiandrosterone is produced by the adrenal zona reticularis (50%) and the ovarian theca (20%), while 30% is a conversion product from circulating DHEAS. The daily production rate is of the order of 6 mg to 8 mg and circulating concentrations 100 ng/dL to 1000 ng/dL (3 nmol/l to 35 nmol/l).

Androstenedione comes from the adrenal zona fasciculata (50%) and the ovarian stroma (50% but varies through the menstrual cycle). Daily production rate is approximately 1.4 mg to 6.2 mg and circulating concentration is in the range 50 ng/dL to 200ng/dL (2 nmol/l to 8nmol/l). The steroid shows a circadian variation and a mid-cycle elevation in concentration parallel with the midcycle peak of estradiol.

Testosterone is produced by the adrenal zona fasciculata (25%) and the ovarian stroma (25%), with the remaining 50% being converted from circulating androstenedione. The daily production rate is in the order of 100 µg to 400 µg, and circulating levels are in the range 20 ng/dL to 70 ng/dL (0.6 nmol/l to 2.5 nmol/l). Concentrations are low in the early follicular phase of the menstrual cycle with a rise to a mid-

cycle peak. Luteal phase concentrations are intermediate. Circadian variation is observable with the highest levels seen in the early morning hours. Both premenopausally and postmenopausally, removal of the ovaries results in a 50% fall in circulating levels. Some recent publications have suggested that the postmenopausal ovary is not an androgen secreting organ,<sup>2</sup> but it has been difficult to reconcile those observations with the demonstration of the fall that occurs following oophorectomy and with the demonstration that testosterone levels in ovarian blood are higher than those in the periphery.

Dihydrotestosterone is primarily a product of the peripheral conversion of testosterone and circulates at approximately 2 ng/dL, with daily production rates calculated to be between 4.3 mg/day and 12.5 mg/day.

## TESTOSTERONE IN BLOOD

As indicated above, testosterone in women circulates in the low nanomolar range of concentration, 10-to 15-fold lower than concentrations found in the normal adult male. About two-thirds of circulating testosterone is bound to sex hormone-binding globulin (SHBG), and most of the remainder is loosely bound to albumin, with only 1% to 2% of total circulating testosterone in the unbound or free form. It is generally accepted that the biologically active moiety is the free testosterone, though that bound to albumin is also likely to contribute significantly. It is widely held that it is the free fraction which most reliably reflects testosterone biological activity.

Sex hormone-binding globulin is a major determinant of the bioavailability of sex steroids. Sex hormone binding globulin is a product of the liver, and its production and circulating concentration are raised by estrogens, particularly during pregnancy and following oral estrogen administration with its first-pass effects on the liver. Its levels are also increased in hyperthyroidism, liver cirrhosis, and by

some anti-epileptic medications. Its levels are decreased in obesity, hyperinsulinism, glucocorticoid or growth hormone excess, hypothyroidism, and in hyperandrogenic states.

Because two-thirds of testosterone is tightly bound to SHBG, knowledge of the latter's concentration is essential to a proper interpretation of circulating testosterone concentrations. Particularly when testosterone deficiency is suspected, it is recommended that blood should be drawn in the early morning and after day 8 of the menstrual cycle and before day 20, given the changes during the cycle. Both total testosterone and SHBG should be measured. Free testosterone can then be calculated reliably, using the law of mass action.<sup>3</sup>

Knowledge of the SHBG concentration provides an index of whether an apparently normal total testosterone concentration in blood reflects the biologically available steroid or is reflecting a cause of raised SHBG. In recent years, several commercial assays have been developed which purport to measure free testosterone directly by analogue direct radioimmunoassay. Such assays have been shown to be unreliable and should not be used.

Commercially available testosterone immunoassays may not be reliable. In a recent study, 10 such assays were compared with a gold standard assay using isotope dilution gas chromatography-mass spectrometry. Results from the commercial assays were on average two-fold inaccurate and sometimes five-fold.<sup>4</sup> A major need continues for reliable, commercially available assays.

It has been argued that the interpretation of serum testosterone levels is further complicated by the known conversion of DHEAS to testosterone at the cellular level, its so-called intracrine action. The tissue sensitivity to androgens will vary according to the concentration and activity of enzymes capable of peripheral endocrine conversions, and the levels

of androgen receptor and its biological activity are all variable.

In contemporary endocrinology, however, a reliable assay for total testosterone together with an assay for SHBG and calculation of free testosterone provide the best available compromise for an assessment of androgenic activity. As noted below, however, absolute levels of testosterone are not proving to be discriminatory in the diagnosis of androgen deficiency in women.

---

*“An understanding of testosterone physiology in women is an important aspect of contemporary endocrinology.”*

---

#### **CHANGES IN TESTOSTERONE AND RELATED STEROIDS WITH AGE AND MENOPAUSE**

The most striking feature of pro-androgen and androgen physiology in women is the substantial decline which occurs in circulating concentrations from the peaks seen in the early 20s to the age of 40 to 45.<sup>5</sup> In particular, both DHEAS and testosterone concentrations fall by 50% or more between the ages of 21 and 40. Using sensitive and specific testosterone measurements, Zumoff et al.<sup>5</sup> showed that the expected testosterone concentration in a woman of 40 would be 0.61 nmol/l, about half of that of a 21-year-old woman (1.3 nmol/l). They showed that the percentage of free testosterone did not vary significantly with age, so that free testosterone concentration similarly showed a steep decline.

The ratios of DHEA to testosterone and DHEAS to testosterone were age invariant because of the steep declines in DHEA and DHEAS with age. For many years it had been assumed that there was a further substantial decline in testosterone concentrations as a result of the menopause. This was primarily due to studies in which circulating concentrations of testosterone in women in their 50s and 60s were compared to those in a normal young control group aged in their 20s.

The premenopausal decline in androgens had not been envisaged. There are now a number of studies which have clearly shown that there is little, if any, change in circulating testosterone concentration across the menopausal transition and menopause; and if anything, free testosterone levels may rise because of the concomitant fall in SHBG concentrations.<sup>6</sup>

The focus on the menopause as a possible cause of female androgen insufficiency would thus seem to be not entirely appropriate, with many women presenting with symptoms suggestive of androgen deficiency in their 30s and early 40s while still continuing to cycle regularly.<sup>7</sup> Several studies have demonstrated an actual increase in total testosterone levels with age postmenopausally.<sup>8</sup> Current studies have also addressed the influence of ethnicity on circulating androgen concentrations with DHEAS concentrations being shown to be highest amongst Chinese and Japanese women and lowest in African-American and Hispanics.<sup>9</sup>

#### **FEMALE ANDROGEN DEFICIENCY**

A Consensus Conference held in 2001<sup>10</sup> suggested that a female androgen deficiency syndrome could be defined by a pattern of clinical symptoms and signs in the presence of decreased circulating concentrations of bioavailable testosterone and normal estrogenic status. The clinical symptoms included decreased libido, sexual receptivity, and pleasure,

together with a diminished sense of well-being, dysphoric mood and/or blunted motivation, and persistent unexplained fatigue. In the advanced case, bone loss and decreased muscle mass and strength might be observed together with the redistribution of adipose tissue, decreased sexual hair, changes in cognition and memory. Many of the symptoms of course are non-specific and common to other disorders such as depression and can be affected by multiple variables including socioeconomic, environmental, and life circumstances.

Androgen deficiency might be observed in those women who have circulating androgen concentrations in the lower ranges for their age, but it has been clearly shown to occur in a number of medical conditions including hypopituitarism, premature ovarian failure, following bilateral oophorectomy or ovarian damage as a result of chemotherapy or radiotherapy and in Turner syndrome. Similarly, androgen deficiency may occur especially in primary and secondary adrenal insufficiency.<sup>11</sup>

A potent iatrogenic cause of androgen insufficiency is the administration of oral estrogens, particularly synthetic estrogens as in the oral contraceptive pill or as used in postmenopausal hormone therapy. Here the androgen insufficiency is primary the result of an increase in sex hormone-binding globulin and a consequent decrease in bioavailable testosterone.<sup>12</sup>

Despite the above considerations, it has been difficult to relate circulating testosterone concentrations to alterations in female sexual function in particular.<sup>13</sup> While the organic causes of testosterone deficiency clearly result in markedly low circulating testosterone concentrations,<sup>11</sup> women presenting with loss of libido without any other obvious cause cannot be clearly distinguished from their normally functioning counterparts on the basis of particularly low circulating testosterone levels. This has been evident in studies of testosterone during the menopause

transition where circulating levels are not different in women with poor sexual function, compared with those with normal sexual function.<sup>13</sup>

It is this author's belief that, although as an endocrinologist, it is important to measure circulating concentrations in women presenting with poor libido for investigation, the primary role is to exclude those women with testosterone concentrations at or above the middle of the normal range, rather than using the concentrations as a discriminatory diagnostic tool. Low concentrations of DHEAS can support the diagnosis.

### SUMMARY

The major circulating androgen in women is testosterone, though its production in peripheral target tissues raises questions about the relevance of circulating testosterone concentrations to overall androgen physiology. Circulating testosterone concentrations fall by approximately 50% between the ages of 20 and 40 but do not normally continue to fall thereafter and may in fact increase postmenopausally. The measurement of circulating testosterone requires a reliable sensitive assay for total testosterone together with a measurement of SHBG. The assays nevertheless are not diagnostically discriminatory but are helpful in excluding women from consideration for testosterone treatment whose concentrations are at or above the mid-normal female range.

*The author has revealed the following potential conflicts of interest: Receipt of Honoraria: Wyeth, Novo Nordisk, Servier; Membership on a company advisory board, board of directors or other similar group: Wyeth, Novo Nordisk, Servier; Participation in a company sponsored speakers' bureau: Wyeth, Novo Nordisk, Servier*

### REFERENCES

1. Rivera-Woll LM, Papalia M, Davis SR, Burger HG. Androgen insufficiency in women: diagnostic and therapeutic implications. *Hum Reprod Update*. 2004;10:421-32.
2. Couzinet B, Meduri G, Lecce M, Young J, et al. The postmenopausal ovary is not a major androgen-producing gland. *J Clin Endocrinol Metab*. 2001;86:5060-6.
3. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. *J Steroid Biochem*. 1982;16:801-810.
4. Taieb J, Mathian B, Millot F, Patricot MC, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin Chem*. 2003;49:1381-95.
5. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab*. 1995;80:1429-30.
6. Burger HG, Dudley EC, Cui J, Dennerstein L, et al. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. *J Clin Endocrinol Metab*. 2000;85:2832-8.
7. Goldstat R, Briganti E, Tran J, Wolfe R, et al. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause*. 2003;10:390-8.
8. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, Von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 2000;85:645-51.
9. Lasley B, Santoro N, Randolph J, Gold EB, et al. The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. *J Clin Endocrinol Metab*. 2002; 87:3760-7.
10. Bachmann G, Bancroft J, Braunstein G, Burger H, et al. Female androgen insufficiency: Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril*. 2002; 77:660-5.
11. Miller K, Sesmil G, Schiller A, Schoenfeld D, et al. Androgen deficiency in women with hypopituitarism. *J Clin Endocrinol Metab*. 2001;86:561-7
12. Vehkavaara S, Hakala-Ala-Pietila T, Virkamaki A, Bergholm R, et al. Differential effects of oral and transdermal estrogen replacement therapy on endothelial function in postmenopausal women. *Circulation*. 2000; 102:2687-93.
13. Dennerstein L, Randolph J, Dudley E, Burger H. Hormones, mood, sexuality, and the menopausal transition. *Fertil Steril*. 2002; 77:S42-8.

# Osteoarthritis and the Postmenopausal Woman



**Roger W. Lidman, M.D., F.A.C.P.**  
President, Center for Arthritis and Rheumatic Diseases, PC  
Associate Professor of Clinical Medicine, Eastern Virginia Medical School, Norfolk, Virginia

## INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the world. It has been found in skeletal remains dating to Neolithic times.<sup>1</sup> In Western populations, radiographic evidence of osteoarthritis occurs in the majority of patients over 65 years of age and in 80% over 75,<sup>2</sup> and approximately 50% will be symptomatic.

While some studies indicate an equal incidence of isolated osteoarthritis of the hip and knee in women and men,<sup>3</sup> there is a marked female predominance for polyarticular osteoarthritis<sup>4</sup>, the prevalence of which increases sharply after menopause or hysterectomy.<sup>5</sup> Thus, osteoarthritic joint pain will be a common complaint to those providing primary care to these patients.

## DEFINITION

Any working definition of osteoarthritis mandates consideration of pathologic, radiographic, and clinical components. The key pathologic changes are a focal destruction of articular cartilage followed by changes in the subchondral bone, but much of the pathology represents real or attempted repair rather than degeneration.<sup>6</sup> It is now recognized as an age-related dynamic response of a joint to insult or

injury, and all tissues of the joint are involved, though loss of cartilage and changes in the adjacent bone remain the most striking features.

## PATHOPHYSIOLOGY OF OSTEOARTHRITIS

The articular cartilage is a meshwork of collagen fibers arranged both parallel and perpendicular to the articular surface. Proteoglycan molecules are arranged throughout and because of their hydrophilic nature, help to maintain the water content of the cartilage. When the collagen network is damaged, there is initial increase in the water content followed by net increased synthesis of proteoglycan. Chondrocytes, the cells involved in cartilage production, increase their activity in an attempt at repair, but their new products have inferior mechanical properties. Eventually, the cartilage softens, and vertical clefts appear (fibrillation). Fibrillated cartilage is lost into the joint space, causing low grade inflammation and exposing subchondral bone. The bone is less successful at absorbing load and develops micro-fractures through

its trabecular structure, which may then coalesce to form cysts. In an attempt to compensate for cartilage loss, there is new bone growth forming osteophytes.

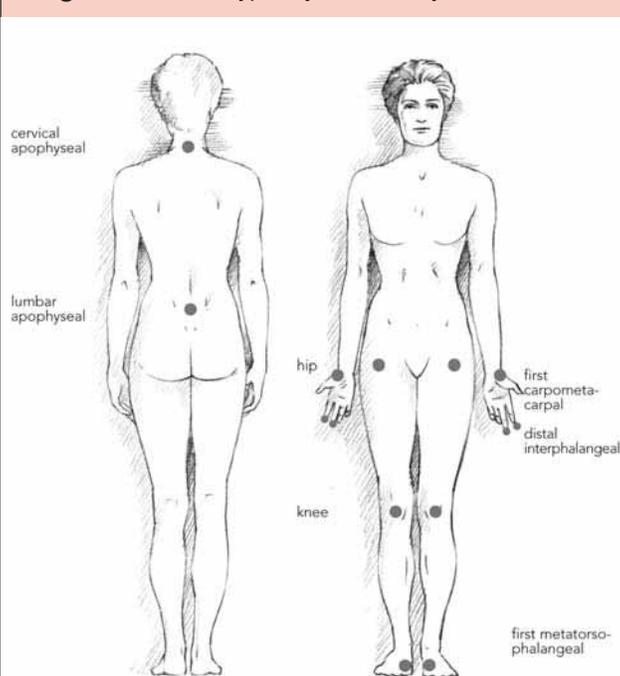
Ordinarily, deformation of subchondral bone serves as a major shock absorbing structure. However, the micro-fractures caused by increasing stress on the subchondral bone heal with stiffer, less deformable trabeculae. Stresses are then concentrated on a smaller articular cartilage surface, the cartilage fails, more stress is placed on subchondral bone, and the process accelerates. Eventually, there is bone-on-bone, thickening of the joint capsule, muscle atrophy, and chronic synovial inflammation.<sup>7</sup>

## CLASSIFICATION

Osteoarthritis may be primary, that is, without an underlying cause, or secondary which implies a likely cause can be identified. Primary osteoarthritis of the hands, classically involving the distal interphalangeal, proximal interphalangeal, and 1st carpometacarpal joints of the hands is commonly seen in postmenopausal women, suggesting a hormonal influence, though genetic factors seem to be operating as well. There is polyarticular symmetric bony enlargement in the proximal and distal joints of the hands with early inflammatory symptoms. When large joints such as the hip are affected, cartilage loss is usually bilateral and diffuse.<sup>8</sup>

Secondary osteoarthritis may have multiple causes including metabolic (calcium pyrophosphate deposition, ochronosis, etc.), anatomic (slipped capital femoral epiphysis, hypermobility, congenital hip dislocation, etc.), traumatic (osteonecrosis, fracture through a joint), and inflammatory (any underlying inflammatory arthritis, septic arthritis), all conditions that initially injure the articular cartilage.<sup>9</sup>

**Figure 1: Joints Typically Affected by Osteoarthritis**



©1997. Reprinted with permission of the Arthritis Foundation, 1330 W. Peachtree St., Atlanta, GA 30309. To order the 12th edition of the *Primer on the Rheumatic Diseases*, call 1.800.268.6942 or visit [www.arthritis.org](http://www.arthritis.org)

## CLINICAL FEATURES OF OSTEOARTHRITIS

The most prominent feature of osteoarthritis is pain, though it is usually not present at rest, except in advanced cases. Physical activity with concomitant stress on the joint aggravates the discomfort which may be described as a dull ache or sharp, stabbing sensation, and rest usually relieves it. Stiffness with inactivity, such as after prolonged sitting, is a frequent complaint as is morning stiffness upon first arising, though this is not as great a problem as with an inflammatory condition such as rheumatoid disease.

Sometimes pain from an involved joint will radiate such that hip pain usually experienced in the groin may radiate to the anterior thigh or knee or radiate to the lateral thigh simulating trochanteric bursitis. Knee pain may radiate distally and inframedial radiation may mimic anserine bursitis.

The cardinal physical findings are pain with motion and possible limitation of motion of the involved joint. Crepitus, or the palpable or audible sensation of “bone against bone” may be present. Effusions may occur, but significant warmth or redness suggests a more inflammatory etiology such as an associated crystal-induced process.

The radiographic hallmarks of osteoarthritis include joint space narrowing reflecting the loss of articular

cartilage, osteophyte formation, and subchondral cysts; the latter two generally reflect advanced disease.

## MEDICAL MANAGEMENT OF OSTEOARTHRITIS

Guidelines for the management of osteoarthritis have been published by the American College of Rheumatology and stress both nonpharmacologic and pharmacologic modalities.<sup>10</sup> They are to be used together with the goal of relieving pain, maintaining function, and improving quality of life. Patient education, weight loss when necessary, and muscle strengthening, along with the occasional use of assistive devices help joint protection and drug therapy is more effective when combined with this strategy.<sup>11</sup>

While simple non-narcotic analgesic therapy (i.e., acetaminophen, tramadol) is sufficient for most osteoarthritis patients, studies have shown greater benefit from nonsteroidal anti-inflammatories for moderate-to-severe disease.<sup>12</sup> For patients at risk for GI adverse events (age > 65, history of peptic ulcer disease or GI bleed, co-therapy with corticosteroids), cyclo-oxygenase 2 (Cox 2) inhibitors are recommended, though the withdrawal of Vioxx® has raised as yet unanswered concerns whether its cardiovascular effects extend to other members of the class.<sup>13</sup> Moreover, all nonsteroidal anti-inflammatory drugs including Cox 2 inhibitors may

impact renal function. Finally, for select patients with osteo-arthritis of the knee, viscosupplementation using the synthetic hyaluron in a series of injections may be helpful though the duration of effect is unpredictable.<sup>14</sup>

## ROLE OF ESTROGEN IN OSTEOARTHRITIS

The role of estrogen in osteoarthritis has been reviewed in detail<sup>15</sup> and multiple studies addressing the issues have been inconclusive and/or contradictory. Estrogen interacts with cellular growth factors, adhesion molecules, and cytokines, so that one would expect a significant effect of estrogen on the disease process. One study using T1 weighted fat suppressed sagittal MRI to assess tibial cartilage volume showed that women using long-term estrogen replacement therapy (ERT) have more knee cartilage than controls, and the authors postulated a protective effect on articular cartilage.<sup>16</sup> Another study evaluated estrogen and a SERM and showed decreases in articular cartilage degradation both in rodents and humans.<sup>17</sup>

However, clinical data seem to dispute the theoretical benefits of estrogen as an adjunct therapy in osteoarthritis. A study of women undergoing total hip replacement that evaluated prevalence of osteoarthritis among users and nonusers of ERT showed no difference between the two groups.<sup>18</sup> In a group of 1,001 post-

### Updated ACR Guidelines: Pharmacologic Therapy for Patients with Osteoarthritis<sup>10</sup>

#### Oral:

- Acetaminophen
- Coxibs/Cox2 selective agents
- Nonselective NSAID, plus misoprostol or a Proton Pump Inhibitor (PPI) for patients at risk for GI complications
- Nonacetylated salicylates
- Other pure analgesics (e.g., tramadol)

#### Intra-articular:

- Glucocorticoids
  - Hyaluronan
- #### Topical:
- Capsaicin
  - Methylsalicylate

menopausal women mean age 72, adjusted for age, body mass index, smoking, exercise, and type of menopause, women who used estrogen were more likely to have osteoarthritis of the hip. Moreover, among estrogen users, duration of use was longer for women with osteoarthritis.<sup>19</sup>

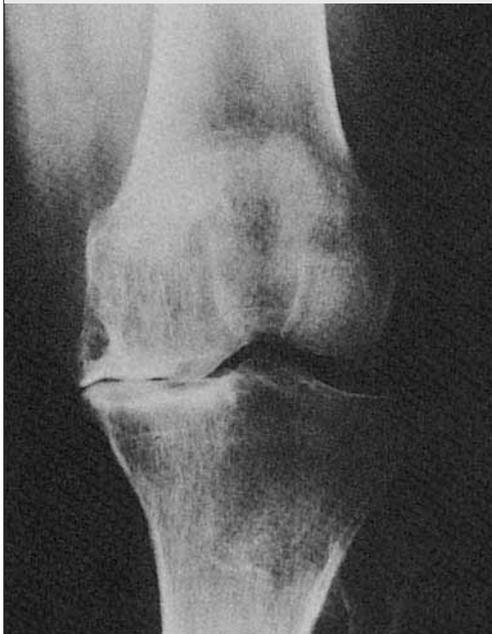
In a group of postmenopausal women mean age 66 who participated in the HERS trial, there was no effect of estrogen plus progestin therapy compared to placebo on knee pain and related disability.<sup>20</sup> Thus, while large-scale observational studies and trials assessing other benefits of ERT suggest no benefit for symptomatic relief in osteoarthritis, no randomized prospective trials have specifically addressed the impact of ERT on symptomatic or structural progression of osteoarthritis. Based on the results of the Women's Health Initiative suggesting health risks of HRT may outweigh benefits, hormone replacement as first-line therapy against the progression of osteoarthritis cannot be recommended.<sup>21</sup>

## CONCLUSION

Osteoarthritis is the most common skeletal disorder and is associated with pain, disability, and impaired quality of life. With predilection for the older population, it will commonly be encountered in the postmenopausal population and warrants accurate diagnosis and treatment to maintain the patient's functional abilities and quality of life.

*The author has revealed the following potential conflicts of interest: Speakers Bureaus of Merck, Boehringer-Ingelheim, Aventis, and Centacor.*

**Figure 2:**  
Radiograph of the knee showing moderate-to-severe osteoarthritis with marked joint space narrowing, osteophytes, and bony sclerosis



©1997. Reprinted with permission of the Arthritis Foundation, 1330 W. Peachtree St., Atlanta, GA 30309. To order the 12th edition of the *Primer on the Rheumatic Diseases*, call 1.800.268.6942 or visit [www.arthritis.org](http://www.arthritis.org)

## REFERENCES

1. Rogers J, Dieppe P, Watt I. Arthritis in Saxon and medieval skeletons. *Br Med J (Clin Res Ed)*. 1981;283:1668-70.
2. Inoue K, Hukuda S, Fardellon P, Yang ZQ, et al. Prevalence of large-joint osteoarthritis in Asian and Caucasian skeletal populations. *Rheumatology (Oxford)*. 2001;40:70-3.
3. Wilson MG, Michet CJ Jr, Ilstrup DM, Melton LJ 3rd. Idiopathic symptomatic osteoarthritis of the hip and knee: a population-based incidence study. *Mayo Clin Proc*. 1990; 65:1214-21.
4. Spector TD, Campion GD. Generalised osteoarthritis: a hormonally mediated disease. *Ann Rheum Dis*. 1989;48:523-7.
5. Spector TD, Brown GC, Silman AJ. Increased rates of previous hysterectomy and gynaecological operations in women with osteoarthritis. *BMJ*. 1988;297:899-900.
6. Sokoloff L. The biology of degenerative joint disease. Chicago, IL. Chicago University Press. 1969.
7. Mankin MJ, Brand KD. Pathogenesis of osteoarthritis. In *Textbook of Rheumatology*. Kelly WN, Harris ED, Jr., Ruddy S, Sledge CB. Philadelphia. Saunders. 1993;1417-31.
8. Cooper C, Egger P, Coggon D, Hart DJ, et al. Generalized osteoarthritis in women: pattern of joint involvement and approaches to definition for epidemiological studies. *J Rheumatol*. 1996;23:1938-42.
9. Dennison E, Cooper C. Osteoarthritis: epidemiology and classification. In Hochberg M, Silman A, Smolen A, et al. *Rheumatology*. New York. Mosby. 2003;1981-84.
10. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum*. 2000;43 1905-15.
11. The management of chronic pain in older persons: AGS Panel on Chronic Pain in Older Persons. American Geriatrics Society. *J Am Geriatr Soc*. 1998;46:635-51.
12. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis. The North of England Non-Steroidal Anti-Inflammatory Drug Guideline Development Group. *BMJ*. 1998;317:526-30.
13. Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med*. 2004;51:1709-11.
14. Kirwan JR, Rankin E. Intra-articular therapy in osteoarthritis. *Baillieres Clin Rheumatol*. 1997;11:769-94.
15. Gokhale JA, Frenkel SR, Dicesare PE. Estrogen and osteoarthritis. *Am J Orthop*. 2004;33:71-80.
16. Wluka AE, Davis SR, Bailey M, Stuckey SL, et al. Users of oestrogen replacement therapy have more knee cartilage than non-users. *Ann Rheum Dis*. 2001;60:332-6.
17. Christgau S, Tanko LB, Cloos PA, Mouritzen U, et al. Suppression of elevated cartilage turnover in postmenopausal women and in ovariectomized rats by estrogen and a selective estrogen-receptor modulator (SERM). *Menopause*. 2004;11:508-18.
18. Erb A, Brenner H, Gunther KP, Sturmer T. Hormone replacement therapy and patterns of osteoarthritis: baseline data from the Ulm Osteoarthritis Study. *Ann Rheum Dis*. 2000;59:105-9.
19. Nevitt MC, Felson DT, Williams EN, Grady D. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/ Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2001;44:811-8.
20. Reginster JY, Kvasz A, Bruyere O, Henrotin Y. Is there any rationale for prescribing hormone replacement therapy (HRT) to prevent or to treat osteoarthritis? *Osteoarthritis Cartilage*. 2003;11:87-91.
21. Von Muhlen D, Morton D, Von Muhlen CA, Barrett-Connor E. Postmenopausal estrogen and increased risk of clinical osteoarthritis at the hip, hand, and knee in older women. *J Womens Health Gend Based Med*. 2002;11:511-8.

# Ultrasound in Postmenopausal Women: Ovarian and Endometrial Applications



**Steven R. Goldstein, M.D.**  
Professor of Obstetrics & Gynecology  
New York University  
School of Medicine,  
New York, New York

Initially sonography was a tool of the obstetrician. Early equipment had very limited resolution and was used to obtain limited obstetrical information including placental localization, fetal lie, and measurement of structures such as biparietal diameter. As equipment and resolution improved, the use of sonography in gynecology, including postmenopausal women began. The vaginal probe has opened new doors to the application of ultrasound to postmenopausal patients.

## ULTRASOUND IN THE POSTMENOPAUSE: OVARY

Ovarian cancer is a deadly disease. Although uterine cancer is the most prevalent of gynecologic malignancies, ovarian cancer accounts for more deaths than cervical and endometrial cancer combined. It is the leading cause of death from gynecologic cancer in the United States. It is the fifth leading cause of all cancer deaths in females; 80% of such cases involve women over 50 years of age, hence its importance in menopausal women is obvious. Approximately one in 70 women will develop ovarian cancer in their lifetime. This increases to 4% to 6% if there is a family history in a first-degree relative. Five-year survival rates continue to be disturbingly low, mainly because of a lack of early detection.

In 1971<sup>1</sup> the "palpable postmenopausal ovary" syndrome was first described. Hugh Barber stated "an ovary

[that] would be considered normal sized in a premenopausal woman should be considered abnormal in a postmenopausal women...and probably harbors a tumor not necessarily malignant but not functional or dysfunctional." More than a decade later Barber was still stating that "patients with palpable postmenopausal ovary syndrome should not be followed or reevaluated but must be promptly investigated for the presence or absence of an ovarian tumor...the only method of diminishing the mortality from ovarian cancer is the acceptance of more liberal indications of surgery."<sup>2</sup>

As the use of gynecologic ultrasound has expanded, many women with any postmenopausal cystic masses were mistakenly treated as "cancer until proven otherwise" and subjected to a surgical approach. In the mid-1980s, data began to appear relative to the very low incidence of malignant disease in such cystic masses. One of the first studies by Hall and McCarthy<sup>3</sup> looked at 13 postmenopausal women with cystic structures, only 10 of which were unilocular. There was one borderline malignancy in a 3.5-cm simple cystic structure. Thus the incidence of malignancy was 8% of the total or 10% of the unilocular structures. This caused the authors to state "...the simple postmenopausal adnexal cyst may not necessarily be an ominous finding." Personally, I do not agree with the conclusion of that early study. A 10% incidence of malignancy is rather high for any abnormality detected on screening. If I believed that 10% of such postmenopausal cystic ovarian structures were borderline malignancies, a surgical

approach would seem appropriate. However, subsequent studies have failed to indicate that unilocular unilateral cystic structures < 5 cm will have such a high level of malignancy.

A study by Rulin and Preston<sup>4</sup> dealt with a four-year experience with adnexal masses (not necessarily simple cysts). They divided the masses into < 5 cm, between 5 cm to 10 cm, and > 10cm. Of 33 masses, < 5 cm, there was one 3-cm endometrioid carcinoma. This caused those authors to state "...our findings cast out on the concept that all menopausal women with minimally large ovaries should undergo laparotomy."

Another study<sup>5</sup> of postmenopausal simple cystic masses looked at 48 postmenopausal patients ranging in age from 46 to 86. None had had any menses for at least 12 months. All had unilateral, simple cystic structures, <5 cm maximum diameter, with no areas of solid components, septations, or pelvic ascites. Although the study was prospective, it was not randomized. Twenty-six patients had prompt surgical evaluation. All of these had benign findings on pathology. Sixteen patients had serial sonographic evaluations every three to six months. Six patients were lost to follow-up. Of the 16 followed conservatively, 14 were followed from 10 to 73 months (average 29 months) with no change in size, or character of the cystic structures. One patient was operated on after six months of observation for increase in size and development of a septation. On pathology, this was a serous cystadenoma. One patient was operated on after nine months of observation for increased pain. This mass was a degenerating myoma. The authors concluded that "small (< 5 cm) unilocular, unilateral, postmenopausal cystic adnexal masses with no septations or ascites would have a very low incidence of malignant disease. Therefore, serial ultrasound follow-up without surgical intervention may play a role in clinical management of such patients."



**Figure 1:** Normal premenopausal ovary (3.0 cm x 2.2 cm) on day 11 of the cycle. A dominant follicle of 16 mm is outlined by the calipers (+).

## ULTRASOUND OF MENOPAUSAL OVARIES

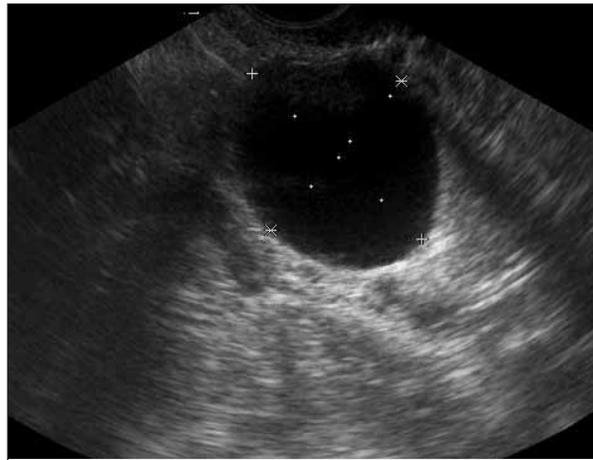
To better understand the ultrasonographic appearance of postmeno-

pausal ovaries, one must first understand what happens anatomically. Folliculogenesis ceases. The tunica albuginea becomes very dense causing the surface of the ovary to become scarred and shrunken. Eventually the ovary is inert, consisting mainly of connective tissue and clings to the posterior leaf of the broad ligament. The ovaries are no longer palpable on bimanual exam, the basis for Hugh Barber's original thesis.

What do these findings mean sonographically? Contrast this with the ultrasound findings in premenopausal ovaries. In such patients the sonolucencies of the follicles make visualization relatively simple. In addition, when a woman assumes the lithotomy position, freely mobile premenopausal ovaries will fall lateral to the uterus and easily be seen with a vaginal probe immediately adjacent to the pelvic side wall, which is next to the iliac artery and iliac vein. Realize that if a patient were placed into a knee-chest position, freely mobile ovaries would move towards the anterior abdominal wall but the iliac structures, since they are retroperitoneal, will not. Thus, in premenopausal women, the iliac vessels serve as important landmarks for ovarian identification.

In the postmenopausal patient, there are no sonolucent follicles because folliculogenesis has ceased. Ultimately the ovaries do not reach the pelvic side wall, and iliac vessels are not helpful in identification. In addition there are loops of bowel everywhere. Such bowel contains gas and fecal material, the shadowing from which may often obscure the observer's ability to find a postmenopausal ovary. However, in some instances, the swirling of bowel and fecal material around a solid non-moving structure (i.e., postmenopausal ovary) may in fact aid in its identification.

So a lingering question is: Will the failure to identify normal ovaries on ultrasound be as reassuring as definitively locating them and seeing them as atrophic? Rodriguez et al.<sup>6</sup> found that 82% of ovaries were seen with transvaginal ultrasound. All abnormal ovaries were visualized. The mean surgical



**Figure 2:**  
*Simple unilocular cyst (3.9 cm x 3.3 cm) in the right ovary of a 78-year-old patient.*

diameter of non-visualized ovaries was 7.3 mm (range 5 mm to 12 mm). No ovaries that appeared normal on sonography were abnormal at surgery. One ovary that appeared grossly normal on transvaginal ultrasound and on gross inspection at surgery, contained a microscopic Brenner tumor. Obviously the percentage of normal postmenopausal ovaries identified on ultrasound depends on the skills of the ultrasonographer.

The ultrasound community has long been concerned with adnexal cysts. This is because of the fact that 85% of ovarian tumors are epithelial, and virtually all of these will have some cystic component at some point in their growth. In addition cystic structures are easily visualized on ultrasound. Levine et al.<sup>7</sup> studied 184 women who were asymptomatic and postmenopausal; 17.3% had simple adnexal cystic structures at initial exam (range 0.4 cm to 4.7 cm). Of these, 50% were 1 cm or less and 90% were 3 cm or less. There was no statistical difference between women on menopausal hormone therapy and those who were not. What percentage of patients with a "cyst" had previous adnexal surgery was not provided. However, 47 of the 184 women had prior hysterectomies. Thus, some of these may have been peritoneal inclusion cysts. Of the six patients who did come to surgery, there was one stage I-C ovarian cancer. It was however a complex mass, not a simple cyst.

A more recent analysis of cystic structures in asymptomatic postmenopausal women greater than 50 years of

age was reported by Bailey et al.<sup>8</sup> Of 7,705 women scanned, unilocular cysts were present in 3.3% (N = 256). Of these, 49% resolved in 60 days, 51% persisted. Forty-five women who were operated on displayed no malignancies; 32 (71%) were cystadenomas. This is the same ratio as the simple cysts operated on in one of the original papers in the mid-1980s.<sup>5</sup> In the series by Bailey et al., 86 women were followed every three to six months with no development of any malignancies.

Another study<sup>9</sup> screened 1,769 postmenopausal women who were asymptomatic with no previous gynecologic pathology; 6.6% (n=116) had simple ovarian cysts <5 cm. Among those, 23% resolved spontaneously, 60% persisted and 17% were lost to follow-up. Eighteen women with persistent cysts underwent surgery, and no malignancies were identified.

Modesitt et al.<sup>10</sup> at the University of Kentucky Ovarian Cancer Screening program identified 2,763 women with unilocular ovarian cysts <10 cm, out of 156,106 women over 50 years of age who were screened. That is an 18% incidence, similar to Levine.<sup>7</sup> Of these cysts, 70% resolved, 17% developed a septum, 6% developed a solid area, and 7% persisted as a unilocular lesion. No woman with an isolated unilocular cystic ovarian lesion developed ovarian cancer in that study.

Finally to better understand the management of persistent unilocular ovarian cysts < 5 cm and with normal CA 125 levels, Nardo et al.<sup>11</sup> identified postmenopausal women with unilocular ovarian cysts who were then followed for a five-year period. This was not a screening program. The women were initially evaluated for "postmenopausal symptoms, abdominal discomfort or postmenopausal bleeding." There were 226 women with < 5 cm unilocular cysts and normal CA125. Of these, 76% did not change while 24% (54 women) had an increase in cyst size. Of those 54, six women also developed elevated levels of CA125. All 54 women underwent surgical management and two out of 54 had Stage 1B cystadenocarcinomas.

Both of those were among the six with elevated CA125 levels.

It is important to remember that not all cystic adnexal structures are ovarian in origin. Some will be paraovarian, peritoneal inclusion cysts from prior surgery, or even hydrosalpinges. In addition, vaginal probe ultrasound will identify many small ovarian sonolucencies (up to 18% in some series). The evidence suggests that the majority of unilocular ovarian cysts  $\leq 5$  cm are benign and remain unchanged or resolve. These lesions can be managed expectantly as long as there is no increase in size, change in morphology, or abnormal levels of CA125.

### POSTMENOPAUSAL BLEEDING

In the past, the first clue to possible endometrial carcinoma in postmenopausal women was vaginal bleeding. With the introduction of the vaginal probe for ultrasound endometrial detail not previously imaged transabdominally can be discerned.

After menopause the endometrium becomes thin and atrophic because there is no epithelial stimulation by estrogen. Normal postmenopausal endometrium will have a thin “pencil line” echo-genicity. Atrophic mucosa is prone to superficial punctate ulceration. In the past this was referred to as “senile endometritis.” It is the most common cause of postmenopausal bleeding but obviously it must be distinguished from hyperplasia or adenocarcinoma.

Endometrial carcinoma has a peak age of 55 years; 75% of cases are postmenopausal. The role of unopposed estrogen, as well as the risk factors of obesity, diabetes, hypertension, and low parity, are well known. Patients with postmenopausal bleeding are considered to have cancer until proven otherwise. In the past, such patients routinely were subjected to dilatation and curettage (D&C), first described in 1841. In the past, this was the most common operation in women. As early as the 1950s, however a review of 6,907 curettage procedures<sup>12</sup> found the technique missed endometrial lesions in 10% of cases. Of these, 80% were polyps.

A study of curettage before hysterectomy<sup>13</sup> found that in 16% of specimens less than one-quarter of the cavity was curet-

ted, in 60% less than one-half of the cavity was curetted, and in 84% less than three-quarters of the endometrial cavity was effectively curetted. Ultimately D&Cs were largely replaced with equipment like the Vabra aspirator (Berkeley Medevices, Berkeley, CA) which utilized a resterilizable metal cannula attached to suction that was like a “mini D&C” in an office setting. This was found to be 86% accurate in diagnosing cancer.<sup>14</sup> Subse-



**Figure 3:** Long axis view of a patient with postmenopausal bleeding. The central uterine echo measures 9.4 mm (calipers) and is not compatible with inactive atrophic endometrium.

quently, cheaper, smaller, less painful plastic catheters with their own internal pistons to generate suction became popular. One of these, the Pipelle® (Unimar, Wilton, CT.) device, was found to have similar efficacy but better patient acceptance when compared with the Vabra.<sup>15</sup> Rodriguez et al.<sup>16</sup> did a pathologic study of 25 hysterectomy specimens. The percentage of endometrial surface sampled by the Pipelle® device was 4% versus 41% for the Vabra aspirator.

In one widely publicized study<sup>17</sup>, the Pipelle had a 97.5% sensitivity to detect endometrial cancer in 40 patients undergoing hysterectomy. The shortcoming of that study was that the diagnosis of malignancy was known before the performance of the specimen collection.

In another study<sup>18</sup>, Pipelle® aspiration biopsy was performed in 135 premenopausal patients before curettage. Thirteen patients (10%) had different histologic results on Pipelle® biopsy as compared with curettage. It is interesting that only five of these patients had polyps, of which Pipelle® sampling missed three. In total, 18 patients had hyperplasia, of which Pipelle® sampling missed the diagnosis in

seven (39%), thus underscoring the often focal nature of that pathologic process.

Finally, in yet another study<sup>19</sup>, Guido et al. also studied the Pipelle® biopsy in patients with known carcinoma undergoing hysterectomy. Among 65 patients, Pipelle® biopsy provided tissue adequate for analysis in 63 (97%). Malignancy was detected in only 54 patients (83%). Of the 11 with false negative results, five (8%) had disease confined to endometrial polyps and three (5%) had tumor localized to <5% of the surface area. The surface area of the endometrial involvement in that study was <5% of the cavity in three of 65 (5%); 5% to 25% of the cavity in 12 of 65 (18%), of which the Pipelle missed four; 26% to 50% of the cavity in 20 of 65 (31%), of which the Pipelle® missed four; and >50% of the cavity in 30 of 65 patients (46%), of which the Pipelle missed none. These results provide great insight about the way endometrial carcinoma can be distributed over the endometrial surface or confined to a polyp. Because tumors

localized in a polyp or a small area of endometrium may go undetected, the authors in that study concluded that the “Pipelle® is excellent for detecting global processes in the endometrium.”

From these data, it seems that undirected sampling, whether through curettage or various types of suction aspiration, may provide false negative results, especially in cases in which the abnormality is not global but focal (polyps, focal hyperplasia, or carcinoma involving small areas of the uterine cavity.) Although there are many brands now available, clinicians often refer to these as a “Pipelle” much the same way that we will ask for a “Kleenex” when one wants a tissue or go to the “Xerox” machine even if it is a different brand of copier.

With the introduction and popularization of transvaginal ultrasound in the mid-1980s, investigators began to investigate women with postmenopausal bleeding. Nasri et al.<sup>20</sup> studied 93 patients with bleeding. All of the 51 women whose endometrium was 5 mm or less had inactive histology on pathologic evaluation. Of six patients with cancer, endometrial thickness ranged from

8 mm to 35 mm. In the first American study<sup>21</sup>, 30 women with postmenopausal bleeding were evaluated. Cancer was found in one woman with a 7 mm endometrial echo. Patients with inactive endometrium measured 6mm or less. The authors concluded that no cancer would be missed if curettage was not performed when the endometrium measured <5 mm in thickness. Moreover, this treatment path reduced the number of D&Cs by 37%.

Varner et al.<sup>22</sup> looked at 80 women, of whom 65 were asymptomatic and 15 had bleeding. In that group, 60 of the 60 (100%) with endometrial thickness (EM) <4 mm had inactive endometrium on biopsy. Of five women with a 5-mm endometrial thickness, two had inactive, one proliferative, one hyperplasia, and one carcinoma. The thickest endometrium associated with inactive was 5 mm. Two cancers were identified and they measured 5 mm and 9 mm, respectively. Granberg et al.<sup>23</sup> evaluated 205 women with postmenopausal bleeding. The endometrial cancers were found in endometria measuring from 9 mm to 25 mm in thickness. Atrophic endometrium ranged from 1 mm to 15 mm thick, although 150 out of 157 were ≤5 mm in thickness. It is unclear what the authors measured up to 15 mm and considered inactive and atrophic, but in retrospect, clearly some of these patients must have had polyps that were missed at the time of blind biopsy. They found that no curettage for endometria ≤5 mm in thickness would reduce the need for a D&C by 70% and not miss any cancers.

There has been tremendous confusion regarding the endometrial thickness. Acknowledging that an endometrial echo <4 mm to 5 mm in thickness in patients with bleeding seems uniformly associated with inactive, atrophic endometrial tissue on pathology (high negative predictive value) is not nearly the same as saying that endometrial measurements >4 mm to 5 mm are pathologic, especially if they are found incidentally in a non-bleeding patient.

The PEPI Study (Postmenopausal Estrogen Progesterone Intervention) had an endometrial surveillance arm.<sup>24</sup> In a multi-centered trial of 448 women the



**Figure 4:** Same patient as in Figure 3 after the introduction of saline at the time of sonohysterography showing a sessile posterior wall endometrial polyp (2.7 mm x 0.9 mm). The endometrium is otherwise thin and atrophic.

authors found that at a threshold of 5mm for endometrial thickness, transvaginal ultrasound had a negative predictive value of 99%. This caused the authors to conclude “when the endometrial echo measures 5 mm or less there is little need for tissue sampling for histologic evaluation.” However in that study the positive predictive value of endometrial echo >5 mm was 9% and for serious pathology (carcinoma, or hyperplasia) it was only 4%! Thus, the conclusion is that transvaginal ultrasound is not a good screening tool in non bleeding women.

Because ultrasound will not yield a tissue diagnosis, it is important that it be appropriately performed and documented. I am convinced that if one angles the transducer enough, eventually one can always find something linear and white, freeze the frame, place calipers, and call this the “endometrial echo.” A well-defined endometrial echo should be seen taking off from the endocervical canal. It should be distinct. Often fibroids, previous surgery, marked obesity, or an axial uterus may make visualization sub-optimal. If so, it is perfectly acceptable and in fact appropriate to conclude “endometrial echo not well visualized.” In these cases, the ultrasound can not be relied upon to exclude pathology. Saline infusion sonohysterography or hysteroscopy are both appropriate next steps in endometrial evaluation of such patients if such patients have a history of bleeding. If the scan is being done for other reasons inadequate visualization should be noted and recorded but no further evaluation is mandatory.

Endometrial echo measurements per-

formed by transabdominal ultrasound have not been studied or validated. Endometrial thickness should be measured on a sagittal (long axis) image of the uterus and the measurement should be performed on the thickest portion of the endometrium excluding the hypoechoic inner myometrium. It is a “double thickness” measurement from basalis to basalis. If fluid is present, usually associated with cervical stenosis and atrophy<sup>25</sup>, the layers are measured separately and should be symmetrical and can be added together, excluding the fluid.

The endometrial cavity is a three-dimensional structure and attempts must be made to image the entire cavity. Finally, recognizing the potentially pivotal role of transvaginal ultrasound in a diagnostic evaluation, a statement should be included in the report regarding the technical adequacy of the scan.

In summary, in women with bleeding, transvaginal ultrasound (and sonohysterography when necessary) forms a simple inexpensive well tolerated office procedure to triage patients to: **1.** no anatomic endometrial pathology (treated expectantly or hormonally); **2.** globally thickened endometrial tissue (candidates for blind sampling); or **3.** abnormally thickened focal tissue (including polyps and non global pathology) in need of visually directed sampling.

In women without bleeding, incidental abnormal findings on various imaging studies have not been scientifically evaluated. Benign quiescent anatomic structures may be common, never before detected, and easily seen with the improved resolution of all imaging modalities. Additional testing and evaluation has not been shown to be necessary or clinically relevant and in some cases may result in more harm to patients than good.

Obviously, decisions about what to do with incidental unexpected findings should be made on a case by case basis depending on a multitude of factors, but certainly a thin distinct endometrial echo in a woman with bleeding has a very high negative predictive value, but a thick endometrial echo in a women without bleeding (especially in women on estrogen) is unvalidated and does not require automatic tissue sampling.

The author revealed no potential conflicts of interest. The radiographic images in this article are courtesy of Dr. Goldstein.

## REFERENCES

1. Barber HR, Graber EA. The PMPO syndrome (postmenopausal palpable ovary syndrome). *Obstet Gynecol.* 1971;38:921-3.
2. Barber HR. Ovarian cancer: diagnosis and management. *Am J Obstet Gynecol.* 1984;150:910-6.
3. Hall DA, McCarthy KA. The significance of the postmenopausal simple adnexal cyst. *J Ultrasound Med.* 1986;5:503-5.
4. Rulin MC, Preston AL. Adnexal masses in postmenopausal women. *Obstet Gynecol.* 1987;70:578-81.
5. Goldstein SR, Subramanyam B, Snyder J, Beller U, Raghavendra N. The postmenopausal cystic adnexal mass: the potential role of ultrasound in conservative management. *Obstet Gynecol.* 1988;159:810-4.
6. Rodriguez MH, Platt LD, Medearis AL, Lacarra M, Lobo RA. The use of transvaginal sonography for evaluation of postmenopausal ovarian size and morphology. *Am J Obstet Gynecol.* 1988;159:810-4.
7. Levine D, Gosink BB, Wolf SI, Feldesman MR, Pretorius DH. Simple adnexal cysts: the natural history in postmenopausal women. *Radiology.* 1992;184:653-9.
8. Bailey CL, Ueland FR, Land GL, DePriest PD, Gallion HH, Kryscio RJ, van Nagell JR Jr. The malignant potential of small cystic ovarian tumors in women over 50 years of age. *Gynecol Oncol.* 1998;69:3-7.
9. Conway C, Zalud I, Dilena M, Maulik D, Schulman H, Haley J, Simonelli K. Simple cyst in the postmenopausal patient: detection and management. *J Ultrasound Med.* 1998;17:369-72; quiz 373-4.
10. Modesitt SC, Pavlik EJ, Ueland FR, DePriest PD, Kryscio RJ, van Nagell JR Jr. Risk of malignancy in unilocular ovarian cystic tumors less than 10 centimeters in diameter. *Obstet Gynecol.* 2003;102:594-9.
11. Nardo LG, Kroon ND, Reginald PW. Persistent unilocular ovarian cysts in a general population of postmenopausal women: is there a place for expectant management? *Obstet Gynecol.* 2003;102:589-93.
12. Word B, Gravlee LC, Widemon GL. The fallacy of simple uterine curettage. *Obstet Gynecol.* 1958;12:642-5.
13. Stockh RJ, Kanbour A. Prehysterectomy curettage. *Obstet Gynecol.* 1975;45:537-41.
14. Vuopala S. Diagnostic accuracy and clinical applicability of cytological and histological methods for investigating endometrial carcinoma. *Acta Obstet Gynecol Scand Suppl.* 1997;70:1.
15. Kaunitz AM, Masciello AS, Ostrowsky M, Rovvira EZ. Comparison of endometrial Pipelle and Vabra aspirator. *J Reprod Med.* 1988;33:427-31.
16. Rodriguez MJ, Platt LD, Medearis AL, Lacarra M, Lobo RA. The use of transvaginal sonography for evaluation of postmenopausal size and morphology. *Am J Obstet Gynecol.* 1988;159:810-4.
17. Stovall TG, Photopolus GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial cancer. *Obstet Gynecol.* 1991;77:954-6.
18. Goldchmit R, Katz A, Blickstein I, Caspi B, Dgani R. The accuracy of endometrial Pipelle sampling with and without sonographic measurement of endometrial thickness. *Obstet Gynecol.* 1993;82:727-30.
19. Guido RS, Kanbour A, Ruhn M, Christopherson WA. Pipelle endometrial sampling sensitivity in the detection of endometrial cancer. *J Reprod Med.* 1995;40:553-5.
20. Nasri MN, Coast GJ. Correlation of ultrasound findings and endometrial histopathology in postmenopausal women. *Br J Obstet Gynaecol.* 1989;96:1333-8.
21. Goldstein SR, Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. *Am J Obstet Gynecol.* 1990;163:119-23.
22. Varner RE, Sparks JM, Cameron CD, Roberts LL, Soong SJ. Transvaginal sonography of the endometrium in postmenopausal women. *Obstet Gynecol.* 1991;78:195-9.
23. Granberg S, Wikland M, Karlsson B, Norstrom A, Friberg LG. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. *Am J Obstet Gynecol.* 1991;164:47-52.
24. Langer RD, Pierce JJ, O'Hanlan KA, Johnson SR, Espeland MA, Trabal JF, Barnabei VM, Merino MJ, Scully RE. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. Postmenopausal Estrogen/Progestin Interventions Trial. *N Engl J Med.* 1997;337:1792-8.
25. Goldstein SR. Postmenopausal endometrial fluid collections revisited: look at the doughnut rather than the hole. *Obstet Gynecol.* 1994;83:738-40.

Non-Profit Org.  
U.S. Postage  
PAID  
Permit No. 1547  
Birmingham, AL

AMERICAN SOCIETY FOR  
REPRODUCTIVE MEDICINE  
1209 Montgomery Highway  
Birmingham, Alabama 35216-2809

Menopausal  
MEDICINE  
Volume 13, Number 1, Spring 2005