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# Care of the Surgically Menopausal Woman

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*Adapted from presentations on October 5, 2002, at the 13th Annual Meeting of the North American Menopause Society Supported by an Unrestricted Educational Grant from Solvay Pharmaceuticals*

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## Acute and Long-term Consequences of the Untreated Surgically Menopausal

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**S**urgical menopause is a primary indication for hormone therapy (HT), as well as an extremely important subject with many implications for younger women. Surgical menopause can occur 10, 20 or even 30 years before a natural menopause. Approximately 20% of all women 15 years of age and older have had a hysterectomy; and by age 60 the rate is just over 40%.<sup>1</sup> In fact, after Caesarean section, hysterectomy is the most common major surgical procedure among women, with an average of about 600,000 hysterectomies performed in the United States each year.

The clearest candidates for HT are younger women who have had a hysterectomy and concomitant oophorectomy. Although most women with oophorectomy are in the 40 to 44 age group, many women aged 35 to 39 also have had the procedure. These groups include hundreds of thousands of women who are candidates for HT.

The main indications for hysterectomy in the United States are uterine

leiomyoma, endometriosis and uterine prolapse. Among women under age 30, the main reasons for hysterectomy typically are related to menstrual disturbances and cervical dysplasia. Endometriosis is the primary reason for hysterectomy among women aged 30 to 34, leiomyoma among those aged 35 to 54 and uterine prolapse and cancer among those aged 55 and older. This suggests that younger women most commonly have conditions associated with compromised ovarian function. In addition, they likely have not been experiencing adequate hormone production from their ovaries for quite some time.

### Loss of Ovarian Function

Ordinarily, when considering the consequences of hysterectomy, we primarily concern ourselves with the loss of the ovaries. However, there is substantial literature suggesting that even when ovaries are retained after hysterectomy, they often do not function normally. In one study, 92% of women who had a hysterectomy before age 40 but retained their ovaries had symptoms of ovarian failure and hormone deficiency within two years of the procedure.<sup>2</sup> In another study of women coming to a menopause program in London, symptoms of ovarian failure developed in approximately 26% of the women within a year of their hysterectomy, even with their ovaries retained.<sup>3</sup> Within three years of the procedure, 40% had symptoms. Such results illustrate the importance of following up with these women, monitoring them for adequate

hormone replacement from their endogenous source and watching for early failures of ovarian production.

### Surgical versus Natural Menopause: Differences and Variations

Hysterectomy—with or without oophorectomy—is associated with a greater frequency and severity of symptoms compared with natural menopause. These symptoms include hot flashes, cardiac symptoms (angina, Syndrome X), migraine, urinary tract symptoms, sexual dysfunction and depression. In a survey of over 400 women who underwent natural or surgical menopause, those who had a surgical menopause reported more chest pressure, head pressure, changes in heart rate, changes in respiration and depression during the hot flash than women who had a natural menopause.<sup>4</sup> It has been shown that some women who present to cardiology clinics or emergency departments with crushing chest pain are found on further evaluation also to be suffering from migraines and hot flashes, as well as estradiol depletion. When no obvious evidence of coronary disease is present, the diagnosis often is presumed to be Syndrome X. The clinical definition of this is crushing chest pain that affects capacity to function, with an electrocardiogram that shows ischemic changes on exercise treadmill testing but a coronary angiogram indicating normal arteries.<sup>5</sup> Approximately 75% of all Syndrome X patients are women, and 60% of all women with Syndrome X have had a hysterectomy.<sup>6</sup> This clinical picture suggests that many women experience a system-wide vascular distur-

bance secondary to estradiol depletion.

In addition to symptoms, there also is a greater frequency and severity of medical conditions associated with hysterectomy with or without oophorectomy as compared with natural menopause. These conditions include higher incidences of cardiovascular disease/myocardial infarction, stroke, osteoporosis and clinical depression. In the Nurse's Health Study, for instance, the relative risk (RR) for coronary artery disease after bilateral oophorectomy was 2.5.<sup>7</sup> The RR after simple hysterectomy was 1.5. This represents a very real and substantial increase in risk that occurs without HT.

Establishment of a relation between atherosclerotic disease and female castration dates back to the 1940s. By the 1950s an association was made between female castration and angina.<sup>8</sup> Later studies showed that up to 95% of women who underwent surgical menopause 15 or more years before the age of natural menopause had atherosclerosis, compared with 74% of women who experienced natural menopause.<sup>9</sup> Yet another study found an adjusted RR of MI of 7.7 among women who underwent the procedure before age 35 and did not receive hormone replacement.<sup>10</sup> These younger women especially need to be counseled not to fear HT in the wake of the Women's Health Initiative (WHI) announcement. It is important to emphasize that the average age of women when they enrolled in WHI was 63. It is not reasonable to extrapolate those findings to women in their 30s or early 40s. Nevertheless, many younger women have rejected HT based on the WHI findings and their lack of knowledge about the potential benefits of HT in their particular situation.

### Other Issues Related to Surgical Menopause

Several studies have indicated that surgical menopause predisposes women to bone loss. Hysterectomy with or without oophorectomy has been associated with significantly diminished bone mineral density and increased risk of osteoporosis compared to natural menopause.<sup>11, 12</sup>

Women also may experience vaginal dryness and dyspareunia after hysterectomy. There is a clear relationship between estradiol levels and dyspareunia. In addition to the physical implications of these problems, there also is the emotional and psychological impact of vaginal dryness and dyspareunia to consider. Many women will experience anger, fear, depression and/or loss of sexual feelings and interest. They may feel as though they are no longer sexual beings. HT is important for these women because it not only can reduce vaginal dryness but also restore sexual desire, enhance arousal and improve the frequency of sexual intercourse and orgasm.

While the issue sounds simple, only 8% to 10% of postmenopausal women have used HT for more than two years. One-third of women have never even had a consult with a physician regarding HT.<sup>13</sup> Another third have had a consult regarding HT but have never used the medication.

### Conclusions

Hysterectomy-induced early menopause is common and occurs most frequently among women aged 40 to 44. Hysterectomy with or without oophorectomy is associated with a greater frequency and severity of symptoms and medical conditions compared with natural menopause.

Women should be offered HT after hysterectomy, but many are not offered the hormones or decline to take them due to lack of knowledge about the benefits and risks, misinformation about their effects and fear of heart disease or cancer stemming from the publication of the WHI report. Improved knowledge and counseling regarding the benefits of HT can help more women take advantage of a treatment that reduces many adverse experiences that occur after hysterectomy, including sexual and psychological issues.

**Dr. Sarrel serves on the Speakers Bureau for Solvay Pharmaceuticals and Pfizer Inc.**

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## Pharmaceutical Treatment Options for the Female Androgen Insufficiency Syndrome

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### Introduction

The Princeton Consensus Statement of June 2001 defines the female androgen insufficiency syndrome as diminished sense of well-being, dysphoric mood and/or blunted motivation with persistent or unexplained fatigue and sexual functioning changes, including decreased libido, pleasure and sexual receptivity.<sup>1</sup> Other potential signs and symptoms include bone loss, decreased muscle strength and changes in cognition and memory. Since most of these

symptoms are non-specific, symptoms alone are clearly not enough for the diagnosis of androgen insufficiency.

Improving vaginal dryness and dyspareunia through estrogen replacement must be done prior to setting goals for androgen insufficiency therapy. However, the goal with regard to vaginal dryness should be to provide normal genital tissue, which transcends simply treating the vaginal dryness. The importance of appropriate estrogen and/or androgen replacement therapy extends beyond the vaginal epithelium. Such therapy is critical to the vasodilation and normal female sexual arousal response. The goal should be normal functioning of both the vascular and nervous systems in the genital area, ultimately facilitating a normal sexual response.

Testosterone, the bio-identical naturally occurring compound, is easily and rapidly changed to estrogen in most tissues in the human body. In women, marked changes in the production rates of all androgens, including dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (Andro) and testosterone, occur as women age and are distinct from changes occurring at menopause.<sup>2</sup> In oophorectomized women, a small additional decrease in androstenedione and testosterone may be present compared to women who have undergone a natural menopause. The most significant changes in bioavailable androgens in postmenopausal women occur with the introduction of oral estrogen therapy (ET). Data indicate that the introduction of oral estrogens may cause as much as a 300% increase in sex-hormone-binding globulin (SHBG). In women, only about 1% of testosterone circulates freely in the blood. Of the remaining 99%, about 80% is strongly bound to SHBG; and approximately 19% is loosely bound to albumin.<sup>3</sup> Given the already low levels of circulating free testosterone in postmenopausal women, a 300% increase in SHBG could have a profound effect on the final concentrations of free and bioavailable testosterone.

Estrogen is the “female hormone” in name only. In fact, androgens are far more “female” hormones than estradiol. Men actually produce similar or greater amounts of estradiol compared to women. Both estrogen and testosterone should be more correctly labeled “human” as opposed to “male” or “female” hormones. These facts should be included in discussions with patients.

Androgens decline with age beginning as early as age 20 and continuing throughout a woman’s life. Importantly, oophorectomy initiates an additional decline in androgens not seen in women who undergo a natural menopause. For women with androgen insufficiency syndrome, ET is necessary to reduce the vaginal and genital symptoms and to increase vascular responses and androgen receptor content. Androgen replacement therapy in physiologic doses can be used to treat the androgen insufficiency syndrome, although additional larger scale studies are necessary to confirm and expand our knowledge on this point.

### **ET’s Impact on Endogenous Androgens**

In a study that examined the effects of ET on endogenous androgens in 301 current users and 676 non-users, Tazuke and colleagues found that while total testosterone was not significantly changed, free testosterone was significantly reduced because of the estrogen-induced SHBG increase.<sup>4</sup> These same investigators found a significant reduction in both the adrenal androgens DHEA-S and androstenedione. To assess these findings in a prospective randomized placebo-controlled clinical trial, we examined the effects of standard doses of estrogen or estrogen and androgen together.<sup>5</sup> We used esterified estrogens 0.625 mg and 1.25 mg (Estratab®) or an estrogenically equivalent combination of esterified estrogens and the androgen methyltestosterone (Estratest HS® or Estratest®). In this study, we demonstrated a clear dose-response relationship with ET leading to a significant increase in SHBG, while the orally-

administered estrogen/androgen compounds decreased SHBG. Bioavailable testosterone decreased with ET and increased with estrogen/androgen treatment because of the decreases in SHBG noted earlier. We also observed similar, although less dramatic, reductions in DHEA-S and androstenedione during ET as reported previously.<sup>4</sup> Importantly, we observed no such changes in the adrenal androgens with the combination of estrogen and androgen.

### **Estrogen’s Effects on Adrenal Androgens**

There are several possible mechanisms of action that may explain estrogen’s inhibitory effects on adrenal androgen production. The most plausible of these effects is that estrogen inhibits 17-20 desmolase, an enzyme that is present in both the fetal and adult human adrenal gland and is responsible for the production of androgen precursors in both men and women.

### **Other Androgen Therapies**

It has been generally accepted that women experience an increase in overall genital sensation and desire for sex if they are started on estrogen or switched from estrogen to estrogen/androgen in combination. In addition, studies involving tibolone, an agent with weak estrogenic, progestational and androgenic properties that is *not* currently available in United States, have been promising. Tibolone has 1/50th the estrogenic potency of ethinyl estradiol, 1/8th the progestogenic potency of norethisterone and 1/20th the androgenic potency of methyltestosterone.<sup>6,7</sup> In one study of 437 women who had been postmenopausal for at least one year, tibolone 2.5 mg/d was compared with 17-beta estradiol 2 mg/d and norethindrone acetate (NETA) 1 mg/d. The end-point was the McCoy Sex Scale Questionnaire. Both groups of women reported positive effects on sex life with improvement in dyspareunia, vaginal dryness, arousal, enjoyment of sex, sexual satisfaction and increased frequency. The tibolone group reported

greater improvement in sexual event frequency, satisfaction and enjoyment compared to the NETA group.<sup>8</sup> It should be noted, however, that this study had no placebo group.

DHEAS is currently in development for the treatment of androgen insufficiency in women. In one study, treatment with DHEA improved the frequency of sexual thoughts or fantasies, degree of sexual interest, level of mental satisfaction with sex and level of physical satisfaction with sex.<sup>9</sup> However, studies regarding the content of over-the-counter DHEA supplements suggest that all DHEA is not the same. Of 16 supplements of DHEA purchased by investigators, three products contained absolutely no DHEA, four contained less than 20% of the amount suggested on the label—with some as low as 70% of label claim—while one product had 150% of label claim in the capsule or tablet.<sup>10</sup>

Well-designed placebo-controlled trials clearly are needed in this area. While a few studies of testosterone administered via transdermal patches have shown improvements in pleasure, orgasm and frequency of sex, dramatic placebo responses also were seen.<sup>11</sup> Additionally, improvements have been seen in libido, sexual activity, satisfaction, pleasure and orgasm in studies involving sublingual estrogen pellets. At the same time, there are a number of pastes, gels and emulsions in development that have been shown to convey very constant levels of testosterone. One testosterone gel in development called LibiGel® (BioSante) currently is being tested for its efficacy of testosterone delivery and its impact on sexual function.

### Side Effects

One drawback of estrogen/androgen therapy is its side effects. Although serious side effects are uncommon, mild ones may occur. They include oily skin, acne and hirsutism. In one study of 311 women randomized to Estratest HS, Premarin 0.625 mg/d, Estratest or Premarin 1.25 mg/d, hirsutism was

uncommon in all groups at two years.<sup>12</sup> Early data from studies of a transdermal testosterone patch showed no differences in hair loss, hair gain, breast pain, hot flashes or acne even on doses as high as 450 mcg/d of transdermally administered testosterone.

An additional long-term concern with therapeutic androgen use is the effect on the lipid and lipoprotein profile. Some research has demonstrated a decrease in triglycerides in surgically menopausal women on oral androgens, but there also have been decreases seen in high-density lipoprotein (HDL) cholesterol.<sup>13</sup> The testosterone patch data (mentioned above) have shown generally unchanged lipid profiles with the exception of a small decrease in HDL in those on the highest dose patch (450mcg/d). Those on the two other patch doses (150mcg/d and 300 mcg/d) showed no decreases in HDL and no other effects on lipids.

### Conclusions

Androgen insufficiency syndrome, which is present in some postmenopausal women, presents as a constellation of common, nonspecific symptoms. In some women, these symptoms may be wrongly attributed to other conditions or accepted as traditional signs of aging. It is important for clinicians to be receptive and willing to have a dialogue with postmenopausal patients, particularly concerning problems of libido and sexual enjoyment, to determine if the androgen insufficiency syndrome may be causing their complaints.

Although we are just beginning to understand how best to treat androgen insufficiency, therapeutic options are available and many others are on the horizon. Androgen therapy—in the form of pills, patches, troches and gels—offers the potential for restoring well-being, sexual function, libido, sexual receptivity and pleasure among women and their partners struggling with hormone deficiency. More studies are needed in this important area of research to weigh the long-term health implications of andro-

gen therapies against the risks of long-term hormone deficiency.

**Dr. Simon reports no conflicts.**

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## Indications for Bilateral Oophorectomy and Treatment of Residual Pathology

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**M**ost clinicians know the usual and common indications for bilateral

oophorectomy—ovarian, endometrial or fallopian tube cancers; stage IV endometriosis; bilateral tubo-ovarian abscess (ruptured or chronic); familial breast-ovarian cancer syndrome; severe premenstrual syndrome; and prophylactic oophorectomy. Approximately 600,000 hysterectomies are performed each year in the U.S.; and about 50% of those procedures involve oophorectomy.<sup>1</sup> Unfortunately, because the ovaries are so easily removed at the time of hysterectomy and because this has been a long-practiced technique, there has been less than optimal investigation of other ovarian-cancer prevention techniques—such as screening and early diagnosis. As a result, despite ovarian ultrasound, the CA 125 antigen test and other tumor marker and genetic tests in development, nothing has proven to be sensitive or specific enough to detect the early presence of cancer. This is important because of the prevalence of ovarian cancer and the fact that 70% of ovarian cancer patients present after the disease has spread beyond the ovary.

To put the urgency of this issue into perspective, ovarian cancer is the fourth most common cause of cancer death, accounting for more than 14,000 deaths each year in the U.S. A woman's lifetime risk of ovarian cancer is approximately 1 in 70. Between 4% and 14% of women diagnosed with ovarian cancer have had a previous hysterectomy with retention of the ovaries.<sup>2</sup> On the other hand, primary peritoneal cancer occurs in 2% to 11% of women who have had a previous hysterectomy with oophorectomy, so removal of the ovaries does not offer complete lifetime protection from cancer.<sup>3</sup>

The ovary is a complex metabolic organ. The follicles produce both androgens and estrogens, and stromal tissue synthesizes androgens only. During menopause, when follicles decrease, both androgen and estrogen levels decrease as well. However, the ovary remains a source of endogenous androgens that are converted to estrogen. The role of those endogenous andro-

gens and the consequences of their premature removal through oophorectomy may be significant, but research has yet to shed much light on this issue.

### Determining Risk

According to the 1995 National Institutes of Health Consensus Conference, there are three main factors contributing to ovarian cancer risk: low parity, decreased fertility and delayed childbearing with no oral contraceptive use. More recently, studies have suggested that estrogen therapy (ET) in women with or without a previous hysterectomy and ovarian retention also may increase the risk of ovarian cancer.

Researchers have put much time and effort into an attempt to identify women at highest risk. They have determined that genetic markers are helpful; however, only 7% of ovarian cancer patients have a positive family history. Of those, 3% to 9% may have hereditary cancer syndromes. Women in direct genetic lineage of family cancer syndromes may have up to a 50% lifetime risk of ovarian cancer, with *BRCA1* and *BRCA2* increasing risk by 45% and 25%, respectively. The risk is even higher for those women who carry both. In addition, there is Lynch syndrome II, a syndrome of familial colon cancer that also is associated with breast and ovarian cancer. In these women, an annual physical examination with the bimanual rectovaginal examination, CA 125 testing and transvaginal ultrasound are appropriate. Prophylactic oophorectomy is also very appropriate in this population when childbearing has concluded, usually between the ages of 35 and 40 years.

Clinicians commonly encounter women with one or two relatives affected by ovarian cancer. Investigators involved in the Gilda Radner Familial Ovarian Cancer Registry examined the relationship between the relative who had ovarian cancer and affected female family members. In the majority of cases of ovarian cancer, the relationship was mother-daughter (49.5%), with a

smaller percentage being sister-sister relationships (38.5%). Most women with a positive family history do not have one of the recognized hereditary cancer syndromes. However, they do have an increased lifetime risk, ranging from a baseline of 1.6% to a high of 5% to 7%. These women clearly are at increased risk, but this risk is not high enough to warrant routine prophylactic oophorectomy.

Women with no family history of ovarian cancer pose a different problem. If we assume that ovarian cancer has an incidence of about 22,000 new cases per year, at least 1,000 cases could be prevented if prophylactic oophorectomy was diligently practiced concurrent with hysterectomy. On the other hand, prophylactic oophorectomy would lead to a shorter overall life expectancy if ET compliance were less than perfect. Given this conundrum, the decision about whether to perform prophylactic oophorectomy in a woman with no family history of ovarian cancer should be based on the wishes and concerns of the individual woman.

Once the ovaries are removed, exogenous estrogens are almost always needed for symptom relief. The need for continuous ET confers additional concerns, including a lifetime risk of breast cancer of 1 in 8. Similarly, the Women's Health Initiative (WHI) has raised serious concerns that long-term hormone therapy (HT) may increase the risk for cardiovascular disease, pulmonary embolus/deep venous thrombosis, stroke and breast cancer. We currently are awaiting the results of the ET-only arm. If this arm of the WHI confirms these risks, women who have had prophylactic oophorectomy—like women who are diagnosed with breast cancer—will be faced with the decision to discontinue ET. If they choose to do so, some of these women will experience intense symptoms such as hot flashes, night sweats and insomnia.

### Residual Disease

In women who have had a hysterecto-

my with retention of the ovaries, additional surgery is needed in up to 5% of patients.<sup>4</sup> The most common reason for reoperation is pain in the retained ovary or ovaries. Ovarian remnant syndrome is a fairly uncommon complication of oophorectomy that involves functional ovarian tissue being left in situ after an intended bilateral oophorectomy. Symptoms include chronic pelvic pain and/or dyspareunia. Rectoperitoneal fibrosis can occur because the ovary becomes a retroperitoneal organ after removal. Occasionally, ureteral obstruction has been reported. The diagnosis of ovarian remnant syndrome is made based on the presence of pelvic tenderness with or without mass. An FSH or estradiol test, as well as an ultrasound, may be helpful.<sup>5</sup> Hormonal manipulation (i.e., Depo-Leuprolide) can assist in the diagnosis and medical treatment of ovarian remnant syndrome. Preoperatively, ovulation induction with clomiphene citrate can be used to identify the remnant. If removal is necessary, a high frequency of bowel and ureteral injuries are reported with reoperation, so it is important to remember a bowel prep has to be performed. Additionally, consideration should be given to a planned joint surgery between a general surgeon and a urologist on standby.

Ovarian remnant syndrome appears to be more common with laparoscopic procedures. In a study of 19 patients who had undergone bilateral oophorectomy or unilateral oophorectomy, the increased risk of ovarian remnant syndrome was attributed to improper tissue extraction or misapplication of the loops and the stapler or the cautery on the infundibulopelvic ligament.<sup>6</sup>

Another study of 109 patients who had symptom recurrence after hysterectomy for endometriosis found that 11 (1 in 10) had recurrent pain and 4 (1 in 20) required reoperation.<sup>7</sup> Of 29 women in the same study who had ovarian conservation, a majority (18 of 29) had recurrent pain and about one-third (9 of 29) required additional surgery. In other

words, women with ovarian conservation and endometriosis were six times more likely to have recurrent pain and eight times more likely to require surgery. There was no advantage in this particular cohort of delaying hormone treatment after oophorectomy to see if the residual endometriosis would resolve on its own.

Studies of women with recurrent pelvic endometriosis have found no increased risk of recurrence among women not receiving HT. In one study of 115 women who were on hormone therapy and 57 who had received no hormones, there was no recurrence rate in women receiving hormone therapy and a small recurrence rate of 3.5% in women who had not received HT. The risk factors for recurrence included peritoneal involvement > 3 cm or incomplete primary surgery.<sup>8</sup>

Some women will have endometriosis that persists after oophorectomy. An observational study of 75 such women who had biopsy-proven endometriosis prior to bilateral oophorectomy found that those requiring additional surgery for recurrent or persistent endometriosis were older than women who had their ovaries retained. The women who required additional surgery also were more likely to have intestinal involvement.<sup>9</sup> Fortunately, pain improves in most of these patients after surgical excision.

Finally, although it is not common, endometriosis of the bladder should be considered in the diagnosis of a patient presenting with recurrent endometriosis. The symptoms are very similar to overactive bladder syndrome and include urgency, frequency, urge incontinence, pain and dyspareunia. The symptoms are very similar to interstitial cystitis. Bladder resection is not required in these cases; and good clinical improvement usually is seen with combination oral contraceptive pills or the addition of a progestin to ET.

## Conclusions

Approximately half of all hysterec-

tomies involve oophorectomy. While there are reasonable arguments in favor of prophylactic oophorectomy concurrent with hysterectomy, there are a number of equally reasonable counterarguments for retaining otherwise healthy ovaries.

Residual pathology is a concern, since a significant percentage of women who have had their ovaries retained will require additional surgery for pain in the retained ovary or ovaries. Residual endometriosis is also a concern and can occur even in women who have had their ovaries removed, since remnants occasionally can be left in situ during an intended bilateral oophorectomy. A careful assessment of symptoms before and after hysterectomy is crucial to making the choice about whether to remove or retain the ovaries. Assessment also will facilitate understanding of additional problems that may occur following hysterectomy with or without oophorectomy. ■

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