Fertility Following OCP Use

A review of fertility following the discontinuation of oral contraceptives (OC) was done for study publications between 1960 and 2007. The return to fertility within 12 months of OC discontinuation was 72% to 94% and was similar to that of discontinuing the levonorgestrel IUD (75%–79%), the copper IUD (71%–92%), and barrier methods (95%). One study even demonstrated an increase in fertility with 1 to 2 years of OC use (97%) compared with 6 months or less (84%). (Fertil Steril 2006;85) Fertility after extended use of OC was also not affected, and there currently appears to be no difference in post-pill fertility in those who use continuous or cyclic regimens. The authors did acknowledge that their review revealed a slight delay in fertility within the first 3 months of OC discontinuation.

Comment: Many women, and even clinicians, especially alternative practitioners, still promote the notion that fertility is altered as a result of past use of OC. While the authors did not point this out, a 95% fertility rate post barrier methods vs. a 75% to 79% rate with post-levonorgestrel IUD does present a meaningful difference. Other than that ... clinicians should offer the science-based information found in this review to help women understand that their fertility post-OC use is not hampered compared with other methods of contraception.


More Results from the WHI: Time of Initiation of Hormone Therapy

The Women's Health Initiative (WHI) results should be well known by most clinicians by now: postmenopausal hormone therapy (HT) with conjugated equine estrogens either alone in hysterectomized women or in combination with medroxyprogesterone acetate did not lower the risk for coronary heart disease (CHD). Most women in the WHI were more than 5 years past menopause, and it was thought that this might be too late to benefit from the potentially cardioprotective benefit of HT. WHI researchers have reexamined the data in an attempt to determine whether initiating HT within the first 5 years of menopause might impart a different result than if initiated later after menopause. Their reanalysis included the estrogen-only subcohort and the estrogen/progestin group.

Both the estrogen-only HT users and the estrogen/progestin HT group had a slight increased risk for CHD, stroke, and venous thromboembolism, regardless of whether they initiate HT 5 years or more than 5 years after menopause. Women who started either regimen within the first 5 years of menopause had a higher risk for invasive breast cancer than did those who initiated HT later. It should be pointed out that the nature and duration of HT use before entering the WHI study might influence the results, but the researchers still conclude that the risk outweighs the benefits for combined estrogen/progestin use and there is lack of a cardioprotective benefit for estrogen-only users who start HT within 5 years of menopause.

Comment: The initial WHI findings were a surprise to most, in that estrogen/progestin did not reduce the risk of CHD, despite several decades of observational studies concluding that it did. The slight increase for risk of breast cancer in the estrogen/progestin group was less of a surprise, but certainly did alter the habits of clinicians and menopausal women. In at least the past couple of years, many clinicians have been reading the research which proposed that women who initiate HT within the first 10 years of menopause may have a lower risk of CHD than those who initiate it 10 years or more past menopause (JW Women's Health. June 2007:43; JAMA. 2007;297:1465). The WHI findings in the current report do not support this thinking, but one might ask why there is a difference. The current analysis is different in that they analyzed the time between menopause and first use of HT vs. time between menopause and study entry, with prior use of HT now seeming more important. It is important to keep in mind that the overall absolute increased risk for breast cancer in combined HT users is very small: 4 cases per year per 1,000 women on HT vs. 3 cases per year per 1,000 women not taking HT.

Hormone Therapy and Ovarian Cancer

Two previous studies published in 2007 reported that HT is associated with an increase in risk of ovarian cancer. In a prospective study throughout Denmark, 910,000 women 50 or older were followed for an average of 8 years, whereby 3068 ovarian malignancies were diagnosed. Of the study participants, 63% had never used HT, 22% were previous users, and 9% were current users.

Current and previous HT users had a higher risk for ovarian cancer compared with women who had never used HT. Current users had a relative risk of 1.38 and previous users had a 1.15 relative risk. Even use of HT for less than 4 years was associated with the excess risk, and using HT longer than 4 years did not particularly increase risk further. Ovarian cancer risk fell and was similar to that in never-users by the second year after discontinuing HT. The risk was similar in women whether they had used estrogen only, or estrogen and any type of progestin. In women who used estrogen only, oral delivery had a relative risk of 1.34, but transdermal only 1.13, compared with never-users. Vaginal estrogen delivering systemic doses was associated with a relative risk of 1.23.

Comment: Once again, modest elevations in risk of ovarian cancer are seen in HT users. However, this is an observational study, with inherent bias such as more medical care in HT users than nonusers and thereby more diagnostic testing. This bias is even more likely in this study, with the finding that women who even just started HT had an excess ovarian cancer risk. The overall incidence of ovarian cancer is very small, so this finding, even if true, has less impact in patient counseling and benefit/risk discussions. However, in a woman with a first-degree relative history of ovarian cancer, this study would have more influence in my thinking. In addition to using risk-reduction strategies backed by some evidence, such as green tea, maintenance of optimal weight, and preventive use of OC during the reproductive years, I would try to find nonhormonal solutions to menopause management in women with a family history of ovarian cancer.


Hormone Therapy and Lung Cancer

In a post-hoc analysis of the Women’s Health Initiative (WHI) estrogen/progestin study, investigators assessed the incidence and mortality rates of lung cancer during treatment and posttreatment follow-up. Patients in this placebo-controlled trial received estrogen/progestin or placebo for an average of 5.6 years and were followed for an average of 2.4 years postintervention.

The overall incidence of lung cancer was similar in the hormone therapy (HT) and placebo groups after 5 years of follow-up, although there were more cases of non-small-cell lung cancer diagnosed in the HT group. Metastatic non-small-cell cancer was more prevalent in the HT group and mortality from non-small-cell lung cancer was more common in the HT group. Mortality from small-cell cancer did not differ between HT and placebo groups.

Comment: Previously published observational data show inconsistent associations between HT and lung cancer incidence and mortality. A finding juxtaposed with the current study is the Nurse’s Health Study, suggesting that women with a bilateral oophorectomy have an excess risk for lung cancer. (JW Women’s Health. June 2009:44; ObGyn. 2009;113:1027). Not to be forgotten: smoking is the most significant risk factor for lung cancer.

I would conclude from the current study that in smokers with menopausal symptoms, HT should be discouraged. However, it should be remembered that smokers tend to have more severe vasomotor symptoms and lower bone density with a higher risk for osteoporotic fractures. These are two more reasons to be more aggressive about stop-smoking strategies. In addition, in women on HT and with non-small-cell lung cancer, it would seem prudent to discontinue HT, while providing alternatives for menopause symptom management and bone health.


Salivary Testosterone Testing in Postmenopausal Women Receiving Testosterone Treatment


Fifty-six women were given either a 300 mcg transdermal testosterone patch or placebo twice weekly for the treatment of their hypoactive sexual desire disorder (HSDD) in a double-blind, parallel group, placebo-controlled study. Investigators compared circulating serum levels of total testosterone, free testosterone, and bioavailable testosterone (consisting of free testosterone and albumin-bound testosterone) with salivary levels in postmenopausal women with HSDD. Serum and salivary samples were collected concomitantly at weeks 24 and 52 in the naturally menopausal women and at weeks 12, 24, and 52 in the surgically postmenopausal women. Serum samples were validated by Quest/Nichols Institute and salivary measurements by radioimmunoassay at Aeron Laboratory.

Salivary levels of testosterone measurements did not increase at weeks 12, 24, or 52 after testosterone treatment, while serum levels were increased and in the physiological range of premenopausal women after use of the transdermal testosterone patch. Salivary testosterone measurements did not increase with treatment, and did not correlate strongly with serum testosterone measurements. This finding was true of bioavailable testosterone, free testosterone, and total testosterone.

Comment: Levels of testosterone are even lower in the saliva than in the plasma. Salivary levels can also vary greatly, depending on how the salivary secretion is stimulated and the method of testing used (radioimmunoassay or ELISA). Other technological challenges exist for both serum and salivary testing in the accuracy of actual measurements of testosterone using radio-labeled testosterone in cross
Intravaginal DHEA and Sexual Function in Postmenopausal Women

This prospective, randomized, double-blind placebo-controlled trial evaluated the effect of daily local intravaginal DHEA ovules for 12 weeks in postmenopausal women. The main assessment criteria were sexual dysfunction parameters of libido, arousal, orgasm, and dyspareunia in postmenopausal women who have vaginal atrophy.

Two hundred eighteen postmenopausal women were randomized to receive a daily ovule of placebo or 3.25, 6.5, or 13 mg of DHEA. The ovules contained Prasterone in a lipophilic base manufactured by Recipharm of Sweden.

At 12 weeks, compared with placebo, the 13 mg ovule improved ratings by 68% in the Abbreviated Sex Function arousal/sensation domain, the arousal/lubrication domain by 39%, orgasm by 75%, and dryness during intercourse by 57%. DHEA also fared better than placebo in the desire domain of Menopause Specific Quality of Life 49% to 23%.

Comment: The main thing I can say here is, “way cool.” This study opens the door for new options for sexual dysfunction in women — including the difficult-to-successfully-treat low libido. In a related study by the same authors, serum levels of vaginal DHEA showed no or minimal changes during the study period of up to 12 weeks. All values remained within the normal range of postmenopausal women. (Labrie F, Archer D, Bouchard C, et al. Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. Menopause. 2009;16(3):897–906.) This bodes well for safety issues. I will be adding 13 mg of a DHEA suppository to my compounding pharmacy prescriptions.


Vaginal Estriol/Progesterone in Postmenopausal Women

The objective of this study was to assess the efficacy and safety of intravaginal estriol and progesterone in postmenopausal women with atrophic vaginitis. Nineteen healthy postmenopausal women with atrophic vaginitis received a suppository of 1 mg estriol and 30 mg of progesterone. One suppository was inserted vaginally once daily for 2 weeks and three times weekly for a total of 6 months. Evaluations included vaginal pH, maturation index, urinalysis, self-reported vaginal dryness, menopausal quality of life, serum estriol and progesterone levels, and endometrial biopsies.

The maturation index, vaginal pH, and vaginal dryness ratings significantly improved at 3 and 6 months compared with baseline. The average maturation index improved from 40 at baseline to 57.5 at 3 months and 55 at 6 months. Vaginal pH also improved from an average of 6.0 at baseline to 4.5 at 3 and 6 months. Self-assessment of vaginal dryness improved from an average value of 9.0 to 2.0 at 3 months and 1.0 at 6 months. Seventeen of the 19 women were sexually active, and all 17 reported improvement in vaginal dryness during sexual activity. The average values also improved for both libido and urinary frequency, two other issues related to vulvovaginal atrophy. None of the women reported mastalgia, urinary tract infections, or nausea. One woman had vaginal spotting during the first 2 weeks of suppositories. Endometrial biopsy at 6 months showed an inactive endometrium. No hyperplasia or cancer was seen in any of the participants. Serum estriol concentrations were similar to baseline at week 2 and months 3 and 6, suggesting minimal systemic absorption. Serum progesterone levels significantly increased from enrollment but did not continue to do so during the maintenance period of three times weekly.

Comment: This pilot study is not really a surprise to those of us accustomed to using vaginal estriol in postmenopausal vulvovaginal atrophy. Most practitioners do not add progesterone to their compounded estrogen vaginal suppositories because it is generally agreed that 2 to 3 times weekly long-term vaginal estrogen (whether estriol, estradiol, or conjugated equine estrogens) is considered safe for the endometrium. However, there may be cases where this current study will have clinical meaning and provide guidance for patient care. It is always important for practitioners to remember that improving vaginal health, and particularly vaginal dryness and dyspareunia, is the first step in improving libido.


Oral Contraceptives in Women with Family History of Breast Cancer

World Health Organization researchers identified 10 case-control or cohort studies and 1 pooled analysis in which breast cancer risk in oral contraceptive (OC) users was compared with nonusers in women with a family history of breast cancer. Seven of the case-control or cohort studies and the one pooled analysis showed no association between OC use and invasive breast cancer in women who had a family history of breast cancer. That leaves three studies that did show higher risk among OC users compared with nonusers, but those associations were only among specific subgroups. In addition, one study observed that OC use in women with a positive family history was not associated with increased risk for ductal carcinoma in situ.

Comment: Most of my patients with a family history of breast cancer believe that they should not take OC because it would increase their risk. This systematic review provides some level of reassurance that using OC will not increase
breast cancer risk further in women with a positive family history of breast cancer.

New Developments in Emergency Contraception
A single-dose formulation for an emergency contraceptive pill (ECP) has been approved by the FDA. Plan B One-Step is a single tablet that contains 1.5 mg of levonorgestrel. The original Plan B was two tablets, each containing 0.75 mg levonorgestrel, with each tablet taken 12 hours apart. Plan B One-Step is available without a prescription but behind the counter for women 17 and older and by prescription only for women younger than 17. "Next Choice," a generic version of the two-dose levonorgestrel ECP product, has also been approved. This is available by prescription for women younger than 17 and without a prescription for women 17 and older.

Comment: Simpler will likely be better in this case, resulting in improved effectiveness of ECP. Overall, unintended pregnancy rates have not dropped in the US, despite the availability of ECPs. With the availability of the new generic, "Next Choice," costs will be about $10 lower and more women will likely have access. Perhaps in time, retail pharmacies that have $4 generics may add generic ECPs to their list.

Is It Beneficial to Stop HRT Before Screening Mammography?
Some clinicians have proposed that menopausal women discontinue their hormone therapy (HT) prior to screening mammography, in the hopes of decreasing breast density and improving the mammographic breast cancer detection rate. Women using HT were randomized to no suspension of HT or 1-month or 2-month suspension prior to their screening mammography.
There was a similar recall rate in all three groups (11% no suspension, 12% 1-month suspension, and 10% 2-month suspension), although suspension of HT was associated with significantly lower mammographic breast density. In women who suspended their HT, more than 85% of them had a return of their hot flashes.

Comment: Additional imaging is recommended in more than 10% of women receiving their screening mammogram. Fortunately, at least 95% of the recalls are not associated with diagnoses of breast cancer within the coming year. Higher breast density is associated with an increased risk for breast cancer, combination estrogen/progestin in particular is associated with increases in breast density, and breast density is associated with a lower mammographic sensitivity and specificity. It appears that the clinical idea of discontinuing HT for 1 or 2 months prior to screening has no advantage in breast cancer detection, and most women will also have a return of their hot flashes within this amount of time. It is interesting to note that when recruiting for this study, almost two thirds of the 4884 eligible women chose not to participate because they were not willing to discontinue their HT.

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