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INSIDE

The WHI Reports on Fracture and Gynecologic Cancers

ABSTRACTS & COMMENTARY

THE WOMEN'S HEALTH INITIATIVE (WHI) REPORTS THAT ESTROGEN-progestin therapy reduces fractures, but the number of gynecologic cancers observed precludes a definitive statement on the risk of endometrial and ovarian cancers.

The report on fractures from the canceled arm of the WHI was based on an average of 5.6 years of follow-up, comparing placebo treatment with daily 0.625 mg conjugated estrogen and 2.5 mg medroxyprogesterone acetate (*see Table 1*).

The WHI concluded the reduction in fractures was not great enough to alter their position that hormone therapy had no net benefit on their model of the global risk:benefit ratio. The gynecologic cancer diagnoses are listed in Table 2.

The WHI concluded that combined estrogen-progestin treatment prevented the increase in endometrial cancer associated with unopposed estrogen, and that this treatment may increase the risk of ovarian cancer. Not unexpectedly, the women in the treated group underwent interventions (biopsies and ultrasound) at a greater rate. (Cauley J, et al. *JAMA*. 2003;290:1729-1738; Anderson GL, et al. *JAMA*. 2003;290:1739-1748).

COMMENT BY LEON SPEROFF, MD

The Fracture Report

There are reasons to believe that the impact of hormone therapy could be greater than reported by the WHI. The Kaplan-Meier estimates of the impact of hormone therapy indicated that the reduction in fractures continued to increase over time, suggesting that a very powerful effect would be achieved with treatment of a long duration. In addition, spinal fractures included only clinically symptomatic fractures (known to represent about one-third of vertebral fractures); again the overall effect was probably greater if all vertebral fractures had been included. The beneficial effect was achieved even though the use of a bisphosphonate increased from 1% at baseline to about 6% in the hormone group and 10% in the placebo group. The effect would have been even greater if

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bisphosphonates had not been prescribed by the participants' clinicians. The reduction in fractures was also underestimated because the WHI participants were not selected to obtain a group of women at high risk for fracture, but to the contrary, these women overall were at low risk for fractures.

The diagnoses of hip fracture in this update were centrally adjudicated, resulting in a 6% disagreement. Whether this was balanced or favored one group or another is not shared with us.

There are some puzzling conclusions. For example, the report states that there was no evidence that the effect differed by years since menopause. However, the reduced risk of hip fracture was 0.58 (0.36-0.94) for women 20 or more years since menopause in contrast to a nonsignificant 0.80 (0.42-1.53) in women 10-19 years since menopause. The report states that there was no evidence of an interaction between treatment and race/ethnicity, but at the same time it is pointed out that the small number of fractures in the subgroups limited meaningful conclusions.

Table 1

Fractures

	Estrogen/Progestin	Placebo	Hazard Ratio
Osteoporotic fractures	733 cases	896 cases	0.76 (0.69-0.83)
Spinal fractures	41	60	0.65 (0.46-0.92)
Hip fractures	52	73	0.67 (0.47-0.96)
Lower arm/wrist fractures	189	245	0.71 (0.59-0.85)

Table 2

Cancer Diagnoses

	Estrogen/Progestin	Placebo	Hazard Ratio
Ovarian cancer	20 cases	12 cases	1.58 (0.77-3.24)
Endometrial cancer			
All cancers	27	31	0.81(0.48-1.36)
Adenoca	8	9	—
Cervical cancer	8	5	—

The report stated that hormone therapy decreased the risk of hip fracture by 60% among women with adequate calcium intake at baseline, but not in those with a lower intake. This underscores the importance of emphasizing to patients the consequences of inadequate calcium and vitamin D intake. The effect of hormone therapy was greater in leaner women, as one would expect.

Most importantly, the WHI concluded in the discussion that the fracture results indicated that this benefit did not outweigh the risks of cardiovascular disease and breast cancer. However, this conclusion could be influenced by several important points. The conclusion depends upon the judgment that the global index created by the WHI is a valid measure. For example, vertebral fractures were not included in the WHI global index. The cardiovascular risk was derived from the initial July 2002 report and not from the updated report a year later where after central adjudication the results were no longer statistically significant.[1] In addition, because the WHI trial underestimated the impact of hormone therapy on fractures, a more representative population may have yielded a greater overall benefit. Finally, the WHI buttresses its conclusion with their previous report of a two-fold increase in dementia among older, treated women. However, keep in mind that the only statistically significant finding was increased dementia in elderly women (75 and older)

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who had been exposed to a relatively short term of estrogen-progestin therapy, and that this was vascular dementia, not Alzheimer's.[2]

The GYN Cancer Report

The strength of the gynecologic cancer report is diluted by the small number of cases. To respond to this publication as if hormone therapy increases the risk of ovarian cancer, as some media reports did, is not justified. The WHI appropriately concludes that this is a worrisome issue and requires further epidemiologic assessment. A major problem is that the risk of ovarian cancer is influenced by so many factors. The WHI report stated that many observational studies have found a modest increase in the risk of ovarian cancer, but in fact most studies have not, and those reporting an increased risk have been plagued by incredibly small numbers making it impossible to control for all influencing factors.

The WHI found no interaction with previous oral contraceptive use, parity, family history of breast, ovarian, or colorectal cancer, and the WHI appropriately observed that the power to examine these relationships was too limited by the small number of cases. Thus even its overall conclusion regarding ovarian cancer could be modified by a shift of a few cases. Only greater numbers and longer duration of treatment could clarify this subject; for example, there were 2 cases of endometrioid ovarian cancers in the treated group and none in the placebo group, a result that should be reversed, and I believe a reversal would ultimately be achieved.

The results with endometrial cancer are also hampered by small numbers. Note that adenocarcinoma of the endometrium (the cancer most likely to be affected by estrogen-progestin therapy) accounted for only 8 cases in the treated group of 8506 subjects and 9 in the placebo group of 8102 subjects. The literature on hormone therapy and the risk of endometrial cancer does not suggest that a beneficial reduction in risk with estrogen-progestin combined treatment should be expected within a time period of a few years.

Conclusion

These 2 reports from the WHI should have no appreciable effect on current decision-making regarding postmenopausal hormone therapy. The reduction in fractures associated with hormone therapy agrees with the accumulated literature (although it probably underestimates the impact). The effect on the risk of endometrial cancer is consistent with what we have learned from smaller trials, case-control studies, and cohort follow-up reports. The effect of hormone therapy on the risk of ovarian cancer remains an unsettled issue, although the majority of case-control studies find no increase. It is noteworthy that the media highlighted ovarian cancer and neglected the good news in the report on fractures, especially because the prevalence, mortality, and morbidity of osteoporotic fractures in postmenopausal women add up to one of the most expensive and important health problems in modern life. ■

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'It's Déjà vu All Over Again' *

ABSTRACT & COMMENTARY

Synopsis: *Weekly injections of alpha-hydroxyprogesterone caproate resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.*

Source: Meis PF, et al. *N Engl J Med*. 2003;348(24): 2379-2385.

The National Institutes of Health (NIH) supported perinatal network recently conducted a study that was published in the *New England Journal of Medicine* this summer. It was a randomized control trial (RCT) to evaluate the ability of intramuscular progesterone to prolong pregnancy in patients at historical risk of preterm delivery.

Four hundred sixty-three women with a history of prior preterm birth (PTB) were randomized in 19 centers to have either weekly injections of 17 alpha-hydroxyprogesterone caproate (310) or an inert oil as placebo (153). The progesterone group had significantly lower rates of PTB before 37 weeks (36% vs 59%), before 35 weeks (20.6% vs 30.7%), and before 32 weeks (11.4% vs 19.6%). Compared with placebo, the progesterone group had significantly lower risk of necrotizing enterocolitis, interventricular hemorrhage, and need for oxygen in their infants compared with those given placebo in the same weekly regimen after 20 weeks.

■ COMMENT BY JOHN C. HOBBINS, MD

Off and on progesterone has been used in pregnancy in various ways through the years with

enough supporting reports to suggest it could be the obstetricians' "magic bullet." Our colleagues in reproductive endocrinology have distributed it to far more patients in early pregnancy than could possibly have a true luteal phase defect, and as far back as 1960 Fritz Fuchs suggested its use to prevent preterm labor.[1]

There is certainly enough compelling evidence from basic investigations to suggest the possibility of its efficacy in prolonging pregnancy. In vitro progesterone prepared uterine muscle will not contract when stimulated electronically. Also, progesterone suppresses the action of estrogen (which at least indirectly stimulates contractions) by inhibiting replacement of estrogen receptors, and it also suppresses the contractile effect on the myometrium of prostaglandin F2-alpha. In nonhuman primates and in sheep, progesterone levels decrease prior to labor and it has been shown that there is a drop in progesterone receptors during labor.

It seems that the intramuscular delivery of progesterone (which at face value would not seem to be able, by weekly injections, to get to the myometrial cells in high enough quantity to work) is not the only route that is effective. For example, in a report in February 2003, a Brazilian group reported similar impressive results in pregnancy prolongation with daily application of progesterone vaginal suppositories.[2] These investigators also found that patients on progesterone had fewer uterine contractions during periodic assessment with a tocodynamometer than those using placebos.

In general, studies assessing the ability of various tocolytics to stop labor have suffered from the inclusion of patients not in true labor—not so with the above *New England Journal of Medicine* and Brazilian studies, which had quite high rates of PTB in the placebo groups (54.9% and 28.5%, respectively). In fact, the rate in the *New England Journal of Medicine* study was unusually high for a mixed group of patients with only a history of at least one PTB. Nevertheless, these studies have to get our attention. ■

*** — Quote attributed to Yogi Berra**

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Special Feature

External Version: Can We Spare Patients from a Cesarean Section?

By John C. Hobbins, MD

As pointed out in previous *OB/GYN Clinical Alerts*, about 1 in 4 patients in the United States are delivered by cesarean section, a procedure still classified as a "major operation." Newer figures from year 2002 are not available, but the cesarean section rate (CSR) is sure to increase based on the apparent backlash against vaginal birth after cesarean section (VBAC). Also, a relatively recent randomized controlled trial (RCT) suggests greater neonatal morbidity when breeches are delivered vaginally, rather than by elective section.

Many women with breeches would prefer to avoid a cesarean section and are requesting an attempt at external version (EV). This Special Feature will deal with the risks and benefits of EV and will touch upon a few of the maneuver's ramifications.

Success Rates of EV

Success rates vary appreciably in the literature and often reflect single operator experience. These figures vary between 20% to more than 70% and, along with representing operator skill, zeal, and patient tolerance, also depend upon which patients are selected for EV (where in some clinical situations any effort is doomed from the start). Also, in these studies many variables, other than the procedure itself, are put into play such as the use of conduction anesthesia, tocolytics, etc. Last, the timing of the version may have a significant effect on success rates.

Early vs Late EV

Some of the same authors that published the above *New England Journal of Medicine* RCT that set the stage for a move toward elective cesarean section for all breeches, recently published an RCT comparing early (34-36 wks) vs late (36-38 wks) versions for breeches. They carefully selected nulliparous women with any breech presentation and multiparas with frank breeches (feeling these would represent the fairest test of the maneuver).

Two hundred thirty-three women were randomized in 25 centers around the world. Tocolytics were used in about half of the patients, but conduction anesthesia was used rarely.

The rate of noncephalic presentation at birth was 56.9% in the early group and 66.4% in the delayed group. The CSR in the early group was 64.7% and 71.6% in the late group. The above differences were not statistically significant, but more patients would have had to be recruited to have the power to validate the above 9% difference in presentation at term. The authors concluded that the results were encouraging for early EV, but a larger trial was needed.

There are a number of interesting spin-off findings in this study:

1. Fetal heart rate abnormalities were noted in 7% of the early EVs and 2% of the late EVs, requiring the procedure to be discontinued;
2. Patient discomfort in 8% and 6% of patients, respectively, resulted in discontinuation of the procedure;
3. Spontaneous version occurred in 10% of the early group (while awaiting the procedure) and in 19% of the late group patients; and
4. Spontaneous reversion to breech was rare in both groups after successful version.

Stepwise Description of the Method

In the past, the technique has consisted mostly of attempting to lift the breech out of the pelvis and muscling the fetus around with brute force until the patient or fetus said, in his or her own way, "uncle." Some operators have even advocated using 2 sets of hands to accomplish this feat.

The following represents a kinder, gentler way of accomplishing this goal while lowering complications and diminishing patient discomfort.

Step 1: Careful Ultrasound Evaluation

Fetal Alignment: Not all breeches are alike. A frank breech deep in the pelvis in a nullipara is going to be more difficult to vert than a floating incomplete breech in a multipara. Ultrasound will allow the provider to roughly predict procedure success.

i) **Presentation:** Oblique lies or transverse lies are easier to vert because the fetus has a shorter arc through which to travel.

ii) **Type of Breech:** Frank breeches theoretically can be more difficult to turn because a fetus in a tenaciously piked position represents a larger north/south axis to deal with than a fetus in a tucked position.

iii) **Station:** One less step is necessary if the breech is already at a high station.

iv) **Position:** Toward term the fetus spends about 75% of the time on his or her side. On ultrasound, if the spine is at 12 o'clock or 6 o'clock, the success rate diminishes appreciably because of the potential pinwheel effect of splayed out limbs.

v) **Fetal Extension:** Much has been made of extended heads when delivering a breech vaginally, but this plays little role in a version, since, barring the extremely rare case of torticollis, an extended head represents only a temporary whim of a fetus who generally can be encouraged to flex.

Placental Position: Many have backed off during a version in the face of an anterior placenta. Although this might make empiric sense, there is little in the literature, other than the potential of transferring fetal cells into the maternal circulation, to contraindicate version in special cases. Placenta previa obviously is a contraindication to version, where malpresentation is common. Here a successful version would represent a very dubious triumph.

Fetal Anomalies: If a patient has slipped through pregnancy without an anomaly assessment, she should have one prior to a version since fetuses with anomalies often present as breeches.

Fluid Assessment: Many have decided that oligohydramnios is a contraindication to version. This would depend upon the clinical situation and the degree of oligohydramnios. Interestingly, I found one report of amnio-infusion of 500-700 cc of saline being used after unsuccessful version followed by a successful version in all 6 cases in which this was attempted.

Umbilical Cord Assessment: About 12-18% of fetuses at term will have a single loop of cord around the neck and 2.5% will have 2 loops. The multicenter RCT study mentioned above indicated that in about 4% of total cases version had to be abandoned because of fetal heart rate abnormalities, and it is rare for us to have to do an emergency cesarean section for fetal distress during a version. Because of the dangerous potential for cord avulsion, tethering, or occlusion, a double loop of cord or a single tight loop of cord could represent a contraindication to version. On the other hand, a loose single loop or a cord in the neighborhood of the shoulder or neck should not be a contraindication, as long as the fetal heart rate is carefully monitored with ultrasound during the procedure.

Step 2—The Technique Itself

The patient should have an empty bladder. Before the rotation portion of the procedure is undertaken, the breech should be out of the pelvis. This can be accomplished often with superpubic pressure upward. If this fails after a very short time, the breech can be gently pushed out of the pelvis by a vaginal hand. A Trande-

lenberg position makes sense during this portion of the procedure, but any length of time in this position makes this maneuver doubly uncomfortable for a full-term patient.

Once the breech is out of the pelvis, the operator, who has decided ahead of time whether to use the forward or backward roll technique, guides the breech into either lateral quadrant of the uterus, while encouraging the head to move downward into the opposite side of the uterus. Everyone has his or her own "wrinkles," but I give more emphasis to the downside hand than the one on the head and will often spend many seconds simply encouraging the breech to move upward before even thinking about the head.

The procedure should be done in stages, and each stage should be accompanied by an ultrasound assessment of the long axis of the fetus and the status of the fetal heart rate. I know of operators who will retry a version after a bradycardic fetus' heart rate returns to normal, but I consider this to be a message to call it a day.

If one can get the long axis of the fetus rotated to more than 90° from the starting point, the success rate (barring a bradycardia) is virtually 100%. For this reason, if this is not accomplished after a reasonable amount of time (a few minutes) and reasonable pressure (no discomfort), an attempt can be made to move the fetus in the opposite direction.

Once the head is in a cephalic presentation, or a reasonable facsimile, gravity can be used to finish the job by having the patient stand and walk (unless she has an epidural).

Variables to Consider When Doing EV

Forward vs Backward Roll: In oblique breeches, the shortest distance to the pelvis should be considered first. When the fetal long axis is straight up and down, "gestalt" gets put into play. The benefit of the forward roll is that the fetus has a tendency to stay tucked during the maneuver, but the backward roll allows the operator better control. My recent informal poll of some experienced operators yielded a 50/50 split regarding this question and I could find nothing in the literature pitting one option against the other.

Placental Position: A very low lying placenta (< 2 cm from the cervical os), or placental previa are contraindications to EV. Rregarding anterior placentas, I found isolated instances where fetal cells were found in the maternal circulation with anterior placentas. However, in a Chinese study looking for evidence of fetal-maternal hemorrhage in 70 patients undergoing EV, the rate of this finding was only 1.8%, irrespective of placental position. Also, a German study showed no relationship between placental position and success of EV, while an Italian study showed better success with a posterior placenta.

Vaginal Birth After Cesarean (VBACs): Many have labeled this as a contraindication to version, but I could find little to back this dictum up. One study showed a remarkable success rate in patients with uterine scars.

Adjunctive Methods

Tocolytics: Almost all of the tocolytic studies in the literature have involved the use of beta mimetics in EV (terbutaline, salbutamol, ritodrine) and the majority have shown a beneficial effect of tocolytics. One study from Hong Kong was very interesting. The investigators pitted ritodrine against a placebo in 50 patients. The overall EV success rate in the ritodrine group was 68% vs 32% in the placebo group, but after the first 20 patients were studied, there was no difference between groups. This suggested that the experience gained by the operators during the early stages of the trial was the most important variable regarding success, and not the tocolytic.

I have been enamored with the use of nitroglycerine in breech extractions for a second twin because of its short-term capabilities as a uterine relaxant. Therefore, I was disappointed to find only one British RCT that suggested its efficacy. Unfortunately, a review of the literature by a Toronto group involving 13 RCTs did not yield information to support the use of nitroglycerine in EV.

Conduction Anesthesia

Some studies in the literature have suggested benefit from epidural anesthesia in EV, but a randomized trial from our group showed no benefit from spinal anesthesia. A group of patients who might particularly benefit from epidural anesthesia would be those who initially failed EV with tocolysis. One study by Neiger et al showed a 71% success rate with epidural in 83 patients with a previously unsuccessful version.

It seems that this expensive and invasive anesthetic method could be used in a pre-cesarean "last ditch" attempt at EV in the operating room in patients highly motivated to avoid a section.

Other Tricks

Through the years one hears of various adjunctive

EV fetishes used by obstetricians. These will not be discussed with one exception—the use of talcum powder to improve traction (or something). I tried this once and it did not seem to accomplish anything except making me sneeze. Counter intuitively many operators will use a lubricant to do the same thing.

Alternative Measures to Encourage Spontaneous Version

Many have advocated the use of gravity a few times a day to encourage spontaneous version (the "ironing board trick"). Although this has not been rigorously tested scientifically, anecdotal experience suggests its usefulness when used 1-2 times a day for 15-20 minutes at a time.

In *JAMA*, a randomized trial using moxibustion, an ancient Asian technique appeared to show benefit in stimulating spontaneous version, and acupuncture techniques have also been described to accomplish the same aim.

It is interesting that about 50% of the patients in the multicenter RCT involving early vs late version, had already tried some form of "alternative" version method before enrolling in the study. This speaks to the fact that today many patients remain highly motivated to avoid cesarean section, and we, as providers, should continue to respect our patients' autonomy, especially when their wishes are not incompatible with sound medical judgment. ■

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CME Questions

13. The following statements are true regarding the WHI reports on fractures and gynecologic cancers *except*:

a. A statistically significant decrease in the treatment arm occurred in all fractures associated with osteoporosis.
b. Not one observation on any gynecologic cancer achieved statistical significance.
c. Hormone therapy can compensate for inadequate intake of calcium and vitamin D.
d. The WHI underestimated the impact of hormone therapy on fractures because the participants were at low risk for fractures, the effect was still increasing when the trial was canceled, and more subjects in the placebo arm started bisphosphonate treatment.

14. The following statements are true regarding the use of progestin to prevent preterm delivery *except*:

a. All progestins inhibit preterm labor.
b. Nonandrogenic progestins inhibit uterine contractions
c. Progesterone withdrawl is associated with the onset of labor.
d. None of the above

Answers: 13: (c); 14 (a)

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PHARMACOLOGY WATCH

Generic Paxil Scheduled to Hit Market this Fall

A generic form of paroxetine (Paxil—GlaxoSmithKline) will soon be on the market. The drug marks the second SSRI antidepressant to go generic after fluoxetine (Prozac) last year. US sales of Paxil reached $2.23 billion last year, and the approval of a generic is a blow to GSK's bottom-line but is welcome news to consumers. Generic paroxetine will be launched by Canadian drugmaker Apotex almost a year earlier than most analysts had anticipated because of continued legal wrangling over patents. If generic companies launch a drug that is later found in violation of the branded drugs patents, they are liable for treble damages, a threat that has impeded generic competition in the past. In this case, Apotex feels it has a strong legal basis for defending any claims by GSK, a pattern that is being seen more frequently among generic companies in the last year. Generic paroxetine should be available this fall in 4 different dosing strengths.

New Study Questions CHD and C pneumoniae

An association between *Chlamydia pneumoniae* infection and coronary heart disease has been suggested by several lines of evidence; however, a new, large, multicenter study fails to confirm this association. Nearly 8000 adults with a recent myocardial infarction and positive *C pneumoniae* titers were randomized to 12 weeks of azithromycin (600 mg/d for 3 days then 600 mg/wk through week 12) or placebo. The primary outcomes were death from any cause, nonfatal reinfarction, coronary revascularization, or hospitalization for angina. After a median of 14 months of follow-up, there was no significant risk reduction with azithromycin vs placebo (any primary event 7% risk reduction with azithromycin, P =.23). Adverse reactions to the study drug occurred in 13.2% of patients randomized to azithromycin and were generally mild—predominately diarrhea. The study represents the largest antibiotic trial to date for the eradication of *C pneumoniae*, and although there were indications that there might be an early benefit, this was not sustained at 14 weeks. The authors suggest that there's no justification for the use of antibiotics in treating patients with coronary disease (*JAMA*. 2003;290:1459-1466).

Warfarin Patients: Limit Cranberry Juice

Cranberry juice may increase the risk of hemorrhage in patients taking warfarin according to British researchers. The British Committee on Safety of Medicines recommended patients taking warfarin should limit or avoid drinking cranberry juice until they can sort out 5 reports of hemorrhage associated with the combination, including 1 death. In all cases, increases in INR were noted when patients who had been stabilized on warfarin started drinking cranberry juice. The committee postulates that the juice inhibits cytochrome P450 activity, thus slowing metabolism of warfarin. Cranberry juice has been touted in recent years for its antioxidant proper-

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ties as well as its purported ability to prevent or treat urinary tract infections.

Therapeutic Magnets Put to Test

A randomized double-blind trial has finally put therapeutic magnets to the test for the treatment of foot pain. Researchers at the Mayo Clinic randomized 101 adults with the diagnosis of plantar heel pain to treatment with cushioned insoles with bipolar magnets and sham magnets. The insoles were worn daily for 8 weeks. The main outcome was reported average daily for pain and the effect of the insoles on work performance and enjoyment. Again, at 8 weeks no significant difference was noted between the 2 groups, with both groups reporting significant improvements in foot pain (33% improvement nonmagnetic group, 35% improvement magnetic group [P = .78]). The authors conclude that embedded bipolar magnets to add nothing to cushioned insoles and the treatment of plantar heel pain (*JAMA*. 2003;290:1474-1478).

St. John's wort Might Block Certain Medications

St. John's wort, the popular herbal product that is widely used to self-treat depression may significantly reduce the effectiveness of at least 50% of all marketed medications. A new study looked at the effect of St. John's wort on cytochrome P450 (CYP) enzymes. Twelve healthy volunteers (6 men and 6 women) were given St. John's wort for 14 days. Participants were given dextromethorphan and alprazolam before and after administration of St. John's wort to assess plasma pharmacokinetics. After 14 days use of St. John's wort, a 2-fold decreased area under the curve for alprazolam plasma concentration and a 2-fold increase in alprazolam clearance was found as well as an elimination half-life that decrease from 12.4 h to 6.0 h suggesting a significantly induced activity of CYP 3A4 (all findings significant at $P <$ .001). Dextromethorphan metabolism, a measure of CYP 2D6, was unchanged. The effect of St. John's wort on CYP 3A4 is quite significant, however, since at least 50% of all medications currently on the market are at least partially metabolized by this enzyme. This, coupled with 2 recent multicenter double-blind, placebo-controlled studies questioning the effectiveness of St. John's wort for the treatment of depression, should alert clinicians to question their patients about their use of herbal medications, especially St. John's wort (*JAMA*. 2003;290:1500-1504).

Parathyroid Hormone and Alendronate Offer No Improved Osteoporosis Treatment

Parathyroid hormone and alendronate in combination offer no advantage and may in fact be less effective than either drug alone in treating osteoporosis according to 2 studies in the Sept. 25 issue of *New England Journal of Medicine*. In a study of 83 men with low bone density, 28 were randomized to receive alendronate 10 mg/d, 27 received parathyroid hormone 40 mg subcutaneously daily, while 28 men received both. The bone mineral density of the lumbar spine, proximal femur, radial shaft, and total body was measured every 6 months and trabecular bone mineral density of the lumbar spine was measured at baseline and 30 months. The most effective treatment was parathyroid hormone alone ($P < 0.001$ for both comparisons), and it appeared that alendronate impaired the ability of parathyroid hormone to increase bone mineral density at the lumbar spine and femoral neck. In the second study, 238 postmenopausal women with low bone mineral density at the hip or spine were randomly assigned to daily treatment with parathyroid hormone 100 mg/d (119 women), alendronate 10 mg/d (60 women), or both (59 women). After 12 months of follow-up, bone mineral density was assessed at the spine and hip. Bone mineral density increased in all treatment groups, but the volumetric density of trabecular bone in his spine increase substantially more in the parathyroid hormone group than either of the other groups. The authors suggest that there is no evidence of synergy between parathyroid hormone and alendronate and there may be evidence that alendronate reduces the anabolic effects of parathyroid hormone in the study group (*N Engl J Med*. 2003;349:1207-1215, 1216-1226).

FDA Actions

Barr laboratories has received approval to market an extended-cycle birth control pill that cuts the number of a women's menstrual cycles from 13 to 4 per year. Marketed under the trade name "Seasonale," the product is a 91-day ethinyl estradiol/levonorgestrel oral contraceptive regimen that includes 84 days of active hormones and 7 days of placebo. The new product seems to be as effective as other oral contraceptives; however, the label does note that the longer interval between menstrual periods may allow for unintended pregnancies to go undetected for longer period of time. ■