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INSIDE

Determining Menopause in Women Using Depo-Provera

ABSTRACT & COMMENTARY

BEKSINSKA AND COLLEAGUES FROM SOUTH AFRICA MEASURED FSH levels in long-term older users of depot-medroxyprogesterone acetate (117 women) and norethindrone enanthate (60 women), long-acting progestin-only methods of contraception. A significant number of these women had postmenopausal levels of FSH (greater than 25 IU/L) at recruitment. The progestin users were compared to 161 nonusers of contraception matched for age. The FSH levels in the groups of women were similar when matched for age. The study did find some suppression of FSH in the first month after injection of the progestin (Beksinska ME, et al. *Contraception*. 2003;68:339-343).

COMMENT BY LEON SPEROFF, MD

I have written for a long time that menopause can be diagnosed in users of progestin-only contraceptive methods by measuring the FSH level beginning at age 50. This recommendation has been based upon the observation that progestins do not suppress FSH secretion in the normal menstrual cycle. Although old studies had indicated that intramuscular progestin contraception suppressed elevated postmenopausal FSH levels, there was great variability and a lack of total suppression. The important point is that when FSH levels are above the menopausal threshold (20 IU/L), pharmacologic progestin suppression will not restore FSH to a premenopausal level. Therefore, a random FSH measurement can indeed be used to document the onset of postmenopause in users of progestin-only methods of contraception. The South African study indicates that greater reliability is achieved if the blood sample is obtained in the 1 month prior to the next injection (it would be most convenient to draw the blood at the time of the next injection).

A common clinical dilemma is when to change from oral contraception to postmenopausal hormone therapy. It is important to change because even with the lowest estrogen dose oral contraceptive available, the estrogen dose is 4-fold greater than the standard postmenopausal dose, and with increasing age, the dose-related risks with estrogen become significant. My approach is the same as

VOLUME 20 • NUMBER 11 • MARCH 2004 • PAGES 81-88

with progestin-only contraception, to establish the onset of the postmenopausal years by measuring the FSH level, beginning at age 50, on an annual basis, being careful to obtain the blood sample on day 6 or 7 of the pill-free week (when steroid levels have declined sufficiently to allow FSH to rise). Friday afternoon works well for patients who start new packages on Sunday. When FSH is > 20 IU/L, it is time to change to a postmenopausal hormone program. I know that many have argued that this approach is not valid because of the variability in FSH levels experienced by women around menopause.[1,2] Indeed, in some women, FSH will not rise until 2 weeks after the last pill. Waiting 2 weeks is not very practical and places the patient at risk for an unwanted pregnancy. The pill-free week method is practical and works for most women. Some clinicians are comfortable allowing patients to enter their mid-50s on low-dose oral contraception, then empirically switching to a postmenopausal hormone regimen (The oldest spontaneous pregnancy in the *Guinness Book of World Records* was 57 years, 120 days). If a patient requires the oral contraceptive for contraception, it is better to follow the empiric route, avoiding an unwanted surprise. ■

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Myometrial Invasion and the Tumor-Free Distance from the Uterine Serosa in Endometrial Cancer?

ABSTRACT & COMMENTARY

Synopsis: *TFD as a single measurement carries significant prognostic importance in women with comprehensively staged endometrial cancer.*

Source: Lindauer J, et al. *Gynecol Oncol*. 2003;91(3):547-551.

LINDAUER AND COLLEAGUES SET OUT TO EVALUATE whether the tumor-free distance from the uterine serosa to the deepest invasive lesion was a better predictor of patient outcome from endometrial cancer than the traditional measure of myometrial invasion. To do this, they retrospectively evaluated all surgically staged endometrial adenocarcinoma patients between 1997 and 2000. Depth of myometrial invasion was defined as the distance in millimeters between the endometrial-myometrial junction and the deepest invasive lesion. Tumor-free distance was defined as the distance in millimeters between the uterine serosa and the deepest area of myometrial invasion. Depth of invasion and tumor-free distance were expressed as continuous variables in this report. To determine their predictive and prognostic significance, these 2 variables were compared with traditional surgicopathologic factors and against outcomes of recurrence and survival. A total of 153 patients met study criteria. The most common stage was IB, and 23 patients had positive nodes. The median depth of invasion was 0.5 cm and the median tumor-free distance was 1.4 cm. At a median follow-up of 29 months, 10 patients recurred. By univariate analysis, both invasion parameters were significant predictors of traditional surgicopathologic variables.

However, only tumor-free distance was predictive of recurrence. In addition, while both tumor-free distance

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Pfizer, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Pfizer, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Drs. Coleman and Hobbins reports no relationships related to this field of study. This publication does not receive commercial support.

and depth of invasion were significant predictors of survival, only tumor-free distance was correlative with surgicopathologic variables and predictive of recurrence and survival in the multivariate model. Depth of invasion became predictive of recurrence when myometrial thickness was included in the model. A tumor-free distance of 1 cm maximized the balance of sensitivity and specificity in predicting recurrence. Lindauer et al concluded that tumor-free distance as a single continuous measurement carries significant prognostic importance in women with comprehensively staged endometrial cancer.

COMMENT BY ROBERT L. COLEMAN, MD

Epithelial malignancy of the uterine corpus remains the most common gynecological malignancy diagnosed in the United States. Characterized by frequent early stage at diagnosis, endometrial cancer is often considered a "curable" lesion. However, more than 20% of clinical stage I cases will have evidence of extrauterine disease, and up to 15% will recur at 5 years.[1,2] Exhaustive evaluation of important clinicopathological risk factors relating to these clinical outcomes, along with survival, led FIGO to modify the staging schema in 1988, incorporating findings at surgery generated from formal exploration. Currently, surgical staging is recommended for all patients with the diagnosis.[3] Nonetheless, it is a rare event for noninvasive lesions to be associated with metastatic disease, prompting some to use a measure of grade and gross myometrial invasion to triage those who should undergo the more extensive surgical staging procedure.[4,5] However, unreliable and inconsistent correlation of intraoperative findings to final postoperative pathology hallmarks the challenge of making an accurate assessment of myometrial invasion and thus, leading potentially to improper staging—raising yet another challenge in determining accurate postoperative therapy.

Lindauer et al study another methodology for quantifying myometrial invasion by looking at, essentially, the complement of the standardized practice. This measure of tumor-free distance from the serosa to the deepest element of invasion is easier to measure and, through multivariate analysis, was better associated with parameters determining survival. A tumor-free distance of 1 cm was associated with the best probability testing characteristics for recurrence. Although not an *a priori* goal, Lindauer et al did have 2 pathologists evaluate a limited number of specimens for this parameter. The reproducibility was quite high, being identical in 4 of 5 cases tested.

It is of note that traditionally measured depth of myometrial invasion became an important independent variable when myometrial thickness was also considered. It is from this "denominator" that percent of myometrial invasion is calculated and reported. In the current study, depth of myometrial invasion was considered as a continuous variable without relation to the uterine wall. In this respect, it is not difficult to see why the variable fell out on multivariate testing. For instance, a 0.75 cm invasive lesion in a 3.0 cm uterine wall (25% invasion) would be expected to behave differently (and staged differently) than the same 0.75 cm lesion in a wall 1.0 cm thick (75% invasion). Calculating a percent invasion "normalizes" to some extent the invasion characteristic and as such brings the measure more in line with what tumor-free distance is essentially measuring. My suspicion is that the 2 variables would explain similar amounts of variance on regression testing if compared. Parenthetically, similar strategies for assessing biological behavior have been reported in carcinoma of the cervix, with short tumor-free distances frequently associated with nodal metastases. Whichever methodology is ultimately used, the growing trend in the surgical evaluation of endometrial cancer is to perform complete surgical staging wherein an accurate picture of the disease state can be constructed to effectively counsel and treat patients with this malignancy.

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Enthusiasm for Cancer Screening in the United States

ABSTRACT & COMMENTARY

Synopsis: *Most Americans believe that screening tests for cancer save lives and that it is irresponsible not to undergo recommended periodic screening. The presence of a large "market" for cancer screening may make Americans vulnerable to unproven and unnecessary testing.*

Source: Schwartz LM, et al. *JAMA*. 2004;291:71-78.

THE AIM OF THE PRESENT INVESTIGATION WAS TO document American's attitudes toward cancer

screening using a telephone survey and a well-honed and validated inventory. The study was limited to women older than age 40 and men older than age 50 who were free of the diagnosis of cancer. Five hundred respondents were queried about 5 possible domains: general screening, colonoscopy or sigmoidoscopy, Pap smears and mammography in women, and prostate-specific antigen in men. The interviews ranged from 10 to 54 minutes.

Most adults (87%) believed that routine cancer screening was a good idea and that screening saved lives. Two-thirds would want to be tested even if nothing could be done if a cancer were discovered. Whereas 35% believed that they had had too few screening tests, only 2% felt that they had had too many. If told by a physician that they needed less frequent testing, most would overrule their physician and want to be tested. Indeed, 77 % of men would undergo PSA testing even if their physician would not advise it, and 58 % of women would want a Pap smear even if their physician said it was unnecessary. Despite the "bad press" regarding the use of mammography, most women believe it is worthwhile. Most respondents felt that it was "irresponsible" to not undergo screening, even if the age of the individual to be screened were 80 years old. More than half of the respondents had had a false-positive screening test in the past, but 98% of those were glad they had the test and were planning to undergo additional testing. After being told that a total-body CT could "look inside your body" and give a very detailed picture of internal organs and that it was quick and painless, 86% volunteered to have one for free. When offered $1000 cash in exchange for the test, most still wanted the test.

COMMENT BY SARAH L. BERGA, MD

In a recent issue, I reviewed the pros and cons of optical vs conventional colonoscopy for screening for colon cancer. I had just seen a huge billboard advertising optical colonoscopy along the highway and it had garnered my interest in the use of this new technique. Apparently, I am not alone in being interested in new ways of being screened for cancer. The present article documents just how thoroughly indoctrinated most Americans are with regard to the necessity and value of cancer screening. Apparently, for the vast majority of us, physicians or not, more screening is clearly better, regardless of cost, discomfort, false positives, and emotional distress. This is a very important and timely topic for those of us practicing obstetrics and gynecology, because a prime reason our patients see us annually is to have their Pap smear and to make sure that they are up to date on well-care screening, especially mammography. Because many patients groan at least a bit when you remind them of the need for interval screening, I was surprised to find that these protests do not actually reflect what patients truly feel and think. Indeed, as noted above, even if the physician said that screening was unnecessary, most would still want to be screened.

Is screening necessary and if so, what type and how often? While physicians and public health experts debate the topic on the basis of cost, cost per saved life, risk, false negatives, and false positives, patients think, "more is better." Indeed, they may lose faith in a physician who does not screen often or thoroughly enough. If the results of this study ring true, then the prudent physician should be certain to create a checklist to review with patients regarding screening exams. The American College of Obstetricians and Gynecologists has created a helpful pamphlet that reviews what is needed by age categories for women. In the meantime, I expect that the hype about newer and more costly methods of screening for cancer will escalate. Those who make and/or perform these tests are well aware of the appetite and market that exists. Schwartz and colleagues conclude that these attitudes make Americans vulnerable to unproven and uninterpretable testing, such as screening for "cancer genes." Physicians have an opportunity and responsibility to provide a balanced viewpoint to counter aggressive marketing. ■

Results of Interval Debulking Surgery Compared with Primary Debulking Surgery in Advanced-Stage Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Survival rates were similar in patients with advanced-stage ovarian cancer who underwent IDS or PDS. The rates of surgical resection and morbidity were reduced after IDS. IDS can be safely used in unresectable advanced-stage ovarian cancer.*

Source: Morice P, et al. *J Am Coll Surg*. 2003;197(6): 955-963.

In an effort to shed light on a controversial approach to advanced ovarian cancer management, Morice and colleagues present intriguing data on the use of interval debulking surgery following pre-operative

chemotherapy. The retrospective study consisted of 2 cohorts, matched for stage, tumor grade, and histology. The first cohort consisted of 57 patients who were determined, largely at surgery, to be unresectable (to less than 2 cm residual disease) by standard debulking techniques. This group received a median 3 courses (range, 2-5) of platinum- and taxane-based chemotherapy followed by a second attempt at cytoreduction. Following this surgery, they were administered a median 5 (range, 3-7) courses of the same chemotherapy. The second cohort—the control group—consisted of 28 patients deemed resectable who underwent standard primary debulking surgery followed by a similar platinum- and taxane-based chemotherapy regimen.

In both cohorts, "optimal" cytoreduction was considered less than 2 cm of residual disease—an achievement made in 84% of the interval debulking surgery group and in 100% of the primary cytoreduction group. Similar rates of complete resection (ie, no gross residual) were achieved in each cohort (51% and 54%, respectively) as well. To document the effects of chemotherapy in the interval-debulking cohort, Morice et al recorded disease volumes in several specific peritoneal and extraperitoneal locations both before and after chemotherapy and compared this disease volume to that found in the control cohort at primary surgery. Following the initial chemotherapy, tumor reduction on specific intra-abdominal structures ranged from 30% on the diaphragmatic peritoneum to 60% on the bowel and rectum regions. In addition, despite the spectrum of disease at entry, the distribution and volume of disease found at cytoreductive surgery was markedly reduced for the interval-debulking group. The rates of bowel resection, large peritoneal, resection and postoperative morbidity were significantly reduced in the interval-debulking group, as well. After adjustment for tumor residual, no significant differences could be determined between the 2 cohorts with regards to disease-free and overall survival. Morice et al conclude that interval-debulking surgery is a viable therapeutic option for patients with unresectable advanced ovarian cancer and is associated with reduced surgical resection and morbidity compared to primary cytoreduction with equivalent survival.

COMMENT BY ROBERT L. COLEMAN, MD

The merits of cytoreductive surgery and chemotherapy for patients with advanced ovarian cancer have been well documented. Typically, the sequence is surgery first and combination platinum- and taxane-based chemotherapy second. In a meta-analysis on the topic of primary cytoreduction, Bristow and colleagues documented that achievement of "optimal" status from surgery was associated with an 11-month (50%) increase in survival compared to "suboptimal" cytoreduction.[1] In addition, each 10% increase in cytoreduction was associated with a 5.5% increase in survival. The result was most notable among institutions and surgeons familiar with the techniques of ovarian cancer resection and goals of debulking. In nearly all studies on this topic, those patients rendered completely disease-free (no gross residual) after primary surgery have the best subsequent performance whether it is reported by intermediate end points such as negative second-look operations and progression-free survival or by durable survival. In an attempt to achieve optimal resection, a variety of surgical techniques and strategies have been reported, such as the radical oophorectomy/posterior exenteration, diaphragmatic resection and stripping, peritoneal implant excision and suprarenal retroperitoneal dissection.[2,3] While these procedures have increased initial cytoreduction rates in some cohorts they have often been associated with increased perioperative morbidity.

An alternative strategy is to "preload" the patient by offering chemotherapy ahead of a cytoreduction attempt. Since ovarian cancer is generally chemosensitive, the strategy has appeal, and most patients will experience a reduction in tumor volume (sometimes elimination of gross disease) before surgery is attempted. The limited number of articles on the topic of neoadjuvant chemotherapy would suggest, as the current article does, that more patients are rendered optimal with less morbidity.[4-7] Unfortunately, there is a confusing assortment of terms that applies to this kind of treatment approach. "Neoadjuvant" chemotherapy, "induction" chemotherapy, and interval cytoreduction have all been used to describe a cohort of patients undergoing chemotherapy ahead of a definitive cytoreduction. To some degree, the disparity in terms may explain the differences seen in clinical trials with respect to survival outcomes. In general, "neoadjuvant" has been used to describe a cohort of patients administered chemotherapy without surgical exploration the diagnosis being determined by cytology or limited biopsy.

Those who have undergone a suboptimal surgical cytoreductive attempt and are to undergo a second exploration are treated with "induction" chemotherapy between the 2 surgeries. Interval cytoreduction, as used in the current study, refers to a cohort of patients undergoing surgical exploration to make the diagnosis and assess cytoreducibility. Chemotherapy is then given prior to a definitive surgical attempt. Retrospective studies involving patients in all 3 of these "designations" are significantly biased by patient selection and are difficult

to interpret even when matched with historical or concomitantly treated "controls." What is generally apparent though, is that most patients do achieve some level of tumor reduction after chemotherapy, and surgery is facilitated with better odds of achieving an "optimal" status.

The answer as to whether the strategy makes a difference in a "hard point" such as survival is really the purview of randomized, prospective trials. Two have been completed and 1 published. Not surprisingly, the conclusions reached by these 2 trials are not uniform. In the trial reported by van der Burg et al, biopsy-proven ovarian cancer patients left with more than 1 cm residual disease following initial surgery were treated with 3 cycles of platinum-based chemotherapy before being randomized to either 3 more cycles of chemotherapy or to a second, interval cytoreduction attempt followed by 3 cycles of chemotherapy.[8]

This latter, experimental cohort demonstrated improved progression-free and overall survival compared to the conventionally treated suboptimally debulked patients. The benefit was significant and amounted to a gain of a median 5 and 6 months, respectively. In the second trial, conducted by the Gynecologic Oncology Group (GOG), all patients underwent a maximal effort at cytoreduction and were left with greater than 1 cm residual disease.[9] All patients received platinum and paclitaxel chemotherapy, but the experimental group underwent a second cytoreduction attempt after 3 cycles if their disease had not progressed (77% of randomization cohort). No difference was observed for either progression-free or overall survival between the interval debulking cohort and the conventionally treated cohort. Operative morbidity was acceptable and similar between cohorts for both trials. Numerous differences between the trials are noteworthy, but unaddressed is the estimation of inherent tumor biology, which may more strongly influence survival and is likely unaffected by "brawn." Currently, a trial by the EORTC is attempting to address this question by randomizing patients ahead of any surgical debulking to either a conventional approach or to neoadjuvant chemotherapy followed by surgery. This ambitious project will help provide a frame of reference to when and where aggressive surgery should be performed and how it will influence the natural history of ovarian cancer. One point is clear, however—patients who never undergo surgery, either because of medical infirmity or incomplete chemotherapy response, fair poorly. Limited options are available for this group. ■

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Special Feature

Quick Hits

By John C. Hobbins, MD

In this feature, Dr. Hobbins offers a quick summary and commentary on some recently published studies.

I. False-Positive "One-Hour" Glucose Screens are Associated with Higher Rates of Perinatal Complications than Negative Screens

In a previous *OB/GYN Clinical Alert*, I alluded to a study indicating that a normal 3-hour glucose tolerance test does not confer upon a patient with a positive 1-hour glucose screen a major lessening of chances of macrosomia. Now there is a study that shows higher rates of shoulder dystocia (OR = 2.85), endometritis (OR = 2.18), as well as macrosomia (OR = 3.66) than in those patients with negative 1-hour glucose screens. There also was a trend toward higher rates of cesarean section and antenatal death. The composite adverse perinatal outcome was substantially higher than in patients with normal screens (OR = 5.96).

All of these statistically significant increases in risk can be related in one way or another to macrosomia. In a recent *OB/GYN Clinical Alert*, a study (Greco et al) was featured in which scrupulously controlled insulin-requiring diabetics were still found to have a high rate of macrosomia, indicating that there was more to excessive birth weight than maternal glucose levels alone.

After writing that piece, I was alerted by a very savvy colleague in internal medicine to an investigation in progress suggesting that in some patients glucose crosses the placenta even faster than expected. While this interesting phenomenon helps to normalize maternal blood sugars, it could elevate fetal blood glucose levels and stimulate a compensatory fetal release of insulin—

the probable culprit in excessive fetal growth.

Unfortunately, while helping to explain why macrosomia continues to happen in well-controlled diabetics and, perhaps, in those with a "false positive" glucose screen, it does not aid us in fashioning a strategy to prevent it.

II. Don't be Mislead by the Short Take

While skimming through the table of contents in the January 2004 *Obstetrics & Gynecology*, I came across a paper by Caughey et al entitled "Complications of Term Pregnancies Beyond 37 Weeks of Gestation." Under this title was the message: "*Rates of meconium, macrosomia, chorioamnionitis, endomyometritis, and intrauterine death all increase before 42 weeks of gestation*."

At first glance, one might conclude that all of these problems increased after 37 weeks. Actually, the study indicates that macrosomia and presence of meconium at delivery occur beyond 38 weeks, that operative delivery and chorioamnionitis occur more often after 40 weeks, and that rates of intrauterine demise rise only after 41 weeks.

From the summary, one might surmise that Mother Nature should have arranged things so that most patients would go into labor by 37 weeks, thereby circumventing all of these nasty problems. In fact, in the discussion section Caughey et al suggest that "given our data, it might be found that the balance of risks and benefits from intervention in low-risk pregnancies should be earlier than current management."

First, there is evidence in the literature that intervening prior to term in patients known to have macrosomic fetuses does not improve outcome or decrease cesarean rates. Second, even when meconium is present, the risk of severe meconium aspiration is rare, and when it does happen, there is a strong suggestion pathologically that the process is chronic rather than acute. In essence, in these patients the meconium is a symptom of trouble, not the cause. Third, the intrauterine demise data in the paper shows an increase only after 41 weeks (OR = 2.6; CI, 7.29). However, the actual percentage of demised fetuses in each age group is not mentioned, nor are we told how many of these had 21st century fetal surveillance.

Inductions are intrusive for some patients and are far from innocuous with regard to morbidity. They require more nursing attention and are darn expensive. Therefore, from now on I would suggest holding the pitocin in patients who have no risk factor other than having succeeded in avoiding a preterm delivery.

III. More Information Regarding Single vs Double Layer Closure of the Uterus During Cesarean Section

In a previous special feature on the technical aspects of cesarean section, the methods of uterine closure were touched upon briefly. A study from Montreal (Bujold E, et al. *Am J Obstet Gynecol*. 2002;186[6]:1326-1330) suggested that single layer closure was associated with a higher rate of uterine rupture in a subsequent pregnancy. In the January 2004 *American Journal of Obstetrics & Gynecology*, a paper emerged in which the authors tracked pregnancies after uteri were closed in the previous pregnancies with either single or double layers. The study was not randomized (nor was the Montreal study). These authors found no difference in the number of uterine ruptures, but less blood loss, shorter operative times, and less endometritis in the single-layer closure group. However, there were more uterine windows noted in those with single-layer closure who needed a subsequent cesarean section.

The authors thought that the possible reasons for the discrepant results between their study and the Montreal study was that they used a nonlocking vicryl suture compared with a locking chromic suture used in Montreal. The authors postulated that a locking stitch predisposes toward tissue ischemia, and chromic has less "staying power" than vicryl. I suppose we will all have to wait for the ultimate randomized trial to get the final answer, but there seems to be no reason at this point to switch back to a double-layer closure. ■

Suggested Readings

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CME Questions

3. Which of the following statements about cancer screening is *false*?

a. Patients who have had a false positive are much more wary about having screening in the future.
b. Most Americans believe that cancer screening detects cancers at an earlier stage.
c. Cost and discomfort have little to do with attitudes held by most Americans regarding cancer screening.
d. Despite several headlines about the lack of utility of mammograms, most American women remain convinced that it is

important to undergo periodic screening mammography.

e. Almost no one thinks that they have had too many screening tests.

4. **The following statements are true regarding hormonal contraception and menopause *except*:**
   a. FSH levels increase with age even in women on long-acting progestin-only contraception.
   b. Many women require contraception after the average age of menopause.
   c. A random FSH level greater than 20 IU/L is an absolute marker of the postmenopausal years.
   d. In most women, FSH escapes sex steroid suppression within 1 week.

Answers: 3 (a); 4 (c)

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

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in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■