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INSIDE

Frequency of Symptoms of Ovarian Cancer in Women Presenting to Primary Care Clinics

ABSTRACT & COMMENTARY

It has been recently recognized and increasingly reported that ovarian cancer patients frequently manifest symptoms, predominately related to their gastrointestinal or urinary tracts, a significant period of time ahead of their diagnosis. Goff and colleagues advance this line of investigation further by conducting a prospective study ascertaining the frequency of self-reported ovarian cancer-associated symptoms between 2 cohorts of patients seeking medical care. The case patients were those about to undergo surgery for a known or suspected pelvic or ovarian mass; the controls were women presenting to one of 2 primary care clinics, in which approximately two thirds were being seen for a specific problem.

The voluntary questionnaire instrument administered to both cohorts asked the respondents to score the severity, frequency, and duration of 20 symptoms generally reported by ovarian cancer patients. In both groups, recurring symptoms were common and non-specific. Symptomatology in control patients was related to the purpose of the visit (general check up vs specific complaint), their underlying disease co-morbidities and their menopausal status.

Not surprisingly, women with the final diagnosis of ovarian cancer generally reported numerically more symptoms of greater severity but of shorter duration of onset compared to either the clinic controls or patients with benign ovarian tumors. Ovarian cancer patients were also statistically more likely to report increased abdominal size, bloating, urinary urgency, and pelvic pain. The combination of the former 3 symptoms was reported 5 times more often in cancer patients than controls. The frequency and severity of these associated symptoms prompted Goff et al to conclude that the symptom triad was important enough to warrant further clinical investigation when identified (Goff BA, et al. *JAMA*. 2004;291:2705-2712).

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COMMENT BY ROBERT L. COLEMAN, MD

One of the more frustrating aspects in the scientific pursuit to identify early stage ovarian cancer is that there is, as yet, no reliable way to accurately allocate individual risk. The prize when such study or modality is discovered would not only be better screening and surveillance but also improved survivorship through earlier stage detection. Currently, clinicians use a variety of radiographic and biologic tests to survey their patients either deemed at increased risk for the disease by history or in response to some symptomatology or physical exam finding that may suggest neoplastic ovarian pathology. Nonetheless, the algorithms developed so far are largely inefficient and imprecise. With respect to symptoms, the imprecision stems from the lack of correlative representation of stage and symptoms experienced and the broad spectrum of these complaints not specifically focused to the ovary or pelvic structures. For instance, many patients will have undergone a series of gastrointestinal diagnostic procedures and interventions before the diagnosis is made or suspected—many times before a pelvic exam is performed.

The current study does affirm previous reports that women with ovarian cancer do have a set of recognizable symptoms. The prevalence is high among women with this disease.[1-3] More than 90% of ovarian cancer patients were symptomatic in the 12 months preceding the diagnosis and two thirds of these reported recurring symptoms. The implication from the identification of the symptom cluster among case patients is that their occurrence should alert the clinician to work-up the patient for ovarian cancer. Unfortunately, strictly using the cluster as a decision tool would miss more than half the cancers and subject many women without cancer to unnecessary and expensive testing and procedures. To bridge this gap, one is called once again to practice the art of medicine. Consideration of these findings obviously can't be done in a vacuum and attest to the importance of appropriate evaluation of key clinical parameters and clues. It also mandates that clinicians hear what their patients are telling them and asking them what they are not. Without more precise diagnostic tools, the detection of early ovarian cancer will rely on this age-old, but arguably diminishing art. ■

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Biophysical Profile with Amniotic Fluid Volume Assessments

ABSTRACT & COMMENTARY

Synopsis: *The AFI offers no advantage in detecting adverse outcomes compared with the single deepest pocket when performed with the BPP. The AFI may cause more interventions by labeling twice as many at-risk pregnancies as having oligohydramnios than with the single deepest pocket technique.*

Source: Magann EF, et al. *Obstet Gynecol.* 2004;104: 5-10.

Assessment of amniotic fluid is a part of all obstetrical ultrasound examinations after the first trimester and has also become a staple in the manage-

ment of high-risk pregnancies as a component of the biophysical profile (BPP). Basically, the methods to estimate the amount of amniotic fluid vary from a rough clinical assessment by, hopefully, an experienced examiner (the gestalt approach), determination of the deepest pocket of fluid, and the full four-quadrant amniotic fluid index (AFI).

Magann et al recently compared AFI with the single deepest pocket technique in a randomized trial involving 537 patients with a variety of high-risk problems. Oligohydramnios was diagnosed when the AFI was 5 cm or less or the deepest pocket was less than 2 × 1 cm. One hundred thirty-two patients (132) of the 264 in the AFI group were diagnosed to have oligohydramnios (38%) vs 46 of the 273 women having the deepest pocket technique (16%). Although the numbers enrolled in the study precluded the statistical power to evaluate many of the morbidity variables, 2 statistically significant differences between groups are worthy of mention. The inductions were doubled in the AFI group (30% vs 15%) and there was a higher rate of cesarean section for fetal distress in the AFI group (13% vs 7%). Yet there were no differences between groups in neonatal complications, Apgar scores, or cord pH.

COMMENT BY JOHN C. HOBBINS, MD

Using standard definitions of oligohydramnios, this study suggests that the AFI labels twice as many patients as having it and, by inference, predisposes twice as many patients to induction of labor.

The major problem with this study is that it was spiked with so many patients with ruptured membranes (22%). Monitoring amniotic fluid volume is a way to indirectly assess fetal condition. In ruptured membranes there is an obvious mechanical reason for the oligohydramnios, initially having little to do with fetal condition. Including these patients simply confuses the issue by mixing apples and oranges.

Amniotic fluid volume can be affected by many factors including maternal hydration, fetal glucose levels, placental perfusion, and fetal surface area. It has been shown that between 100 and 250 cc of amniotic fluid is lost to the placenta at term through an osmotically mediated process that can be affected by changes in villous pressures in conditions such as intrauterine growth restriction (IUGR). Nevertheless, the major common denominator involves fetal urine production, which is diminished when the fetus is deprived. As indicated in previous Alerts, fetuses with IUGR will spare their brains in the early stages of compromise (as evidenced by increasing end diastolic flow in the middle cerebral arteries), and will send less blood to the renal arteries. The oligohydramnios that results simply confirms this shift in priority by the fetus, which also happens in seemingly appropriately grown fetuses towards term and postterm. However, to use this rather gross index of fetal condition as a reason alone to interrupt pregnancy, when other more specific and sensitive Doppler and fetal heart rate information is available, is backward, especially if the pregnancy is preterm. Interestingly, even patients without ruptured membranes in the above study were given corticosteroids if less than 34 weeks and delivered if their oligohydramnios "persisted" during the steroid treatment.

If clinicians are still using oligohydramnios as a reason to deliver, then we better get it right when we tag a pregnancy with oligohydramnios, and the single deepest pocket concept seems to buy us fewer unnecessary inductions and cesarean sections without affecting outcome. ■

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Analyzing Reproductive Performance Before and After Abdominal Myomectomy

ABSTRACT & COMMENTARY

Synopsis: *Abdominal myomectomy might improve reproductive outcome in cases of intramural or subserosal fibroids especially if the patient is less than 30 years of age and the myoma is single.*

Source: Marchionni M, et al. *Fertil Steril*. 2004;82:154-159.

THIS RETROSPECTIVE CASE SERIES OF 72 PATIENTS WITH intramural and subserosal fibroids from an academic center in Italy was designed to look at various reproductive outcome measures before and after surgery over a 3-year time interval. To be considered subserous, the greatest diameter of the tumor had to lie outside the uterine contour. Intramural fibroids had their greatest diameter outside the uterine cavity. Surgical techniques were similar to those used by contemporary gynecologic surgeons.

Prior to myomectomy, the conception rate was 28%. After surgery, it was 70%. For pregnancy loss, the rates were 69% before and 25% after. The live birth rates were 30% and 75% respectively. The only independent predictors of obstetric outcome were age under 30 years of age and numbers of fibroids removed.

COMMENT BY FRANK W. LING, MD

With apologies to the reproductive endocrinologists/infertility subspecialists among our readership, I am enclosing this article within the context of the generalist reviews because of the reality of clinical practice of obstetrics/gynecology. Apologies should also be offered because it is a retrospective analysis and, given our desire for the best evidence possible, it falls short of our gold standard prospective, randomized trial. We should be aware, however, that in our practices we should apply the best data available, and that's what this is—the best recent data available.

All of us have faced the clinical dilemmas presented by infertility and fibroids, either separately or together. This article helps us to put some numbers together with the type of fibroids that we are dealing with. It does not tell us whether or when a particular patient should undergo myomectomy, but it does demonstrate that conception rates are better after myomectomy than they were in the same patients prior to the procedure. However, the difficult questions remain. For example, how do we answer Ms. Smith's questions about her asymptomatic fibroids? How should we deal with the menorrhagia that plagues Ms. Hill? What about Ms. Jones who wants to conceive, but hasn't tried yet? Then there is Ms. Williams who has been trying to conceive unsuccessfully for the past 6 months. What should be done with her?

Well, as always, the traditional principle still applies: treat each patient individually. It is unrealistic to expect the health of the woman with asymptomatic fibroids can be improved. Even though this article does not address this particular problem, Ms. Smith should probably just be followed. Ms. Hill's menorrhagia should be managed medically if possible, using NSAIDs and possibly hormonal management, prior to consideration of myomectomy. Ms. Jones' desire to conceive isn't necessarily affected by the fibroids—at least not yet. Attempts to conceive with the fibroid(s) in situ can be encouraged. If pregnancy doesn't occur, then her situation would be similar to that of Ms. Williams who has failed to conceive the past 6 months.

Putting myomectomy into the clinical perspective of infertility carries with it the responsibility to advise that a basic infertility work-up be done. First of all, the patient's age and reproductive history will go a long way to determine the appropriate options. Certainly a semen analysis to evaluate a patient's partner is mandatory. Similarly, knowing the ovulatory status of the patient is critical. Whether by way of a history of regular menses, or a luteal phase endometrial biopsy, or a day 21-serum progesterone, knowing that the patient is ovulating is also needed before undergoing myomectomy. Finally, some pre-operative evaluation for tubal patency will help the surgeon better provide informed consent. For example, if there is distal tubal obstruction, the surgery will be significantly different from a simple myomectomy. Furthermore, if proximal obstruction is found on a pre-operative hysterosalpingogram, surgery and its outcomes are clouded even more.

The issues surrounding scheduling a myomectomy may be complex and all the factors mentioned above may be interrelated with the pre- and post-myomectomy conception rates listed in the article. The article is a useful tool to both counsel patients and remind us that surgical removal of fibroids by gynecologic surgeons is a potentially effective treatment for the properly selected patients. ■

Long-Term Use of Phytoestrogens and the Endometrium

ABSTRACT & COMMENTARY

Synopsis: *Long-term treatment (up to 5 years) with soy phytoestrogens was associated with an increased occurrence of endometrial hyperplasia. These findings call into question the long-term safety of phytoestrogens with regard to the endometrium.*

Source: Unfer V, et al. *Fertil Steril*. 2004;82:145-148.

UNFER AND COLLEAGUES FROM ITALY CONDUCTED A randomized, double-blind, placebo-controlled study of soy phytoestrogens that lasted 5 years. Two hundred nintey-eight (298) women completed the trial, 179 women receiving daily soy tablets containing 150 mg isoflavones. Although no cases of malignancy were detected, after 5 years there were 5 cases of simple hyperplasia (3.2%) and 1 case of complex hyperplasia (0.6%) in the treated group compared with none in the placebo group.

COMMENT BY LEON SPEROFF, MD

Phytoestrogens is a descriptive term applied to nons-

teroidal compounds that have estrogenic activity or are metabolized into compounds with estrogenic activity. Phytoestrogens are classified into 3 groups: isoflavones, lignins, and coumestans. Soybeans contain isoflavones, the most common form of phytoestrogens (specifically genistein, daidzein, and a little glycitin). The average Japanese intake of isoflavones is about 50 mg per day. The rest of Asia has an average consumption of about 25-45 mg per day, and Western intake is less than 5 mg per day. The dose of isoflavones in this study is therefore relatively high, about twice the recommended dose (60 mg isoflavones) for a lipid response (a dose that is present in 25 g soy). Previous studies have concluded that isoflavones have no effect on the endometrium, but not a single study was longer than a year or two.

There is a case report of adenocarcinoma of the endometrium in a woman using phytoestrogens (Johnson E, et al. *Obstet Gynecol.* 2001;98:947-950). Is it possible that there is a risk of endometrial cancer associated with either high doses of phytoestrogens or long exposure to even standard or low doses or both? This 5-year trial suggests that it is appropriate to be concerned and questions the safety of low-dose estrogen exposure.

Estrogen normally promotes mitotic growth of the endometrium. Abnormal progression of growth through simple hyperplasia, complex hyperplasia, atypia, and early carcinoma has been associated with unopposed estrogen activity, administered either continuously or in cyclic fashion. Only 1 year of treatment with unopposed estrogen (0.625 mg conjugated estrogens or the equivalent) will produce a 20% incidence of hyperplasia, largely simple hyperplasia. In the 3-year PEPI trial, 30% of the women on unopposed estrogen developed adenomatous or atypical hyperplasia. Some 10% of women with complex hyperplasia progress to frank cancer, and complex hyperplasia is observed to antedate adenocarcinoma in 25-30% of cases. If atypia is present, 20-25% of cases will progress to carcinoma within a year.

Approximately 40 case-control and cohort studies have estimated that the risk of endometrial cancer in women on estrogen therapy (unopposed by a progestational agent) is increased by a factor of somewhere from 2 to 10 times the normal incidence of 1 per 1000 postmenopausal women per year. The risk increases with the dose of estrogen and with the duration of exposure (reaching a 10-fold increase with 10-15 years of use, perhaps an incidence of 1 in 10 with very long-term use), and lingers for up to 10 years after estrogen is discontinued. Although most endometrial cancer associated with estrogen use is of low grade and stage, and associated with better survival (probably because of early detection), the overall risk of invasive cancer and death is increased.

A short-term study (2 years) has indicated that one-half the usual standard dose of estrogen (in this case, 0.3 mg esterified estrogens) was not associated with an increased incidence of endometrial hyperplasia compared with a placebo group.[1] However, we have learned that long-term exposure to low levels of estrogen can induce abnormal endometrial growth (it just takes longer), and, in my view, lower dose estrogen therapy requires either endometrial assessment annually or the addition of a progestin to the treatment regimen. This is supported by a case-control study from Washington that contained 18 cases and 9 controls who had exclusively used only 0.3 mg/d of unopposed conjugated estrogens.[2] The use of this half-dose estrogen was associated with an overall 5-fold increased risk of endometrial cancer, reaching a relative risk of 9.2 in current users for more than 8 years' duration. Although limited by small numbers, the conclusion is logical and consistent with our understanding of the importance of duration of exposure to any increased level of endometrial estrogen stimulation. In a randomized trial, endometrial hyperplasia was increased after 2 years of treatment with 0.3 mg conjugated estrogens without a progestin.[3]

The clinical principle appears to be the following: as the dose of daily estrogenic exposure decreases, the duration of exposure required to induce endometrial hyperplasia and cancer increases. This also raises concern regarding vaginal administration of very low doses of estrogen. The systemic absorption of estrogen from the low-dose estradiol ring or tablet is very low, especially after the vagina achieves estrogen-induced maturation (about 3 months). One would expect this low level of absorption to be free of the risk of endometrial hyperplasia; however, all studies have been too short (all 1 year or less, except one 2-year study) to determine long-term endometrial safety. Although systemic absorption occurs, the circulating estradiol levels with these low-dose methods remain in the normal postmenopausal range. Because the small increase in circulating estradiol levels causes distant target tissue responses (eg, an increase in bone density or an improvement in the lipid profile)[4,5] clinicians cannot assure patients that these methods are totally free of systemic activity. Although the change in blood levels is very slight, and for that reason not effective for the relief of vasomotor symptoms, I believe long-term treatment requires ultrasonographic monitoring of endometrial thickness with biopsy when indicated. This ultrasonographic approach is more preferable than complicating the treatment regimen with the addition of a progestational agent. It makes sense for each patient to titrate her dose and schedule of treatment to balance an effective response with minimal dosing.

For women who are breast cancer survivors and are considering this treatment, clinician and patient must accept a small, but real, unknown risk.

Long-term exposure to low doses of estrogen or to weak estrogenic substances (the phytoestrogens) may not be free of risk for endometrial hyperplasia and cancer, and, therefore, clinical concern and monitoring are indicated. ■

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Patient Preferences for Treatment of Dysfunctional Bleeding

ABSTRACT & COMMENTARY

Synopsis: *A majority of patients scheduled for endometrial ablation or a levonorgestrel-releasing IUD were willing to accept a 50% likelihood of treatment failure to avoid hysterectomy.*

Source: Bourdez, et al. *Fertil Steril*. 2004;82:160-166.

These Dutch investigators conducted structured interviews with patients who were scheduled to undergo endometrial ablation (n = 96), insertion of a levonorgesterel-containing IUD (n = 23), or hysterectomy (n = 25). All patients were suffering from dysfunctional uterine bleeding defined as menorrhagia in the absence of intracavitary abnormalities unresponsive to medical management. Patients were asked to describe both their most significant medical problem as well as the reasons for selecting their respective treatment option. After the advantages and disadvantages of all 3 treatments were explained, subjects were given various hypothetical success rates of the treatments to determine at what level of failure the patient would select it. In this interview, the hypothetical success rate for endometrial ablation was initially quoted as 10%. If the patient opted for hysterectomy (given a hypothetical success of 100%), the success of ablation was then increased to 20%. The patient was asked to choose again at that level. This process was repeated until the patient identified a success level at which she would select ablation. A similar process was done with regard to IUD.

The main reasons that patients chose IUD were: did not want hospital admission (9/23), did not want anesthesia (6/23), desired fast recovery (5/23), and did not want hysterectomy (5/23). Among those choosing an ablation, primary motivations included: did not want IUD (21/96), did not want hysterectomy (18/96), and desire for short admission (14/96). Among those choosing hysterectomy, the vast majority, 20 out of 25, desired a definitive solution to their problem.

Among patients scheduled for endometrial ablation, 70% would opt for either ablation or IUD insertion if the presumed success rate of the treatment were 50%. For women choosing the IUD, this would be preferred over hysterectomy by 95% if the proposed success exceeded 50%. Bourdez and colleagues conclude that gynecologists should recognize that fully informed patients might be willing to accept a particular rate of failure if they can undergo a noninvasive technique.

■ COMMENT BY FRANK W. LING, MD

If you have read this up to this point and are thinking that this article is a no-brainer, then my response is, "Great!" You are likely a physician who tries to address the wide array of potential issues that patients want discussed prior to choosing a treatment for dysfunctional bleeding/menorrhagia. How patients ultimately make decisions is an absolutely critical aspect of what we do every day and the better that we appreciate the individual patient's needs, the better that we will be able to cope with them. In the long run, this results in greater patient satisfaction irrespective of success and failure rates.

As a starting point, the importance of complete and accurate information for each patient is a given. Ideally, the data on success/failure rates, complications, implications for sexual functioning, costs, resumption of normal lifestyle, etc, are presented in a fair and balanced fashion. Each of us who advises patients needs to separate ourselves from our favorite technique or hobby horse so that the patient can hear things objectively. Admittedly, patients commonly look to us for advice and guidance, but we should acknowledge that our best efforts to provide truly informed consent are always being filtered.

Access to Internet web sites, consultations from other physicians, advice from well-meaning friends and relatives: these are all factors whether we like it or not. Even before we even see the patient, she may well already have decided on what she wants. Rather than

only telling the patient what she needs, it is our responsibility to also listen to what she thinks she needs. By no means am I endorsing just doing what the patient wants, but I am adamant that those of us who have the privilege to care for the health of women should take care of the whole patient. Let's make sure that the patient is allowed to express her own opinions, explain why she is inclined the way she is, and truly participate in the ultimate decision.

Knowing that each patient is willing to accept a certain risk of failure for this or any procedure is a critical part of the informed consent process. The challenge is to make sure that the good medicine that you practice takes into account the scientific data as well as her idiosyncratic needs. I think that's called the Art of Medicine. ■

Special Feature

Should Gynecologists Screen for Hypothyroidism?

By Sarah L. Berga, MD

IT IS HARD TO BELIEVE, BUT WHOM, HOW, AND WHEN TO screen for thyroid disease is a highly controversial topic. The controversy is fueled by uncertainty about which populations are at risk, short-term cost vs benefit considerations, lack of consensus about when to initiate treatment, whether to use a mix of thyroxine and thyronine, and debate about the long-term risks of treating vs not treating asymptomatic individuals. From the gynecologist's perspective, there are 2 populations that need to be screened for hypothyroidism: those who are getting older and those who might get pregnant. There is less controversy about screening for thyroid disease in older women. The debate centers on when to screen asymptomatic women, but there is generally consensus that it should start no later than age 50 years and be done at intervals of 1-3 years, with some professional groups advocating that screening begin at age 35 years in women but not men. Surprisingly, although the risks to the fetus of undetected maternal hypothyroidism are known and untoward, there is much more controversy about screening younger, asymptomatic women who might get pregnant.

Getting ready for pregnancy has now become a big deal and the responsibility for counseling women about what to do in advance of conceiving generally rests with the gynecologist and his or her designate. At a minimum, we need to counsel women about smoking, alcohol, and other drug cessation, talk about issues such as exposures to cats, workplace toxins, and exercise, ascertain whether she is immune to rubella, review folate use and other nutritional issues, and offer genetic counseling or testing for a growing list of conditions. Less well recognized is the need and rationale for ascertaining thyroidal status.

Why does this responsibility for preconceptual screening for hypothyroidism fall largely to the gynecologist? There are 2 main reasons. The first is that we are already in the business of preconceptual counseling. The second is that few, if any, other specialists are likely to have the opportunity to screen, if only because most women would not think to tell them about their plans to attempt to conceive.

A recent article and accompanying editorial in the *New England Journal of Medicine* (Alexander EK. Timing and Magnitude of Increases in Levothyroxine Requirements during Pregnancy in Women with Hypothyroidism. *N Engl J Med*. 2004;351:241-249) provides a fresh perspective on why it is imperative to ascertain thyroidal status in women prior to conception. The source article by Alexander et al focused on determining thyroxine needs in pregnancy in women with known thyroid disease. Levothyroxine requirements increased as early at the fifth week of gestation, well before the time of the first prenatal visit. The increased requirement was substantial, in the range of 30%. After about 20 weeks of gestation, the increased need for levothyroxine had reached a plateau and remained steady throughout the rest of gestation. In the introduction, the authors point out that 3-10% of women develop primary hypothyroidism and that 1-2% of women of childbearing age take levothyroxine. They estimate that a minimum of 12,000 to 16,000 infants are born each year to women with either inadequately treated or undetected primary hypothyroidism.

The accompanying editorial (Toft A. Increased Levothyroxine Requirements in Pregnancy—Why, When, and How Much? *N Engl J Med.* 2004;351:292-294) points out that there is ongoing concern that "even borderline maternal hypothyroxinemia early in pregnancy may compromise fetal neuropsychological development." This is not entirely surprising when one considers, as an obstetrician-gynecologist might, that the fetal brain is entirely dependent on maternal thyroxine (T4) for making its own triiodothyronine (T3) until the fetal hypothalamic-pituitary-thyroidal axis becomes active, which is certainly no sooner than the second

trimester. Further, since maternal thyroid-stimulating hommone (TSH) is partly regulated by feedback mechanisms that include the circulating concentration of T3, but the fetal brain cannot use maternal T3, it may not be possible to rely on solely on TSH as an indicator of maternal thyroidal status to reflect fetal needs.

On the basis of the foregoing considerations, Alexander et al recommend that women increase their dose of levothyroxine by the equivalent of 2 daily doses each week as soon as pregnancy is confirmed. However, in his editorial, Toft suggests that it would be simpler to immediately raise the daily dose by 25 to 50 microgram daily. Toft further suggests that screening during pregnancy should occur promptly after the diagnosis of pregnancy is made and that screening can be relaxed after the 20th week of gestation. Toft also advocates for universal screening of women of childbearing age, but if universal screening is not adopted, he suggests then that it should certainly be performed for those with any evidence of an underlying autoimmune diathesis, including type 1 diabetes mellitus, and those a family history of thyroid disease. Most authorities now recommend screening with both a TSH and a free thyroxine, as there are many circumstances in which the TSH does not adequately reflect thyroxine status. Now that highly specific and sensitive assays for free thyroxine have been developed and disseminated, it has become nearly universal to bundle the cost of the TSH and free T4, with the usual cost for both in the range of $30 with usual turnaround time of less than 24 hours.

This brings me to my final point. Those of us in the infertility field bear a special burden in terms of screening for maternal thyroid status. First, it is generally recognized that stress suppresses TSH, rendering it unreliable as an index of euthyroidism. The condition of "sick euthyroid syndrome" was first recognized in hospitalized patients, but it is also seen in ambulatory populations as well. Of particular concern is the anovulatory woman who does not have an obvious cause for her anovulation. I am thinking of those who have variants of functional hypothalamic amenorrhea in its subtler, oligo- or eumenorrheic forms. We (Berga SL, et al. *Fertil Steril*. 1997;67:1024-1030) and others have clearly described what amounts to hypothalamic hypothyroidism in women with frank functional hypothalamic amenorrhea, with a deficit of thyroxine in the range of 30% before pregnancy. If pregnancy is to be induced in these women, one would clearly need to be mindful of the notion that the suppressed hypothalamic thyroid-releasing hormone (TRH) drive may not correct during prenancy, that there may be a pre-existing thyroxine deficit, and there may be an even greater need for increased thyroxine than in women with organic forms of hypothyroidism. There are no studies to guide us in this regard, but as both Alexander et al and Toft point out, in pregnancy a little too much thyroxine appears to be a far better tactic than too little. The safest alternative would be to bypass the use of ovulation-inducing agents in favor of measures that reduce stress and the accompanying hypothalamic hypogonadism, such as variants of cognitive behavior therapy (Berga SL, et al. *Fertil Steril.* 2003;80:976-981) or hypnosis (Tschuggel W, et al. *Fertil Steril*. 2004), but I understand that this approach is not always acceptable to patients and physicians.

In summary, the mother is the sole source of thyroxine for the fetal brain during the first trimester and the maternal requirement for thyroxine increases as early as the 5th week of gestation. Obstetrician-gynecologists need to remember to screen for functional and organic forms of hypothyroxinemia in women of childbearing age by obtaining a TSH and free thyroxine prior to conception and to recommend an increase of 25 to 50 micrograms daily as soon as pregnancy is recognized. ■

CME Question

5. The following statements are true regarding the association between endometrial cancer and postmenopausal estrogen therapy except:

a. With standard doses of estrogen, unopposed by a progestin, a substantial number of women develop hyperplasia within one year of treatment.
b. Once a women discontinues estrogen-only therapy, there no longer is an increased risk of endometrial cancer.
c. The risk of endometrial cancer increases with increasing dose and duration of exposure.
d. Even very low dose vaginal administration of estrogen produces systemic effects.

Answer: 5 (b)

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

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stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).