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INSIDE

Does Cervicovaginal Fetal Fibronectin Really Play a Role in the Diagnosis of Preterm Labor?

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships related to this field of study.

A STUDY THAT ATTRACTED SOME ATTENTION AT THE SOCIETY FOR Maternal-Fetal Medicine meeting last year was recently published in the *American Journal of Obstetrics and Gynecology*. It dealt with the usefulness of fetal fibronectin (fFN) and cervical length (CL) in predicting which patients with preterm contractions (PTC) were truly in preterm labor (PTL).

In a collaborative study involving patients in the United States and Chile, Gomez and colleagues evaluated 215 patients admitted to the hospital with PTC and intact membranes with transvaginal sonograms to assess cervical length and examination of vaginal secretions for fFN. All patients were treated similarly with tocolytics.

Forty-three of these patients (20%) delivered prior to 35 weeks. Both tests performed well using receiver-operator curves in predicting those delivering within 48 hours (7.9%), 7 days (13%), and 2 weeks (9%). For example, if CL was < 1.5 cm, 36.7%, 56.7%, and 56% delivered within 48 hours, 1 week and 2 weeks, respectively. If CL was ≥ 1.5, only 3.2%, 5.9%, and 9.2% delivered within 48 hours, 1 week and 2 weeks, respectively. If the cervix was ≥ 3 cm at the time of admission, the chances of delivering within 2 weeks were < 5%.

When fFN was positive 19%, 34.6%, and 42.3% delivered within 48 hours, 1 week, and 2 weeks and, if negative, < 8% delivered within 2 weeks.

Actually, CL was a somewhat better performer than fFN. However, when fFN was added to CL as an adjunctive test at admission, the predictive ability of the combination was impressive. For example, if both

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were positive (CL of < 1.5 cm), 75% delivered within 1 week of admission, 75% delivered prior to 32 weeks, and 81.3% delivered before 35 weeks. If both tests were negative (CL of ≥ 3 cm), then 2.2% delivered within 1 week and 0% delivered < 32 weeks (Gomez R, et al. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. *Am J Obstet Gynecol*. 2005;192:350-359).

COMMENTARY

It is interesting that most early investigation involving both CL and fFN was focused on the ability of each test, performed between 20 and 24 weeks in at-risk patients, to predict preterm delivery later on.[1-5] The concept was to earmark patients who might benefit from preventive therapy (unfortunately, with prophylactic regimens that have yet to materialize).

Frankly, one of the most difficult problems providers encounter today involves patients presenting later in pregnancy with preterm contractions. All of the studies to-date indicate that a majority of these patients are not in PTL and yet are subjected to days of confinement while receiving therapy with uncomfortable side effects and some risk (often at a cost exceeding $1,000 per day). A few studies have addressed the ability of fFN or CL to sort out which patients really are at risk to deliver prematurely, but these studies have largely concentrated on one test or the other. This study, while pitting one test against the other, has now shown us that the 2 tests, when used adjunctively, can give the most powerful information as to which patients really are at greatest risk of preterm birth and, just as importantly, which are not.

The main interpretive drawback of this study is that all patients were tocolyzed. Therefore, we do not know if those with reassuring tests might have had the same favorable outcome without tocolytics, as I suspect is true from data from other studies.

Careful review of the results suggests little extra benefit from fFN in patients with a CL of ≥ 3 cm. Interestingly, only 3.7% of those with long cervices and a positive fFN deliver at < 32 weeks compared with 1.1% when fFN was negative. Therefore, deleting the fFN in those with long cervices would decrease expense with a minimal risk of missing a patient destined to deliver at < 32 weeks.

The greatest drawback today to the use of either test is for providers, despite the reams of data in the literature, to have enough confidence in the negative tests to forego tocolytics and continued hospitalization. ■

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Routine Surgical Staging in Grade 1 Endometrial Cancer Appears Beneficial

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol Myers Squibb, and Ortho Biotech.

Synopsis: *Surgical staging in patients presenting with grade 1 endometrial cancer significantly impacted postoperative treatment decisions in 29% of patients. Omitting lymphadenectomy in patients presenting with grade 1 endometrial cancer may lead to inappropriate postoperative management.*

Source: Ben-Shachar I, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. *Obstet Gynecol*. 2005;105:487-493.

Endometrial cancer is the most common gynecologic malignancy and is usually characterized by limited disease at presentation. Among the number of known prognostic factors, grade of disease is one frequently used to triage patients for formal surgical staging. Ben-Shachar and colleagues address the clinicopathological features and treatment recommendations of well-differentiated (grade 1) endometrial cancer in a retrospective review of surgically staged patients. Over a 6.5-year period, 181 patients were identified with preoperative grade 1 endometrial cancer. Whether defined by endometrial biopsy or dilation and curettage, all patients underwent formal surgical staging including pelvic and para-aortic lymphatic dissection, cytology and for intraoperatively identified high-risk histology, intraperitoneal biopsies or debulking. Final histology of grade 1 was seen in 81% of patients with no difference identified between the preoperative sampling techniques. Two patients with grade 1 preoperative sampling were found intraoperatively to have sarcoma.

In all, half of the patients were found with non-invasive disease. The remainder had myometrial invasion (33%), cervical extension (7%), adnexal metastases or positive cytology (4%), nodal spread (4%), or intra-abdominal spread (3%). Based on commonly used criteria for surgical staging (grade 1-2 with depth of invasion > 50%, grade 3, cervical extension, high-risk histology), 26% of these grade 1 lesions would have warranted complete staging. Importantly, more than half of these of patients (n = 30/54) with high-risk uterine features required no further therapy based on their surgical findings. Overall, 29% of grade I patients (12% treated and 17% untreated) were benefited by information gained by formal surgical staging. Ben-Shachar et al conclude that even this apparent "low-risk" group of patients requires formal surgical evaluation for treatment precision.

COMMENTARY

Following a series of prospective clinico-pathological observational studies, FIGO, in 1988, changed the staging schema of uterine cancer from one derived from preoperative clinical findings to one based on surgical evaluation of the uterine and extra-uterine sites as well as grade. Appropriate assignment of stage now requires resection of the uterus, evaluation of peritoneal cytology, retroperitoneal node evaluation and peritoneal inspection. The immediate implication from this new classification algorithm was that specialized and directed surgical biopsy is needed to provide information that more accurately describes the distribution of disease. While the principal goal of staging is to facilitate communication among physicians and patients regarding a designated disease status, the allocation of a particular stage is often used for treatment triage and in many cases, has prognostic implications. A check on surgical staging in a 1996 report revealed that less than a third of newly diagnosed endometrial patients were undergoing staging procedures.[1] While likely increased today, there is still a prevailing bias that the earliest lesions (grade 1) don't carry enough risk to warrant routine formal surgical staging. This is the principal focus of the current paper by Ben-Shachar et al.

Precision of treatment in this disease implies that those who need adjuvant treatment get it and those who don't, don't get it. For instance, 20 patients with grade I tumors were found with nodal or intraperitoneal metastases, including 4 in whom no other clues to its presence (depth of invasion or higher grade tumor) were apparent. In addition, 30 patients with high-risk uterine features but without metastases were not treated after surgical staging. This mirrors the results of a survey of gynecologic oncologists who would recommend adjuvant therapy based on whether surgical staging data were available. In nearly every category of grade and depth of invasion, a significant "overuse" of adjuvant therapy would be recommended in the absence of surgical staging data.[2] Further, some investigators have advocated complete lymphadectomy as a therapeutic maneuver in patients with uterine cancer.[3] However, study limitations such as

patient selection bias have made this a controversial topic. Fortunately, the merits of this procedure are being evaluated in a prospective randomized trial (MRC-ASTEC trial).[4]

The case for routine surgical staging in medically fit patients is usually counterbalanced by concerns of morbidity and simple availability. Although, experience from prospective randomized trials and retrospective series suggests the morbidity is low, there is little solution for those patients treated in areas where gynecologic oncology expertise is unavailable. Knowledge of staging procedures by the gynecologist can aid other surgeons if called upon to provide the needed samplings. In this regard, an important distinction should be made for high-risk histology (eg, papillary serous), where intraperitoneal spread rates, even among apparent stage I patients, occurs sufficiently high enough to warrant intraperitoneal staging similar to ovarian cancer.[5]

There's little controversy that patients with grade 1 lesions are most likely to have the most favorable uterine findings. However, utilizing that rule of thumb to plan surgical management overlooks more than a quarter of patients who would benefit from formal evaluation. Whether that is accomplished by patient referral or co-management with gynecologic oncology is immaterial as long as the appropriate data are retrieved.[6] ■

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Increased Nuchal Translucency with Normal Karyotype

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Synopsis: *If the fetus survives until midgestation, and if a targeted ultrasound at 20 to 22 weeks fails to reveal any abnormalities, the risk of an adverse perinatal outcome and postnatal developmental delay is not statistically increased.*

Source: Souka AP, et al. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol*. 2005;192: 1005-1021.

SOUKA AND COLLEAGUES HAVE RECENTLY PUBLISHED a review that should be very helpful to the clinician confronted with the dilemma of counseling patients whose fetuses have increased nuchal translucencies (NTs) in the first trimester.

The concept of first trimester screening with ultrasound and maternal biochemistry is taking off in a big way in the United States, and, not surprisingly it has triggered fallout involving standardization of examinations, training of sonographers and sonologists, and the usual politics of who should be overseeing these activities.

The simple reason for the belated but, now, genuine enthusiasm for the first trimester screening process is that it works. The sensitivity of the method to screen for Down syndrome (DS) is around 85%. When combined with second trimester biochemistry and a genetic sonogram, the sensitivity, accordingly to FASTER trial data, is almost 100%. However, until now only sparse information has been available to clinicians regarding what to tell their patients whose fetuses have increased NTs with normal karyotypes.

In the above review, which surfaced in April, 2005, data were combined from Souka et al's extensive experience and from other published studies to enlighten us on the meaning of an increased NT based on size alone.

First, in data from all pregnancies (karyotypically normal and abnormal) if the NT was between 11 and 13 weeks was between the 95th and 99th percentile, the chance of a karyotypic abnormality was 3.7%. Also, the risk of fetal death was 1.3% and risk of a major fetal anomaly was 2.5%. Nevertheless, in the same group there was a 93% chance of being alive and well

after birth. However, if the NT was above 3.5 mm, the risk of fetal death, anomaly, and abnormal karyotype rose exponentially to a point where only 15% would be alive and well when the NT exceed 6.5 mm (*see Table*).

Table

Relation between nuchal translucency thickness and prevalence of chromosomal defects, miscarriage, or fetal death and major fetal abnormalities.

Nuchal translucency	Chromosomal defects	Fetal death	Major fetal abnormalities	Alive and well
< 95th percentile	0.2%	1.3%	1.6%	97%
95th-99th percentile	3.7%	1.3%	2.5%	93%
3.5-4.4 mm	21.1%	2.7%	10.0%	70%
4.5-5.4 mm	33.3%	3.4%	18.5%	50%
5.5-6.4 mm	50.5%	10.1%	24.2%	30%
> 6.5 mm	64.5%	19.0%	46.2%	15%

Source: *Souka AP, et al. Am J Obstet Gynecol. 2005;192:1005-1021.*

Now if one were to concentrate only on those fetuses with normal karyotypes, the data from 27 studies involving 6153 fetuses (in which varying cutoffs for increased NT were used) show that the overall risk of fetal anomalies was 7.3%.

The most common anomalies encountered were a cardiac abnormality. For example, data accumulated from 4 studies involving 3448 patients showed that if the NT was 2.5-3.4 mm, cardiac anomalies occurred in 17/1000 fetuses. If the NT was > 3.4 mm, the risk of cardiac anomalies rose to 78/1000. Most birth statistic centers quote a prevalence of congenital heart disease in the overall population to be about 5-8/1000.

Other common anomalies associated with increased NTs, with or without a cardiac component, are diaphragmatic hernia, exomphalos, body stalk abnormalities, skeletal defects, and various syndromes such as fetal akinesia, Noonan syndrome, Smith-Lemli-Opitz syndrome, and spinal muscular atrophy. Those not seemingly associated with increased NT were neural tube defects, holoprosencephaly, gastroschisis, and renal anomalies.

Last, the few studies that have addressed the relationship between increased fetal NT and developmental delay in the overtly normal infant fortunately have shown no correlation.

COMMENTARY

As indicated in the Souka et al paper, the risk of a chromosome abnormalities when the NT is above the 95th percentile (in relationship to the crown-rump length) exceeds 3.7% and because this risk is easily greater than the risk of invasive sampling either by CVS or amniocentesis, many patients will choose to determine their fetus' karyotype. However, until now, it has been unclear what risk to quote to these patients for an adverse outcome once they are informed of the good news regarding the normal karyotype.

Here are some follow-up suggestions for these patients:

1. Since many fetal anomalies can be identified by an early transvaginal ultrasound exam at 12-15 weeks, most patients would benefit from a fetal survey at this time.
2. At 16-18 weeks, a majority of the anomaly syndromes mentioned above can be suspected with a comprehensive transabdominal examination.
3. Since cardiac anomalies are so prevalent in this fetal population, it is strongly suggested that a fetal echocardiogram be accomplished at 22-24 weeks.

If these are all normal, the authors have shown that the risk of fetal anomalies, fetal death, or neonatal problems is not statistically increased. ■

Special Feature

Endometrial Cancer: Surprising Reports

By Leon Speroff, MD, Editor

Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland

EPIDEMIOLOGISTS AT THE NATIONAL CANCER Institute organized and conducted a retrospective cohort study, recruiting patients treated between 1965 and 1988 from endocrine and infertility practices in 5 academic centers. Data on patient characteristics were collected by questionnaires returned by 5,597 patients from a total of 8,431 originally identified. Clinical information on uterine cancers was obtained from medical records and cancer registries in addition to the questionnaires. Thirty-nine percent of the subjects (a total of 3,280) had been treated with clomiphene. Uterine can-

cers (a total of 39 cases) were tested by statistical analysis for an association with clomiphene treatment. Of the 39 women, the histologic diagnosis could be identified only in 23 (19 adenocarcinoma, 1 clear cell, 1 papillary, 1 papillary serous, 1 unknown). The authors concluded that clomiphene may increase the risk of uterine cancer, with a higher risk associated with higher doses.[1]

The UK Million Women Study reported follow-up data on 716,738 postmenopausal women who used daily, combined estrogen-progestin (22%), sequential estrogen-progestin (45%), estrogen only (4%), and tibolone (9%).[2] The reported results represent an average of 3.4 years of follow-up. The Study data were recorded from questionnaires returned prior to the mammography and the women were followed with another questionnaire 2-3 years after recruitment to determine cancer incidence and death. During the follow-up period, there were 1,320 cases of invasive endometrial cancer. Not surprising, the risk of endometrial cancer was reduced with the use of continuous, combined estrogen-progestin, but surprisingly, increased with the use of tibolone. The use of sequential estrogen-progestin neither increased nor decreased risk, and estrogen-only had an increased risk of 1.45 (1.02-2.06) The adverse effects of tibolone and estrogen-only were greatest in thin women and the beneficial effect of combined estrogen-progestin was greatest in obese women. In fact, in women who were not overweight, daily estrogen-progestin use did not change the risk compared with never users. The results were adjusted for multiple factors, including age, parity, oral contraceptive use, alcohol consumption, and BMI.

Treatment	Cases	Relative Risk	Confidence Interval
Continuous Estrogen-Progestin	73	0.71	(0.56-0.90)
Tibolone	86	1.79	(1.43-2.25)

The Clomiphene Study

Even though respected colleagues of mine are coauthors of this report and Louise Brinton, the senior author, has a long track record in epidemiology, the publication of this paper in a respected journal of epidemiology boggles my mind. I suppose the motivation for the authors' interest can be traced to the similar chemical structure and biologic actions of tamoxifen and clomiphene. But exposure to clomiphene for 5 days monthly for less than one year is very different than daily treatment for several years with tamoxifen at a dose double what is used in Japan to induce ovulation.

The actual number of uterine cancers in clomiphene users that was recorded was 19. This was compared to 8.9 cases, the number expected in the general population in the United States, giving a risk ratio of 2.14 with a confidence interval of 1.3-3.3. Six cases with clomiphene at a total dose less than 900 mg gave a risk ratio of 1.91 that was not statistically significant, and 13 cases with a dose greater than 900 mg provided a ratio of 2.26 with a confidence interval of 1.2-3.9. Overall, infertile patients had an increased risk of uterine cancer: ratio of 1.56 (1.1-2.1). The authors obviously base their overall conclusion on the comparison between the clomiphene users and the general population. We learned from the studies on the risk of ovarian cancer associated with ovulation-inducing drugs, that this is an inappropriate comparison.[3] Infertile women are not the same as women in the general population; these are two different populations, with different characteristics. Even comparing users and nonusers of clomiphene in infertile patients does not achieve the goal of matching the two groups. Users of clomiphene will be mostly anovulatory women (many with insulin resistance) with the remainder being women with unexplained infertility. Nonusers will represent all other diagnoses of infertility, a varied group that would fail to match the personal and hormonal characteristics of the user group. An accurate assessment requires a randomized, placebo-controlled trial in a uniform population of anovulatory women, a study that is unlikely ever to be performed.

When the authors compared clomiphene users to never users, not a single analysis indicated a statistically significant increase in risk, including the assessment of dose and number of cycles of exposure. This didn't prevent the authors from concluding that their study demonstrated a dose-response effect.

When the authors analyzed various risk factors for uterine cancer, they found the expected association with the use of estrogen-only postmenopausal hormone therapy and with obesity, but no reduction was associated with the use of oral contraceptives, a well-documented benefit of oral contraceptive use that lasts for at least 20 years after discontinuation. The failure to find this benefit of oral contraceptives seriously questions the veracity of the study.

The authors adjusted their analyses for anovulation, obesity, and nulligravidy, and concluded that these factors had little effect on the risk estimate, suggesting an independent effect of clomiphene. This is not surprising since the effect of clomiphene analyzed in their infertile population never achieved a statistically significant increase anyway.

In the discussion, the authors emphasize that clomiphene treatment was associated with the highest risk in women who first used clomiphene 20 or more years ago. They argue that this significant latency effect

suggests that clomiphene initiates carcinogenesis and that this is consistent with the fact that uterine cancer is a slow growing tumor. But in fact, the latent period for endometrial cancer is closer to 5 years; exposure for only one year to postmenopausal unopposed estrogen increases the risk of cancer; and when atypia is present, 20-25% of cases progress to carcinoma within a year.[4,5] It makes more sense to me that factors in the 20 years since treatment with clomiphene are more important in these results than the treatment.

This report demonstrates the harm that can be produced by overanalysizing data based on a small number of cases. The authors conclude in their discussion that it is likely that "clomiphene increases uterine cancer risk simply by indirectly increasing estrogen levels during the first half of the menstrual cycle." However, in the majority of cases, clomiphene treatment is followed by ovulation with its progesterone-induced inhibition of endometrial growth. Clinicians should not be impressed with this study of a small number of cases that was hampered by a large percentage of subjects that could not be traced, refused participation, or did not complete a questionnaire.

The Million Women Study

To refresh your memory, the Million Women Study recruited women between 1996 and 2001 from those invited by the UK National Health Service Breast Screening Programme to have screening mammography every 3 years, and about 45% had used postmenopausal hormone therapy. The many flaws in the Million Women Study were listed in various articles and letters to the editor after the publication of the breast cancer results.6 For example, the Million Women Study collaborators like to point out that ". . .self-reported information at recruitment showed 97% agreement with prescription records for the type of HRT currently used, and 95% agreement with self-reported information."[2] These are impressive percentages, but I have reviewed their report, and I discovered that only 527 of the nearly million women had their records evaluated.[7]

The accompanying editorial is written by a team from the National Cancer Institute, headed by Louis Brinton, the senior author of the clomiphene results reviewed above, and offers no criticisms of the Million Women Study. The editorial refers to another report that suggested an increased risk of endometrial cancer associated with long-term use of continuous, combined estrogen-progestin treatment. This was a case-control study that found a doubling of risk associated with a regimen that used 2.5 mg medroxyprogesterone acetate daily, a finding that was based on 18 cases.[8] At the same time, we know that randomized clinical trials have found no hyperplasia associated with lower doses for as long as 2 and 3 years.[9]

A major reason the tibolone results with endometrial cancer are surprising is the biologic implausibility. The predominant, if not exclusive, tibolone metabolite produced within the endometrium is the D-4 isomer, which binds to the progesterone receptor and protects the endometrium from the agonist effects of the two estrogenic metabolites.[10-14] The authors speculate that it is possible that some women are deficient in this important local enzyme activity. It should be emphasized that there is no evidence to support such variability among women. Furthermore, a protective effect on the endometrium has been documented in monkey experiments and in long-term (up to 8 years) human studies.[12,13,15-20] In the major US clinical trial, 3 cases of endometrial cancer were observed, but in each case, pre-existing carcinoma was later detected when the initial biopsy samples were more extensively examined.[21] In the Organon database of 4,269 women who participated in phase III and phase IV clinical trials, there were 2 cases of endometrial cancer in the tibolone-treated women and 2 cases in the placebo group.[22]

Isolated cases of endometrial proliferation have been reported—eg, 4 of 150 women treated with 2.5 mg daily for 2 years.[23] In a 5-year follow-up, 47 of 434 women experienced bleeding, and of these 11 had endometrial polyps, 2 had fibroids, but there were 2 with simple hyperplasia and 2 with endometrial Ca-in-situ.[24]

Abnormal endometrium is more frequently encountered in patients on combination estrogen-progestin when the patients have previously been treated for a period of time with unopposed estrogen. Breakthrough bleeding or unscheduled bleeding in these patients requires endometrial surveillance because an increased risk for endometrial cancer persists beyond the period of exposure to unopposed estrogen, and it is unknown how effective the subsequent protective exposure to a progestin will be.[25-27] It is prudent to assess the endometrium in these patients prior to changing from unopposed to combined therapy. Clinicians should maintain a highly anxious state of mind with patients who have been treated previously with unopposed estrogen. Is it possible that endometrial abnormalities in women using tibolone reflect previous exposure to unopposed estrogen?

The Million Women authors state that their results with tibolone are in "accord with findings from another UK study." The UK case-control study found that

tibolone users were more likely to develop endometrial cancer compared with users of estrogen-progestin products, based on 43 cases.[28] But it is difficult in these studies to know whether the comparison groups are identical, and again, the important influence of previous exposure to unopposed estrogen may be a factor.

The Million Women Study had no significant variation in characteristics at recruitment, including BMI, socio-economic status, alcohol consumption, and smoking, among the users of the various types of treatment. Despite this similarity, an important question has been raised: Do the results with tibolone reflect preferential prescribing? Using the MediPlus primary care database in the United Kingdom, a comparison of personal characteristics among women prescribed various forms of postmenopausal hormone therapy indicted that clinicians often prescribed tibolone to women at increased risks for breast and endometrial cancer.[29] Women prescribed tibolone in the United Kingdom more often had chronic breast disease, a personal history of breast cancer, previous dysfunctional uterine bleeding, hypertension, and previous uterine operations. Most importantly, more women prescribed tibolone had a history of treatment with unopposed estrogen. These data argue strongly that preferential prescribing has occurred in the United Kingdom, and this would affect observational studies like the Million Women cohort, the case-control study, and the case reports noted above. A combined estrogen-progestin program will not totally prevent endometrial cancer,[26] and this is probably true for tibolone as well. This underscores the standard clinical principle to investigate persistent vaginal bleeding in any postmenopausal women. Vigilance on the part of the clinician, however, will detect endometrial cancer at an early stage, a stage that can be treated with excellent results.

Conclusion

It is unlikely that clomiphene treatment increases the risk of endometrial cancer. A large body of evidence suggests that tibolone protects the endometrium against excessive growth. Endometrial safety results with the use of tibolone in randomized clinical trials will soon be available. The studies reviewed above should not change current prescribing practices. ■

Attention Readers

Due to the large amount of references contained within this issue's Special Feature, and space considerations, Dr. Speroff and the staff at *OB/GYN Clinical Alert* will provide copies of the references by request only. If you would like to receive the references, please contact Rob Kimball, Managing Editor, at 404-262-5413, or e-mail at robert.kimball@thomson.com. We will be happy to provide the full references. Thank you. ■

CME Questions

1. **The following statements are true regarding endometrial cancer *except*:**
   a. Staging of endometrial cancer requires surgery.
   b. Surgical staging is necessary to make a correct diagnosis regarding adjuvant therapy.
   c. Grade I lesions require staging.
   d. Surgical staging must be performed by a gynecologic oncologist.

2. **The following statements are true regarding fetal fibronectin *except*:**
   a. A negative test is more predictive than a positive test.
   b. The measurement of fibronectin combined with cervical length provides the best result.
   c. Cervical length cannot be used to decide whether to measure fibronectin.
   d. Not all patients with preterm contractions need intervention and treatment.

Answers: 1 (d); 2 (c)

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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.

Rifamixin for the Prevention of Traveler's Diarrhea?

Rifamixin, a nonabsorbed oral antibiotic, is effective for preventing traveler's diarrhea, according to new research. The study was done in 210 US students traveling to Guadalajara, Mexico. They were randomized to receive rifamixin 200 mg once a day, 200 mg twice daily, 200 mg 3 times a day, or placebo for 2 weeks. Rifamixin effectively prevented traveler's diarrhea for all doses. Overall, traveler's diarrhea developed in 14.74% of participants taking rifamixin and 53.70% of those taking placebo (rate ratio 0.27 [95% CI, 0.17 to 0.43]). All doses of rifamixin were superior to placebo in preventing diarrhea. In test subjects who did not report traveler's diarrhea, rifamixin significantly reduced the occurrence of mild diarrhea (P = .02) and moderate and severe intestinal problems, including pain and cramps (P = .009) and excessive gas (P = .02). Adverse reactions with rifamixin were comparable to placebo, and minimal change in coliform flora was found during rifamixin therapy. The authors conclude that rifamixin effectively prevents traveler's diarrhea in Mexico, with minimal changes in fecal flora. They also suggest that further studies should be performed to evaluate whether the drug is effective in preventing diarrhea in other areas of the world where *E. coli* is not the major pathogen, and whether rifamixin is effective in preventing postinfectious irritable bowel syndrome (*Ann Int Med.* 2005;142:805-812). The accompanying editorial suggests that rifamixin may not be appropriate for prophylaxis of all travelers, but rather selected patients at risk, and that rapid and judicious treatment of diarrhea is best recommended for most travelers (*Ann Int Med.* 2005;142:861-862). Rifamixin is currently only approved for the treatment of travelers diarrhea caused by *E. coli*. The drug is manufactured by Salix pharmaceuticals and marketed under the trade name Xifaxan.

Erectile Dysfunction and Visual Disturbance

Sildenafil (Viagra), Pfizer's blockbuster erectile dysfunction drug, has been implicated along with tadalafil (Cialis) and vardenafil (Levitra) in causing a relatively uncommon form of visual disturbance known as nonarteritic anterior ischemic optic neuropathy (NAION). The first reports of the relationship were published in March of this year. An ophthalmologist at the University of Minnesota noticed 7 patients in his practice who developed NAION within 36 hours after taking sildenafil (*J Neuroophthalmol*. 2005;25:9-13). Since that time, the FDA has received a total of 38 reported cases associated with sildenafil, 4 with tadalafil, and 1 with vardenafil. Pfizer is countering that review of 103 clinical trials

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involving over 13,000 patients. They say they found no reports of NAION and that there is no evidence that NAION occurs more frequently in men taking sildenafil than in men of similar age and health who did not take the drug. And while it is true that the risk factors for erectile dysfunction and NAION are similar and include hypertension and diabetes, the FDA may still require labeling changes for all 3 drugs, listing NAION as a possible risk. NAION results in loss of vision in parts of the visual field that are usually permanent. The FDA is continuing to evaluate the situation, and notes that there is no direct evidence relating erectile dysfunction drugs to NAION, but warns that patients who notice visual changes after taking one of these medications should report it to their physician immediately.

Mixed News on Statins

Good news and bad news about statins. First the good. It appears that statins are associated with a significant reduction in the risk of colorectal cancer. A population-based, case-control study from northern Israel of 1953 patients with colorectal cancer and 2015 matched controls, reviewed whether use of a statin between 1998 and 2004 reduced the risk of colorectal cancer. In comparison to patients who did not use statins, statin use was associated with a significantly reduced relative risk of colorectal cancer (odds ratio, 0.50; 95% CI, 0.40-0.63). This relationship remained significant after adjustment for aspirin use, NSAID use, physical activity, hypercholesterolemia, family history of colorectal cancer, ethnic group, and diet (odds ratio 0.53; 95% CI, 0.38-0.74) resulted in a 47% relative reduction in the risk of colorectal cancer. The authors admit that the absolute risk reduction is likely to be small, and further studies are needed (*N Engl J Med*. 2005;352:2184-2192). An accompanying editorial suggests it is too early to recommend statins as chemoprotective agents against cancer, but notes there is biologic plausibility to their use in this role. There is also the suggestion that statins may target many diseases of aging including osteoporosis and dementia, as well as cardiovascular disease by similar mechanisms (*N Engl J Med*. 2005;352:2238-2239).

Bad news for rosuvastatin (Crestor), AstraZeneca's high-potency statin. The drug has been under scrutiny after related reports of high rates of toxicity in premarketing and some post-marketing studies, compared with other statins. The drug has been a favorite target of the watchdog group Public Citizen, which has petitioned the FDA to withdraw rosuvastatin from the market. Now a report in the May 23rd online version of *Circulation* confirms a higher level of adverse events associated with the drug. Researchers from Tufts University reviewed all rosuvastatin related adverse events reported to the FDA in the drug's first year of marketing. Higher rates of rhabdomyolysis, proteinuria, nephropathy, and renal failure were seen with rosuvastatin, when compared with atorvastatin ($P < 0.001$) , simvastatin ($P < 0.001$), and pravastatin ($P < 0.001$). Adverse events generally occurred early in the course of treatment and at recommended doses. The authors conclude that there are safety concerns associated with rosuvastain, and that healthcare providers should consider other statins as first-line therapy.

FDA Actions

Pegasys, Roche's pegylated interferon, has been approved for the treatment of chronic hepatitis B infections, including both HBeAg-positive and HBeAg-negative disease. The drug was previously approved for the treatment of chronic hepatitis C.

Infliximab (Remicade) is approved for the treatment of psoriatic arthritis affecting at least 5 joints. The biologic agent is a monoclonal antibody that targets tumor necrosis factor alpha. It is also approved for ankylosing spondylitis, Crohn's disease, and rheumatoid arthritis.

Pfizer has received approval to market sildenafil citrate for the treatment of pulmonary arterial hypertension. Sildenfil, which is the active ingredient in Viagra, will be marketed under the trade name Revatio, in a 20 mg tablet that looks different from Viagra tablets to avoid confusion. Sildenafil as Revatio is dosed 3 times a day.

The FDA has approved an extended-release form of dexmethylphenidate for the treatment of attention deficit, hyperactivity disorder. The once daily formulation is approved for adults, adolescents, and children. It will be marketed as Focalin XR by Novartis Pharmaceuticals.

Canadian drug maker Depomed has received approval to market a once a day form of metformin for the treatment of type 2 diabetes. Glumetza will be marketed in 500 and 1000 mg doses. The formulation employs the company's Gastric Retention technology that slows transit and controls drug delivery. ■