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INSIDE

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Desquamative Inflammatory Vaginitis: Prognosis and Treatment

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Desquamative inflammatory vaginitis represents a chronic inflammatory process that responds well to anti-inflammatory treatment and requires long-term maintenance.*

Source: Sobel JD, et al. Prognosis and treatment of desquamative inflammatory vaginitis. *Obstet Gynecol* 2011;117:850-855.

The authors performed a descriptive analysis of all cases of desquamative inflammatory vaginitis (DIV), defined as symptomatic vaginitis (discharge, dyspareunia, pruritus, burning, or irritation) associated with vaginal inflammation (such as focal or linear erosions), a vaginal pH higher than 4.5, and saline microscopy showing an increase in parabasal and inflammatory cells in the absence of an infectious etiology (such as trichomonas, candida, or bacterial vaginosis). A review of clinic charts was conducted to identify women diagnosed with DIV by the lead author between 1996 and 2007 in a referral university-based vaginitis clinic. Clinical findings, laboratory findings, and treatment outcomes were documented during the first 12 months and at 2 and 4 years for subjects with longer follow-up. The authors identified 130 patients who met the case definition, but 32 were excluded (mainly due to a suspicion of erosive lichen planus). All of the patients presented with symptomatic vaginal inflammation and 72% had vestibular findings (e.g., evidence of erythema, erosion, or thinning).

Initial treatments included either topical 2% clindamycin (54%) or 10% hydrocortisone (46%). Both of these treatments relieved symptoms within 3 weeks (median) in the majority (86%) of patients. Among 53 women who discontinued treatment after an initial favorable clinical response, 17/53 (32%) were noted to relapse within 6 weeks. At 1 year, cure was achieved in 25/98 patients (26%) with the initial treatment only, while an additional 57/98 (58%) were asymptomatic but remained dependent on maintenance treatment. Symptoms were only partially controlled in 15/98 (16%). The authors conclude

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that DIV is an inflammatory condition that typically requires long-term maintenance therapy.

■ COMMENTARY

I did not bring this paper to your attention because it was well written (it was not) or great science (single-site case series are the lowest level of medical evidence). However, very little is written about difficult vaginitis, and the problem is highly disruptive to affected women. Vaginitis generally is considered to be a fairly mundane problem for most gynecologists; something for the office nurse to manage over the phone or a midlevel provider to triage in the office. Most cases of common vaginitis are indeed common. We are fortunate to have great treatments for yeast vulvovaginitis, bacterial vaginosis, and trichomoniasis. But, if you've ever seen a patient who presents with recurrent difficult-to-manage inflammatory vaginitis and felt unsure what to do, read on.

Most practitioners recognize a variety of causes of epithelial disorders on the external body surface (including the vulva) due to infectious, allergic, and irritant responses. The immune-based skin disorders, dermatoses (non-neoplastic epithelial disorders such as psoriasis and lichen sclerosus), and neoplastic conditions such as vulvar intraepithelial neoplasia and squamous cancers also generally are recognized by most providers. If not, the presence of a distinct lesion usually leads to the appropriate action (biopsy or referral).

Why then the reluctance to consider that this diversity of disorders also may exist in the vagina? Many clinicians think that vaginal discharge can only mean infection or cancer. When screening tests for these conditions come up empty, the patient often receives yet another round of antifungal or antibiotic treatment. If you haven't found a way to effectively diagnose and manage difficult vaginitis, you may not even know it; these women probably have left your practice.

So what can we learn from this case series? First, the author's practice is a large university referral clinic for vulvovaginal disorders, so the cases represent a substantial accumulation of experience. This case series also comes with long-term follow-up (at least 30 months for most patients), so it provides us with some insight into the natural history of the condition. Finally, the manuscript represents a change in thinking by the author. Although DIV originally was recognized in the 1960s by Gray and Barnes[1] and described by Gardner,[2] the etiology and approach to therapy have been controversial. Almost 30 years after these initial reports, Sobel published a paper describing DIV as an infectious disease, and suggested that the condition was caused by an uncharacterized anaerobic bacterial overgrowth.[3] The absence of protective lactobacillus and clinical response to intravaginal clindamycin provided the basis for this conclusion. Although the science of the 1995 paper was similar to the current manuscript (case series), the lack of competing theories made it influential. The approach to treatment of DIV became antibiotics: usually clindamycin but sometimes penicillin (for the Group B Streptococcus [GBS] culture fans).

How did GBS become a vaginal pathogen? Guilt by association. Some clinicians began culturing difficult vaginitis and not surprisingly GBS was identified. Since GBS is present in about 20% of our obstetrical population, this should not be a surprise, but this colonization was accepted (and treated) as an infection by many providers.

Unfortunately, antibiotic treatment is not without risk. Both penicillin and clindamycin kill lactobacillus, the bacterium we rely on to maintain the normal vaginal ecosystem. Not surprising then that these therapies typically fail to reestablish normal flora. Leclair published an important (but not widely seen) paper last year in the *Journal of Lower Genital Tract Disease* that considered the question of GBS.[4] In this manuscript, non-pregnant reproductive age women with and without vaginitis underwent vaginal culture for GBS. Of the 215 women recruited, 68% showed no evidence of vaginitis, 19% had evidence of a common vaginitis (such as candida, BV, or trich), and 13% showed evidence of inflammatory vaginitis. The overall prevalence rate of GBS was 22.8%. Both common vaginitis (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.1-6.2) and inflammatory vaginitis (OR 2.9, CI 1.1-8.0) were associated with an increased odds of GBS colonization. These findings demonstrate that disruption of the normal vaginal bacterial environment is an important predictor of GBS colonization. In other words,

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Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

GBS fills a void when lactobacillus became scarce. GBS colonization is a result, and not a cause of disrupted flora, and treatment of gynecologic patients with penicillin for vaginitis is not warranted.

What about clindamycin? It works primarily due to its anti-inflammatory effects through a mechanism similar to macrolides and steroids. This is why clindamycin provides an effective benefit in treating acne as a topical product. It is also why metronidazole was not effective in treating DIV. The current manuscript by Sobel corrects the erroneous conclusions reached in 1995 that DIV has an infectious etiology and firmly establishes an inflammatory (possibly autoimmune) basis.

So how should you manage DIV? At our University Vulvar referral practice, we typical initiate therapy with hydrocortisone 25 mg rectal suppositories (used vaginally) at a dose of ½-1 suppository twice daily. See the patient back in 2 weeks to evaluate response. Usually, the inflammation and discharge (and symptoms) are greatly reduced as are the number of parabasal cells seen on wet smear. When adequate control is achieved, wean the therapy, but recognize that many patients will require long-term maintenance. Consider judicious use of intravaginal tacrolimus or clobetasol to manage difficult-to-treat cases. My personal belief is that most DIV represents a variant of erosive lichen planus, so look for signs of this dermatosis on the vestibule and vulva. ■

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Weight Loss Improves Incontinence and Pelvic Organ Prolapse

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, TN

Dr. Ling reports no financial relationship to this field of study.

Synopsis: *After undergoing weight reduction surgery, obese women show improvement in pelvic floor symptoms, urinary function, and anterior vaginal support.*

Source: Daucher JA, et al. Pelvic support and urinary function improve in women after surgically induced weight reduction. *Female Pelvic Med Reconstr Surg* 2010;16:263-267.

Baseline and 6-month data were collected on morbidly obese women who planned to undergo weight reduction surgery. A POP-Q (Pelvic Organ Prolapse Quantification) examination was performed and multiple questionnaires were completed. Six months after surgery, the average body mass index (BMI) was 33 compared to 46 at baseline. Patients who demonstrated stage 2 prolapse or more at baseline improved an average of 0.5 cm in the anterior vaginal compartment. Twelve patients were incontinent at baseline, with six of them becoming continent after surgery and the other six having reduced frequency of incontinent episodes.

■ COMMENTARY

You've seen it. I've seen it. We all talk about it. We discuss it with our patients. It's been studied before with plenty of data showing that incontinence improves when significant weight loss is achieved. Here are some additional data to support those findings, but with the additional examination measures of the POP-Q examination to demonstrate that prolapse also is improved.

I offer this study for your consideration not so much because it demonstrates the mechanism by which weight loss improves incontinence and/or prolapse (it does not), but because it reinforces the notion that morbid obesity significantly impacts urogynecologic health along with the well-understood cardiovascular and general health (type 2 diabetes, hyperlipidemia, hypertension, obstructive sleep apnea, heart disease, stroke, and depression). The authors remind us that although the exact mechanism is unknown, pelvic floor and urethral dysfunction might be related to alterations in the autonomic nervous system associated with increasing BMI. Clearly weight is a modifiable risk factor that greatly impacts many aspects of health, including urinary incontinence and pelvic organ prolapse.

This should serve as a reminder to all of us that obesity is a near-epidemic in our country with plenty of adverse implications. Of specific note, when and if an obese woman complains of incontinence, the concept of weight loss is not an inappropriate treatment strategy. This is not to say that the obesity should be used as an excuse to avoid treating the problem. Unfortunately, I've seen obese patients with significant pelvic pathology that needed surgery being told by their gynecologist that they would not

do the surgery until they had lost "x" number of pounds. Even though it sounds as though it is encouraging the patient to lose weight for her own good, it is often merely an excuse for the surgeon to avoid the challenges and some of the risks associated with such large patients. It almost becomes punitive since it is highly unlikely that the patient will undergo a long-term weight loss plan just to have the surgery. Remember that this study was done over a short period of time with patients who were going to have a relatively "quick fix" to their weight problem, i.e., weight reduction surgery.

How we use the issue of weight loss relative to management of various gynecologic conditions must fall back to individualizing how we treat each of our patients. By using the data in this paper, weight reduction and its affect on incontinence and prolapse certainly can be put into proper context. It can be used both as a carrot and stick when dealing with certain patients depending on what the health problems are. Ultimately, the doctor and the patient must make an informed choice together. Sounds familiar, doesn't it? ■

Preterm Labor and Eating Fish

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *A sub-analysis of data from a randomized trial assessing the possible benefit of omega-3 supplementation to prevent preterm labor shows a protective effect of consuming fish 1 to 3 times per week in patients who have had previous preterm births.*

Source: Klebanoff MA, et al. Fish consumption, erythrocyte fatty acids, and preterm birth. *Obstet Gynecol* 2011;117: 1071-1077.

Dealing with a question about certain dietary items in pregnancy sometimes is daunting because often there is no consensus regarding a proper answer. Here is a study that may help to answer a recurrent question involving fish.

The concept has been circulating that consumption of omega-3 fatty acids can result in a reduction of preterm birth (PTB), so the NICHD Perinatal Network undertook a randomized trial to see if omega-3 supplementation really did improve outcome in patients who have had at least one prior PTB.[2] Interestingly, although the results suggested no obvious benefit from the supplement, data collected during the trial allowed the investigators to look at the relationship of fish consumption, in general, to PTB.[1]

Patients were enrolled at 16 to 21 weeks of gestation, and all had had at least one PTB. All of these patients were on weekly injections of 17 P. At the initial interview, the investigators asked about their consumption of red meat, fish, canned tuna, and shellfish, and the data were analyzed according to how many servings per week they ate. (For example, < 1 serving/month, 1-3 servings/week, > 3 servings/week, etc). The investigators also analyzed levels of various erythrocyte fatty acids at the time of entry. The primary outcome was the incidence of preterm birth, defined as < 37 weeks.

The randomized study included 852 patients and the findings were fascinating. The 253 (29.7%) whose fish consumption was < 1 serving per month had a PTB rate of 48.6%. The 524 who ate fish 1-3 times per week and the 75 with > 3 times per week consumption, together, had a PTB rate of 35.9%. This represented a statistically significant difference. However, the association was nonlinear, resulting in a "u" shaped curve in which there was an increase in PTB after consumption exceeded 3 servings per week. For example, the odds ratio (OR) of PTB in those with 1-3 week consumption was 0.60 (compared to those with low fish consumption), but the OR rose to 1.25 with consumption 7 times per week, and 1.93 with 8 servings a week.

Erythrocyte omega-3 levels were higher with greater fish consumption, and the lowest PTB rate was in the group whose omega-3 levels were in the second quartile. As reported in the original paper,[2] the addition of omega-3 supplementation had no effect on the rate of PTB, and the newest paper from the group[1] showed that this non-effect was irrespective of the erythrocyte omega-3 levels or the amount of fish consumed.

■ COMMENTARY

This study implies that eating fish 1 to 3 times a week can diminish PTB in those who are at greatest risk. The suggestion that some fish is good, but more (> 6 times per week) could be detrimental, is puzzling. However, this trend also was noted in a study from Finland,[3] where the population is known for its fish consumption. So, maybe there is something to the idea that mercury and/or polychlorinated biphenyls (PCBs) sometimes found in pelagic fish (such as tuna) can be associated with adverse pregnancy outcome when consumed in large amounts. The au-

thors also point out that fish are a great source of protein, and that an old study (1980) showed high protein supplementation actually increased PTB in a randomized study undertaken in Harlem.[4]

Why would eating fish work to decrease PTB, while omega-3 supplementation did not accomplish the same result? Perhaps since the supplements were not started until the late second trimester in the study; they need to be on board in the first trimester. Another thought is that the protective factor in fish is something other than omega-3 fatty acids.

Too much protein, too little protein, too much fish, too little fish — what is the pregnant patient to do? I suppose one could roll out the old platitude "everything in moderation," and with fish, that means 1 to 3 servings per week (at least in those with a history of previous PTB). ■

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Is There Negative Impact from Morcellation in Unsuspected Leiomyosarcoma?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationship to this field of study.

Synopsis: *Uterine morcellation procedures are common in the management of uterine leiomyomata, but may adversely impact outcomes and patterns of recurrence when performed in the setting of leiomyosarcoma.*

Source: Park JY, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. *Gynecol Oncol* 2011, doi:10.1016/j.ygynon.2011.04.021.

Uterine leiomyosarcomas (LMS) rarely are suspected preoperatively unless there has been documented rapid growth of the uterus or evidence of extrauterine disease. Thus, it is not surprising that the antecedent procedures performed for a number of these cases are uterine sparing, such as myomectomy, or uterine morcellation at the time of vaginal hysterectomy or under endoscopic guidance. The impact of these procedures on patterns of recurrence and survival was addressed in a retrospective evaluation of a referral population over an 11-year period. In all, researchers identified 77 patients, from which 56 were considered "early stage," that is, corpus-confined or suspected stage I or II. In this cohort, 31 had undergone abdominal hysterectomy as their antecedent procedure before diagnosis of LMS; 25 had undergone morcellation procedures for vaginal hysterectomy (n = 19) or myomectomy (n = 6). Once the diagnosis of LMS was made, all patients who had not undergone hysterectomy had completion procedures, as well as some undergoing additional staging procedures. However, no patient at initial surgery or at the time of reoperation was upstaged based on the pathological assessment of extrauterine tissues. Of interest, the populations were surprisingly well-balanced with regard to age, parity, proportion menopausal, symptoms, and uterine LMS characteristics such as mitotic count and grade. Patients in the morcellation group were less likely to have had a history of prior abdominal surgery, had smaller uterine tumors, and were more likely to have had ovarian preservation. Nevertheless, patients who had undergone morcellation were significantly more likely to recur (52% vs 23%), have abdomino-pelvic sarcomatosis at recurrence (44% vs 13%), and have a shorter disease-free survival (DFS) and overall survival (OS). In the multivariate analysis, only stage (odds ratio [OR] 20.34, 95% confidence interval [CI] 1.27-325.6) and morcellation (OR 3.11, 95% CI 1.07-9.1) were significantly associated with OS. The authors conclude that tumor morcellation at the time of surgery increases the rate of abdomino-pelvic dissemination and adversely affects DFS and OS.

■ COMMENTARY

This manuscript raises a hypothesis that conforms to a concern many oncologists who treat sarcoma share — tumor disruption adversely affects outcome. As such, the practice of intact tumor removal is prevalently recommended in essentially all soft tissue sarcomas, regardless of type or location. However, the prevalence of benign uterine pathology and the lack of discriminating features on preoperative evaluation and imaging for the diagnosis of LMS make a clear recommendation regarding morcellation difficult. Morcellation offers uterine sparing options for very large masses and preservation of minimally invasive surgical options for extirpation. Since uterine LMS is

so rare in the general population, it would be inappropriate to alter management in concern for the diagnosis. However, it is clear that if LMS is suspected, morcellation or even percutaneous biopsy should be avoided.[1,2] Ultimately, the finding becomes another in a long list of adverse prognostic factors, that heretofore, we have had little to offer. In the current series, despite fairly equal postoperative management practices (chemotherapy and radiation), outcomes were still disparate. The lack of upstaging or identified residual disease at restaging was surprising, although the sample was small and the interval between morcellation and reoperation was not stated. Most oncologists are already quite concerned about the recurrence risk of LMS in patients with intact removal; however, the concern is heightened (and for good reason) for women with LMS who have undergone morcellation. Because of this, most oncologists recommend adjuvant therapy — usually chemotherapy in this situation. A decision to restage usually is based on postoperative imaging, but as seen in this series, is generally of low yield in the absence of measurable disease. Fortunately, a cooperative group effort to study adjuvant therapy in these cases has been organized and is exploring new avenues of therapy, including novel hormones, biologically targeted agents, and new cytotoxics.[3] ■

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Special Feature

Painful Sex: How Far We've Come, How Far We've Yet To Go

By Frank W. Ling, MD

Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, TN

Dr. Ling reports no financial relationship to this field of study.

Source: Bergeron S, et al. Genital pain in women: Beyond interference with intercourse. *Pain* 2011;152:1223-1225.

Understanding sexual pain remains limited. with multiple etiologies and lack of evidence-based outcomes research, future investigations should focus on evaluating the intimacy of the couple, the partner relationship, and biomedical sources of pain such as the pelvic floor muscles.

The article by Bergeron et al is not new science, but, instead, is a "Topical Review." In addition, it doesn't appear in a journal that most women's health providers read. Both are reasons it makes a compelling focus for this Special Feature. This is not an article that is likely to get full attention in other publications since it doesn't adhere to the traditional scientific methods that so populate our classic journals. Nonetheless, I think that a summary of this review and its clinical implications for us as patient advocates is warranted.

For those not familiar with the *Diagnostic and Statistical Manual of Mental Disorders-V*, the authors inform us that the upcoming 5th edition of this categorization of psychiatric diagnoses will group vaginismus and dyspareunia into a single entity called "genito-pelvic pain/penetration disorder." Although this appears to be a better descriptor, it is still categorized as a sexual dysfunction with strong emphasis on a specific sexual act, intercourse. The authors suggest that a broader view of the problem would make even more sense, focusing not just on the coital act, but also emphasizing such critical components as the cognitive, affective, behavioral, and interpersonal aspects of pain associated with sex. The new disorder will include specific elements: proportion of successful vaginal penetration, pain with vaginal penetration, fear of vaginal penetration, pelvic floor dysfunction, and medical comorbidities.

The review summarizes what is currently known about biomedical factors; pelvic floor dysfunctions; cognitive, behavioral, and affective factors; and interpersonal factors. Suffice it to say that each of these areas of exploration has been shown to be a potential contributor to the end result of painful sexual experiences. Because of the complexity of any given patient's case, the authors recommend a more holistic approach to research in the future, to allow for understanding more than just the biomedical aspects of this condition.

So what's a well-intentioned clinician to do? Even the best data dealing with dyspareunia are flawed. Randomized, controlled trials are few and far between. Evidence-based medicine offers precious little insight into how best to treat that woman sitting in your office complaining of dyspareunia. The office schedule is full, and time pressures limit what can be offered. Even though this article tended to ask more questions than it answered, it does provide us with food for thought that leads us to some general guidelines which can be extrapolated to

help our patients.

1. **"Dyspareunia is better than no pareunia at all."** Surely you've heard that one, haven't you? This old boys' network adage blatantly ignores the importance of the interpersonal and intimacy aspects of sexual activity. In reality, the devastation between partners caused by sexual pain can be tremendous, even to the point of undermining both the entire relationship as well as the woman's mental health. We've probably all seen it in one way or another. *Message:* Don't ignore or trivialize a woman's complaint of pain with sex.
2. **"HATAH."** Coined by Dr. Ray Good, both a psychiatrist and obstetrician/gynecologist (although many of us think of ourselves as part-time psychiatrists also), this palindrome reminds us to ask the patient "How are things at home?" This is a shortcut into seeing what kind of environment the patient is in. The stressors, the obstacles, the support systems, etc. can be ferreted out using this fairly non-threatening question. *Message:* Identify where the woman is with regard to significant people and circumstances.
3. **"Doesn't it take too long to obtain a sexual history?"** Not really. Here is an easy approach:
   - Question 1: Are you sexually active? (3 seconds including question and answer)
   - Question 2: Do you have any questions or problems? (10 seconds including question and answer and allowing time for the patient to think about her answer)

   So it takes less than 15 seconds to inquire, to open the door, to let the patient see that you consider this aspect of her health to be of significance. After all, if you didn't think it was important, why would you ask? There are three logical outcomes: 1) no issues; 2) issues that are expressed and that can be addressed now and/or at a separate visit; 3) no issues expressed, but she brings up something at a subsequent visit because she sees that you are open to this type of concern. If an issue is raised that can be addressed in an efficient fashion, doing so at the same visit makes sense. If, on the other hand, it sounds more complex requiring more time, then the patient should have her concern acknowledged, but addressed when there is more time to focus on it. This keeps the office from backing up unexpectedly. *Message:* It takes no time at all to take a brief sexual history.
4. **"I don't have the time or interest to be trained as a sex therapist."** That's fine, because, in fact, becoming a certified sex therapist is a significant undertaking. The clinician can, however, with little effort, become a practitioner who identifies a problem and refers the woman/couple to an appropriate resource. Knowing what is available in your community is even something that can be delegated to office staff, but the key is to ask around to find individuals or clinics who can effectively address patients' sexual pain problems. *Message:* There is no shame in referring a patient for "genito-pelvic pain/penetration disorder."
5. **"If I try to take a history, I really don't know how to approach it."** Actually, you already know how to, because you can take a thorough history for pain in your sleep. It's just what we learned in our medical school class on history-taking: describe the pain, where is it, how long has it been there, when does it hurt, does it happen every time, what makes it better or worse, what treatments have helped/not helped it? In this case, it's just a question of focusing on the sexual activity that brings about the pain. For example, does it hurt at the beginning (entrance or insertional dyspareunia) or upon deep thrusting? Such a question might differentiate vestibulodynia (vulvar vestibulitis syndrome) from pelvic endometriosis. *Message:* Taking a history for painful sex is not significantly different from taking a history for any other pain.
6. **"What role can the physical exam play?"** In fact, it can tell you why she hurts with sex. As long as the examination is thorough and systematic, the cause of the pain is likely apparent by the end of the examination. Thinking anatomically, the exam is straightforward including the vulva, vagina, pelvic organs, and pelvic floor muscles.
   - Ask the patient to point to where the pain is, using one finger only (that gives you a better chance to identify the specific location of the pain).
   - Gently palpate the area of pain to see if you can elicit the pain that is bothering her.
   - If the area of pain is over the lower abdomen, ask the patient to tense the abdominal wall by lifting her head off the table/trying to touch her chin to her chest (like doing an abdominal crunch) and/or lift her legs off the table without bending her knees (like doing a leg lift).
   - Ask the patient specifically, "Is this the pain?" (Don't assume that all pain is the same pain that she is complaining of).
   - Palpate the vestibule (specifically the Skene's and Bartholin duct openings) with a moist cotton-tipped swab to identify potential tenderness.
   - Gently insert an index finger into the vagina to press posteriorly and laterally to identify potential pelvic floor muscular pain.

- Rotate the index finger 180 degrees and palpate urethra and bladder.
- Palpate the vaginal cuff (if the patient has had her uterus removed) or cervix to see if that recreates her pain.
- Palpate the adnexa cautiously because the abdominal wall may well be the source of pain.
- Perform a recto-vaginal exam if her symptoms and other signs warrant.

Message: When examining, always ask the patient, "is this the pain?"

7. **"You see what you look for. You look for what you know."** This bit of wisdom sums up how far our diagnostic acumen will take us. Chances are that you will identify the conditions that are in your intellectual and clinical database. The more entities in that database, the more likely you'll be able to find the ultimate diagnosis. Even if your database is small, just trying is more than the patient may have gotten from others; plus, since you actually looked for a cause of the pain, you're far more likely to refer her to someone else who can continue the search. *Message:* The more conditions you know about, the more likely you'll find the right one.

I hope that this expansive application of a brief review article gives at least one person a little more motivation to try to help one more patient a little more than he/she would have before reading this column. Don't worry about saving the world…just try to help save the next patient you see. I think you'll be surprised at how rewarding and fulfilling it can be. ■

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Questions

12. Which of the following does not fit the findings of the reviewed study on fish consumption and preterm labor?

a. Omega-3 supplementation was noted to decrease preterm birth in those with low fish consumption.
b. Those in the second quartile of omega-3 erythrocyte levels had the lowest rate of PTB.
c. Those with low fish consumption had a significantly higher PTB rate than those eating fish 1-3 times per week.
d. Those consuming fish 7 times per week had a higher PTB rate than those eating fish 1-3 times a week.

13. Which of the following statements is false?

a. Morcellation allows for use of minimally invasive abdominal approaches to surgery.
b. Morcellation does not impair prognosis in the setting of a leiomyosarcoma.
c. Morcellation can increase the success of vaginal hysterectomy of a large uterus.
d. Morcellation should not be performed if endometrial cancer is suspected.
e. En bloc removal of a suspected leiomyosarcoma is recommended.

14. Women presenting with symptomatic inflammatory vaginitis in the absence of defined pathogens:

a. should undergo careful evaluation to rule out an infectious etiology.
b. require treatment with penicillin if a culture shows group B strep.
c. respond to intravaginal steroids if parabasal cells and WBCs are seen.
d. require no treatment.
e. have bacterial vaginosis.

PHARMACOLOGY WATCH

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

Two New Drugs Approved for Treatment of Hepatitis C

In this issue: Two new drugs for treatment of hepatitis C; NSAIDs and myocardial infarction risk; AIM-HIGH clinical trial stopped; and FDA actions.

Two new drugs for hepatitis C

The FDA has approved two new drugs for the treatment of hepatitis C — the first new drugs to be approved in years. The approvals came within days of each other, pitting the two drugs (and their companies' marketing departments) against each other in this multibillion dollar market. Both drugs are protease inhibitors and both have similar indications. First to be approved was Merck's boceprevir (Victrelis), which is indicated for adults with hepatitis C who still have some liver function and who either have not been treated previously with drug therapy or who have failed drug therapy. Boceprevir is approved for use in combination with peginterferon alpha and ribavirin. The approval was based on two phase 3 clinical trials of 1500 adults in which two-thirds of patients in the boceprevir, interferon, and ribavirin treatment group experienced a significantly increased sustained virologic response at 24 weeks compared to 38% with interferon and ribavirin alone. Boceprevir is taken orally three times a day with food. The second drug approved was Vertex Pharmaceutical's telaprevir (Incivek), which also was approved for patients with hepatitis C who either have not received interferon-based drug therapy or who have not responded adequately to prior therapies. Telaprevir is also approved for use with peginterferon alpha and ribavirin. Approval was based on three phase 3 clinical trials of over 2000 adults. In previously untreated patients, 79% of patients in the telaprevir group experienced a sustained viral response compared to 46% for standard treatment. Most patients experienced virologic response at 24 weeks suggesting that treatment times may be reduced from 48 weeks to 24 weeks. Telaprevir is also taken orally three times a day with food. Both drugs are approved to treat genotype-1, the most common form of hepatitis C and the most difficult to treat. The drugs have similar side effects, which include anemia and serious rashes. Several other drug manufacturers have similar drugs in the pipeline with approval expected within the next year or two. It is estimated that about 170 million people worldwide and 3.2 million Americans are infected with chronic hepatitis C, which is the most common cause of progressive liver disease leading to liver transplant. Telaprevir is expected to cost nearly $50,000 per treatment course, while bocepavir is expected to cost between $26,000 to $48,000 per treatment course depending on the duration. ■

NSAID use in patients with prior MI

A new study points out the risk of nonsteroidal anti-inflammatory drug (NSAID) use in patients who have had a myocardial infarction (MI) — suggesting that even brief use increases the risk for death and recurrent MI. Researchers from Denmark reviewed the records of nearly 84,000 patients who were admitted with first time MI and their subsequent NSAID use. The risk of death and recurrent MI was correlated to the duration of NSAID treatment. From 1997-2006, 42.3% of patients received NSAIDs. There

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were more than 35,000 deaths or recurrent MIs in the cohort of whom 43% had filled a prescription for an NSAID. Use of an NSAID was significantly associated with an increased risk of death or recurrent MI at the beginning of treatment (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.29 to 1.62) and persisted throughout the NSAID treatment course (HR 1.55; 95% CI, 1.46 to 1.64 after 90 days), returning to baseline soon after stopping the drug. The risk of death or recurrent MI varied with different drugs and was somewhat higher with increased COX-2 selectivity. Diclofenac was associated with the highest risk (HR 3.26; 95% CI, 2.57 to 3.86). Duration of therapy was also reviewed with diclofenac causing an increased risk from the beginning of treatment and persisting throughout the treatment course. Ibuprofen showed an increased risk when used for more than one week, whereas celecoxib showed an increased risk after 14-30 days of treatment. Naproxen was not associated with a statistically significant increased risk of death or MI for the entire treatment duration. The authors conclude that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. This suggests that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and "challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe" (*Circulation* 2011;123:2226-2235). One interesting aspect of this study was the use of rofecoxib (Vioxx) prior to its withdrawal in 2004. While rofecoxib was found to increase cardiovascular risk (the reason for its withdrawal from the market), it appeared to be no more dangerous than other commonly used NSAIDs and was apparently safer than diclofenac. ■

NHLBI stops AIM-HIGH trial

Niacin may not be effective in preventing cardiovascular disease. The National Heart Lung and Blood Institute (NHLBI) has prematurely stopped the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) clinical trial 18 months earlier than planned. Analysis of the data found that adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events. AIM-HIGH participants had well-controlled low-density lipoprotein levels on a statin, however they were at risk of cardiovascular disease due to previous history of cardiovascular disease and a combination of low high-density lipoprotein (HDL) cholesterol and high triglycerides. During the nearly 3 years of the study, patients who took high-dose, extended-release niacin with a statin had increased HDL cholesterol and lower triglyceride levels compared to those who took a statin alone; however, the combination was not effective at reducing fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures. There also was a "small and unexplained increase in ischemic stroke rates in the high-dose, extended-release niacin group" that contributed to the decision to halt the trial. Termination of the AIM-HIGH trial was announced by press release from the NHLBI on May 26. ■

FDA actions

The FDA has approved linagliptin for the treatment of type 2 diabetes in adults. The drug is an inhibitor of DPP-4, an enzyme that degrades incretin hormones (GLP-1 and GIP). It is approved for use as a stand-alone therapy or in combination with other drugs for type 2 diabetes including metformin. The approval was based on eight double-blind, placebo-controlled trials of nearly 4000 patients that showed improved blood glucose control compared to placebo. Linagliptin is marketed by Boehringer Ingelheim Pharmaceuticals as Tradjenta.

The FDA has approved rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of adults with HIV-1 infections who are treatment naïve. Rilpivirine is to be used as part of a highly active antiretroviral therapy (HAART). The approval was based on two phase 3 trials of nearly 1400 adults with HIV who were observed for 48 weeks, and an additional 96-week trial in which the drug was compared to efavirenz as part of multidrug combinations. Rilpivirine was found to be comparable to efavirenz with regard to percentage of patients with undetectable HIV viral load. Patients who failed rilpivirine are more likely to develop drug resistance than patients who failed efavirenz. Rilpivirine is marketed by Tibotec Therapeutics as Edurant.

Rosiglitazone (Avandia) remains on the U.S. market, but its days may be numbered. In a new step to restrict use of the drug, the FDA has updated the Risk Evaluation and Mitigation Strategy to include a restricted access in distribution plan. Physicians and patients must enroll in the distribution program in order to receive the drug. Rosiglitazone will no longer be available in commercial pharmacies after mid-November and will only be available by mail order through certified pharmacies. Use of the drug is limited to patients who are currently on rosiglitazone and whose diabetes is not controlled by other treatments and who are unwilling to change to pioglitazone (Actos). ■