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INSIDE

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An Increased Risk of DVT with Vaginal Ring Contraception — True or Flawed Studies?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *Use of the contraceptive ring or patch was associated with a two-fold increase in venous thrombosis when compared to a standard oral contraceptive pill containing levonorgesterel and 30-40 mcg ethinyl estradiol.*

Source: Lidegaard O, et al. Venous thrombosis in users of non-oral hormonal contraception: Follow-up study, Denmark 2001-10. *BMJ* 2012;344:e2990. PMID:22577198.

THE AUTHORS ASSESSED THE RISK OF VENOUS THROMBOSIS (VT) IN CURrent users of non-oral hormonal contraception using four national registries in Denmark. Non-pregnant women aged 15-49 years (n = 1,626,158) with no prior diagnosis of thrombotic disease or cancer were followed from 2001 to 2010. The main outcome measures were the incidence rate of VT in users of transdermal, vaginal, intrauterine, or subcutaneous hormonal contraception. The incidence rates were used to calculate the relative risk of VT in users of non-oral hormonal contraception compared with non-users of hormonal contraception and with a reference low dose (30-40 mcg) ethinyl estradiol levonorgestrel (LNG) oral contraceptive. Diagnoses were confirmed by records indicating at least 4 weeks of anticoagulation therapy after the diagnosis. In the study population, a total of 5,287 VT diagnoses were recorded in 9,429,128 woman-years of observation, and 3,434 were confirmed. The baseline rate of confirmed VT events in non-users of hormonal contraception was 2.1 per 10,000 woman years. The incidence of VT was elevated in users of the transdermal patch (9.7/10,000) and intravaginal ring (7.8/10,000), yielding adjusted relative risks (RR) of confirmed VT of 7.9 (95% confidence interval [CI] 3.5-17.7) for the patch and 6.5 (CI 4.7-8.9) for the ring. The RR also was increased in women who used subcutaneous implants (RR 1.4; CI 0.6-3.4; not statistically significant) but not in those who used the LNG intrauterine system (RR 0.6; CI 0.4-

0.8). Compared with users of the reference low-dose LNG combined oral contraceptive, the adjusted RR of VT was doubled in users of the patch (RR 2.3; CI 1.0-5.2) and ring (RR 1.9; CI 1.3-2.7).

■ COMMENTARY

The Danish National Database studies provide a gift that keeps on giving. Unfortunately, it is a gift that no one wants to receive and results in a distorted message that confuses providers and patients. The result may be the discontinuation of hormonal contraceptive methods, and an increase in unintended pregnancies, abortions, and pregnancy-related venous thrombosis!

Although it is well-established that combined hormonal contraception (CHC) is associated with an increase in the risk of VT, the absolute risk of an event remains small in most otherwise healthy young users.[1] The risk is higher in obese women and in those with inherited thrombophilias. The importance of the interaction with obesity must be emphasized, since the proportion of obese women is growing in our population.

We also know that the risk is related to estrogen dose, and that the risk with all CHC methods is lower than that seen in pregnancy (where estrogen levels are much higher). But should anyone believe that the contraceptive vaginal ring or patch are actually associated with a higher risk of VT than a low dose LNG pill?

The most recent Lidegaard paper uses the same meticulous methodology of early reports from the same group[2] that has linked drospirenone to an increased risk of VT (reviewed in previous issues of *OB/GYN Clinical Alert*). The database study design allows linkage of prescription data with subsequent events, such that a "retrospective" prospective design is possible. These studies are sometimes called TROHOC (spells COHORT backwards). Unfortunately, these are not true prospective studies. Although the investigator can define the cohorts (in this case by using prescription and health records), there is little control over important variables that are risk modifiers. For VT risk and hormonal contraception, the most important issues are the healthy user effect and prescription bias. Since the risk of VT is highest in the first 6 months after starting a combined hormonal method, these are not insignificant handicaps.[2] Also, providers typically see a new product as potentially safer, and this can adversely affect the incidence of events as providers switch less healthy individuals to these newer methods. Only a true prospective study can overcome these biases. Results of large, well-designed, prospective studies in the United States and in Europe (EURAS) have shown no increased risk of VT with drospirenone pills compared to LNG pills or other pills.[2] The review by Heinemann and Heinemann provides an excellent discussion of the epidemiology of VT and the biases that emerge in studying this rare event in users of hormonal contraception.[1]

Since Lidegaard applies the same methodology in each study, it is not surprising that results from this study lead us in exactly the same direction as his previous work. Imagine an explorer with a flawed compass that reliably reads 20 degrees east of true north. Following this compass will lead the explorer on an accurate course in entirely the wrong direction. If you repeated the adventure, starting at the same point and using the same compass, you would find yourself heading in the same wrong direction. Consistency of the results does not imply they are correct. This is the difference between internal and external validity. Methodology matters. Using a better instrument will lead you on the correct course. The results of database studies can be useful *when no better data are available*, but should be weighted below those of well-designed prospective studies. Repeating a lie (or a misconception) does not make it a truth.

Fortunately, the new Lidegaard paper has received little attention in the American media and among U.S. clinicians, but you can bet the lawyers are interested. My opinion is that there is no clinically important increase in the risk of VT among patch, ring, and implant users compared to users of low-dose LNG pills. We can look forward to publication of another great prospective study by Jürgen Dinger and the ZEG Institute that will help clarify this. This paper was presented at the 2012 ACOG meeting.[3] The "Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing" (TASC) study prospectively enrolled 33,704 new users (starters, switchers, or restarters)

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

of the vaginal ring or combined oral contraceptives in the United States and five European countries and followed them for 2-4 years. Self-reported clinical outcomes were systematically validated. The preliminary results showed no difference in the crude (0.9; CI 0.5-1.8) or adjusted (age, body mass index, duration of use, family history) (0.8; CI 0.4-1.6) hazard ratio for the vaginal ring vs combined oral contraceptives.

The last Lidegaard paper led to FDA hearings and a labeling change for drospirenone pills. The new package insert is actually helpful, as it presents data from the database and prospective studies, but few clinicians and patients will take the time to evaluate this information. Let's hope that the FDA checks its compass, and shows more prudence in the response to this current study. ■

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Maternal Drug Use and Its Effect on Neonates

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports no financial relationships relevant to this field of study.

Synopsis: *This study from Washington State reports that prenatal drug exposure and neonatal abstinence syndrome rates increased from 2000 to 2008, leading to longer hospitalizations for affected neonates and increased perinatal complications.*

Source: Creanga AA, et al. Maternal drug use and its effect on neonates: A population-based study in Washington state. *Obstet Gynecol* 2012;119:924-933.

THE AUTHORS SOUGHT TO ESTIMATE TRENDS IN PRENATAL drug exposure and neonatal abstinence syndrome (NAS) in Washington State from 2000 to 2008. They also identified the types of drugs used, predictors of prenatal drug use and NAS, and outcomes of drug-exposed and NAS-diagnosed neonates. The investigators utilized the Birth Events Record Database maintained by the Washington State Department of Health, which links birth certificate data to mother and infant hospital discharge data that have been validated. To identify prenatal drug exposure and NAS, International Classification of Diseases, 9th Revision, Clinical Modification multiple (ICD-9-CM) codes related to drug use in the mother and infant were used to search the records. Due to limitations in ICD-9-CM codes, the authors were unable to differentiate between illicit and prescription drug use. Drug exposure was categorized into four categories: 1) opioids and related narcotics; 2) cocaine; 3) other psychotropic drugs (including sedatives, hypnotics, and tranquilizers); and 4) other or unspecified drugs.

Between 2000 and 2008, 669,451 medical records had complete data for evaluation. Using ICD-9-CM codes, 9,024 (1.3%) drug-exposed neonates were found. Of these, 18.9% were diagnosed with NAS. Drug exposure rates increased from 10.6 per 1,000 births in 2000, peaked at 16.3 per 1,000 births in 2005, and were 14.3 per 1,000 births in 2008. Similarly, NAS rates increased from 1.2 per 1,000 births in 2000 to 3.3 per 1,000 births in 2008. In 2008, the majority of prenatal drug exposures (41.9%) were to psychotropic drugs, followed by 24.4% to opioids, and 10.5% to cocaine. The proportion of NAS among neonates exposed exclusively to opioids increased from 26.4% in 2000 to 41.7% in 2008 ($P < 0.05$).

Risk factors for prenatal drug exposure included neonates born to Native American or Alaska native women (adjusted odds ratio [OR]. 1.8; 95% confidence interval [CI] 1.7-1.9), being unmarried (adjusted OR 1.8; CI 1.5-2.2), having a diagnosis of a mental health disorder (adjusted OR 3.7; CI 3.4-4.0), and no prenatal care (adjusted OR 11.0; CI 10.0-12.0). Protective factors were having more than 12 years of education (adjusted OR 0.6; CI 0.6-0.7) and private insurance (adjusted OR 0.3; CI 0.3-0.3). These associations also were significant for the diagnosis of NAS. In addition, the older the age of the woman and the more children she had, the more likely it was that the neonate was exposed to drugs prenatally or was diagnosed with NAS.

The mean length of birth hospitalization was 2.6 ± 6.3 days for unexposed neonates compared to 6.5 ± 12 days ($P < 0.001$) for drug-exposed neonates and 14.4 ± 14.3

days ($P < 0.001$) for neonates diagnosed with NAS. Newborns exposed to drugs had 2.6 to 3.4 times and newborns diagnosed with NAS had 4.1 to 9.2 times the odds of being born preterm, with low birth weight, having feeding problems, respiratory distress syndrome, or other respiratory conditions compared to unexposed newborns. After adjusting for prematurity and low birth weight, the odds ratios for these perinatal outcomes declined but were still significant.

■ COMMENTARY

Most commonly associated with prenatal opiate use, NAS is a drug withdrawal syndrome in newborns following birth. NAS is characterized by increased irritability, hypertonia, tremors, feeding intolerance, emesis, watery stools, seizures, and respiratory distress.[1] The fact that prenatal drug exposure and NAS in the United States has increased in recent years has been well-documented in the medical literature and national press.[2,3] Although this study is somewhat limited by its reliance on ICD-9-CM codes for case identification,[4] the authors mention other research that documents a rise in opioid-exposed newborns in Washington State. A national study with similar methods recently found a substantial increase in maternal opiate use between 2000 and 2009, from 1.19 per 1,000 births per year to 5.63 per 1,000 births per year as well as an increase in NAS from 1.2 per 1,000 births per year to 3.4 per 1,000 births per year.[2] Therefore, the problem is not limited to Washington State.

The American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine recommend that all pregnant women be screened for substance abuse including alcohol, illicit drugs, and prescription drugs.[1] The use and abuse of prescription opioid medication has become more common in the United States.[1] In addition, in certain areas of the country, methamphetamine abuse is a concern.[5] Identifying substance abuse in pregnancy allows the prenatal provider to refer women for treatment and manage the pregnancy accordingly. Each state has different reporting requirements concerning substance abuse during pregnancy. Fourteen states require health care professionals to report suspected prenatal drug abuse and four states require them to test for prenatal drug exposure if they suspect abuse.[6] These reports can then be used as evidence in child-welfare proceedings. Fifteen states consider substance abuse during pregnancy to be child abuse under civil child-welfare statutes. Unfortunately, these requirements disrupt the relationship between the woman and her provider, and often deter women from disclosing substance abuse and even seeking prenatal care.[7] This is regrettable because both the treatment of opioid addiction in pregnancy and prenatal care has many benefits. Treatment with methadone or buprenorphine in pregnancy prevents complications of illicit opioid use and narcotic withdrawal as well as reduces the risk of obstetric complications.[1] NAS is an expected outcome of this treatment and is treated in collaboration with the pediatric team.

The trend toward the criminalization of substance abuse during pregnancy is alarming.[3,8] Depending on the state, women may face incarceration, involuntary commitment, loss of custody of her children, and loss of housing.[7] We have all seen women suffer from these policies. It is not surprising that harsh drug enforcement policies may dissuade women from seeking prenatal care or may even promote pregnancy termination to avoid prosecution.[3] Addiction should be managed as a disease, not as negligent or criminal behavior.[7] Furthermore, certain states mandate reporting of substance abuse in pregnancy and consider such behavior child abuse but do not have any drug treatment programs specifically targeted to pregnant women nor give pregnant women priority access to state-funded drug treatment programs.[6] Thus, even women who desire substance abuse treatment in pregnancy may not be able to find it. It is more appropriate that states work with prenatal care providers and addiction specialists to promote positive legislation to help women with substance abuse issues.[7] ■

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Gestational Diabetes

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Using California birth statistics, the authors indirectly found there was no statistically significant difference in perinatal death rate in gestational diabetes when comparing immediate delivery with expectant management until 39 weeks, when there was a higher rate of stillbirth if delivery was delayed by 1 week.*

Source: Rosenstein MG, et al. The risk of stillbirth in infant death stratified by gestational age in women with gestational diabetes. *Am J Obstet Gynecol* 2012;206:309.e1-7

GESTATIONAL DIABETES (GDM) NOW COMPLICATES ABOUT one in 15 pregnancies, but, undoubtedly, the prevalence will increase even further if we cannot curb the concerning rise in obesity in this country. There is ample evidence that controlling blood sugars in GDM will diminish neonatal morbidity and mortality. However, there has been no unanimity of opinion as to when to deliver well-controlled GDM patients whose fetuses show no signs of compromise.

This recent study in the *American Journal of Obstetrics & Gynecology* indirectly assessed the effect of a week's worth of expectant management in GDMs in late pregnancy by comparing stillbirth and infant deaths at each week of gestation from 36 to 41 weeks with perinatal deaths occurring over, and at the end of, the next week.

The authors mined information from the now often-used California Vital Birth and Death Statics data set from 1997 to 2006. Of the more than 4 million deliveries occurring during this time, 193,228 patients were labeled as having GDM. The risk of stillbirth between 36 and 39 weeks was greater in GDMs than non-diabetics (relative risk [RR] 1.45; 95% confidence interval [CI] 1.1-1.9). When comparing expectant management with immediate delivery using the method above, the risks of perinatal death were slightly lower with the former at 36 weeks, similar at 37 weeks, slightly higher at 38 weeks, and were significantly higher at 39 to 40 weeks (RR 1.8; $P = 0.05$).

The authors calculated that the number of GDM patients who needed to be pre-emptively delivered to prevent one perinatal death was 1518 at 39 weeks, and 1311 at 40 weeks.

■ **COMMENTARY**

The authors admit that there were problems with their study. For example, there were no available data on the adequacy of diabetic control or the status of antenatal testing, and they did not deal with maternal or neonatal morbidity — factors that are far more common in GDM than the rare perinatal death. In fact, it took 9 years' worth of California birth statistics to unroof a significant difference in perinatal deaths (15.2 per 10,000 vs 8.7/10,000) when delivery occurred at 39 weeks, compared with 1 more week of expectant management. Before 39 weeks, there were no statistically significant differences.

For years the controversy regarding when to deliver GDMs has been all about macrosomia, shoulder dystocia, and neonatal hypoglycemia. However, using the authors' pure endpoint (death) and some interesting calculations, those taking an aggressive stance might say that GDM pregnancies should not go past 38 weeks. Those favoring the more conservative, expectant management approach would point to the need to deliver more than 1300 babies early (by 39 weeks) to avoid one perinatal death — likely at the expense of a higher cesarean section rate.

The answer is probably somewhere in between. If the patient has an unripe cervix, is in good control, and has reassuring testing, expectant management should carry an extremely small risk. However, if there is the slightest hint of trouble, then there is a suggestion from this paper that delivery at or after 38 weeks would be the most judicious course to take (just as I expect most clinicians are doing now). ■

Special Feature

Making Strides in Provoked Localized Vulvodynia

By Catherine Leclair, MD

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Dr. Leclair reports no financial relationships relevant to this field of study.

YOU'VE SEEN HER BEFORE. SHE'S OFTEN YOUNG AND PARTnered, but might be midlife and changing the status of her relationship. Sometimes she presents for an annual exam and mentions her pain later during the visit. Occasionally she actually presents with the complaint of dyspareunia. Either way, you listen and empathize, hoping that she may just have a yeast infection or an ovarian

cyst — something easy and straightforward to fix in the 15 minutes you are allotted for office visits these days. Yet, this time she does not have a simple explanation and you are faced with a more challenging problem.

Provoked localized vulvodynia (PLV), formerly known as vulvar vestibulitis syndrome, is a complex sexual pain disorder affecting 8-15% of the population and believed to be the most common cause of dyspareunia.[1,2] Despite descriptions of sexual pain disorders in early gynecologic textbooks, only recently have clinical experts begun to make progress describing the spectrum of this common and distressing pain condition and in identifying knowledge gaps for research. The American College of Obstetricians and Gynecologists, the American Society for Colposcopy and Cervical Pathology, the International Society for the Study of Vulvovaginal Disease (ISSVD), and the National Vulvodynia Association have worked diligently to educate clinicians and the National Institutes of Health has issued specific requests for proposals for research in this field.

For most women with PLV, the condition exists as part of a complex triad with localized pain in the vulvar vestibule coexisting with tender pelvic-floor muscles and psychosexual dysfunction. It's understandable why the focus has been more on the painful vestibular skin than the other parts of the triad. Many patients and practitioners easily identify the tender vestibule as the source of the problem. However, increasing evidence shows that each part of the triad can contribute significantly to compromises in quality of life, sexual function, and psychological well-being.[3,4] Women with PLV report high rates of sexual dysfunction with poor arousal, low desire, and impaired orgasm. Mood disturbances, anxiety, psychological distress, and relationship compromise are frequently identified comorbidities in women with PLV, as the extremely personal nature of vulvar pain is difficult to discuss with family, friends, or physicians. Although millions of women have vulvar pain, only 70% will seek care for this pain, and the average patient will visit at least three health care providers before a diagnosis is secured.[5] It's likely you will see her in your office after she's failed to improve after seeing one of your local colleagues. She's hoping that you have the answer to the question of why she has pain.

Clinically, we use Freidrich's criteria to diagnosis PLV: complaint of penetrative pain with vaginal intercourse, provoked tenderness (allodynia) of the vestibule upon Q-tip examination, and erythema of the vestibule. A diagnosis of PLV is made after all other vulvar conditions (dermatologic, infectious, anatomic) are ruled out. Although the cause of PLV remains unknown, the vestibule of affected women shows histologic changes — increased inflammation and nerve tissue density — not seen in controls.[6,7] These observations led the ISSVD to propose in 2004 that the term vulvar vestibulitis syndrome be replaced with provoked localized vulvodynia or vulvar vestibulodynia, since the evidence suggested a local neuro-inflammatory etiology rather than a traditional inflammatory or infectious response.

With the precise pathophysiology of PLV unknown, a wide variety of treatments has been proposed including oral and topical neuromodulators, pelvic floor rehabilitation, psychosexual counseling, and vestibulectomy (surgical excision of painful vestibule). Most clinical trials have evaluated therapies that address only one component of the pain triad (e.g., either painful vestibular skin or tender pelvic floor muscles or sexual dysfunction) with improvement ranging from 38-80%. These inconsistent results from single modality therapies suggest the pain of PLV reflects a complex interaction. An expanded theory of PLV as a complex *pain triad* with disruption in pelvic-floor muscle function and behavioral changes coexisting with localized vestibular allodynia may explain the inconsistent results with vestibulectomy, a single modality therapy directed only at the painful skin. Despite recognition that a multidisciplinary approach may have benefit, few studies have approached PLV in this manner.

So as she sits in your office hoping for a simple cure for her pain, what do you have to offer her? Since PLV is believed to be a chronic pain disorder, direct treatment to the nervous system, whether central or local, has been advocated. Oral neuromodulators such as tricyclic antidepressants (amitriptyline, nortriptyline, desipramine), gabapentin, pre-gabelin, and the mixed serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine) are often offered as first-line therapy. Topical neuromodulators represent another option for PLV treatment since local therapy maximizes drug delivery to the painful vestibular skin and lowers the potential for systemic side effects. However, it is unclear whether the pain of PLV is best managed by medications targeting central (brain and spinal cord) or local (pain receptors and peripheral nerves) pathways. Only a limited body of research has focused on local therapies. Topical 5% lidocaine, 2-6% gabapentin cream, and 2% amitriptyline-baclofen cream have been reported to be effective, but the evidence comes primarily from case series. A randomized, blinded clinical trial by Foster found that topical 5% lidocaine ointment was no better than placebo cream in treating chronic pain at the vestibule.[8] Despite this disappointing result, topical lidocaine (4% aqueous or 2% gel) should be offered for *palliation of pain with intercourse* since it will successfully reduce vestibular pain for some women who attempt intercourse. For best results, you should instruct your patient to place lidocaine on the vestibular skin at least 10-15 minutes before attempts at penetration.

Diagnosing pelvic floor musculoskeletal pain is challenging for most gynecologists. Pelvic floor dysfunction — termed pelvic-floor myalgia or vaginismus — may in-

clude signs and symptoms of hypertonicity (tense, contracted muscles), tenderness (burning pain with touch), and poor function (inability to contract/relax pelvic-floor muscles). A history of burning pain inside the vagina with clenching and anticipatory anxiety often correlates with pelvic floor myalgia on exam. Although the prevalence of pelvic-floor myalgia with PLV has not been formally reported, data from the Program in Vulvar Health at Oregon Health & Science University suggest that at least 50% of women with vulvar pain have concomitant pelvic-floor myalgia. It is unclear whether vestibular pain precipitates secondary pelvic-floor myalgia or whether the tense musculature leads to difficult penetration and subsequent PLV. Nonetheless, a talented pelvic floor physical therapist is a vital participant in the therapy team. Rehabilitation of pelvic-floor muscles through physical therapy has been shown to reduce PLV.[9] Pelvic floor rehabilitation includes mind-body awareness, muscle manipulation, biofeedback, and dilator training; these are proven strategies that slowly but surely allow women with PLV to gain control over painful and tense muscles and confidence to proceed with penetrative sexual activity. Importantly, studies evaluating a combined approach of PT and other therapies (vestibulectomy, topical or oral neuro-modulator) demonstrate enhanced efficacy in reducing dyspareunia compared to either therapy alone.[10,11]

Vestibulectomy is the gold standard therapy for women with PLV, with a wide reported range in the success (60-80%). Studies evaluating surgical outcome have found a close relationship between pain outcomes and other components of the pain triad (psycho-sexual well being and pelvic floor muscles). An important factor affecting recovery is emotional well-being.[12] This suggests that successful resumption of sexual intercourse after vestibulectomy may require attention to the emotional state of the woman. Other studies have documented improved surgical outcome and decreased dyspareunia when pelvic floor rehabilitation is performed perioperatively. These results suggest that successful recovery requires more than the simple removal of painful skin. In other words, most women require additional treatment (pelvic-floor muscles and/or psychosexual support) beyond vestibulectomy to become fully functional.

Perhaps your patient has the nerve to convey to you that she is suffering — not only physically but also emotionally and sexually. If you listen carefully, you may hear heart-wrenching stories of unconsummated marriage or unwanted sexual touch from a beloved partner that generates anxiety and terrible guilt. Sexual dysfunction is the norm for women suffering from PLV, and this leads to high rates of depression and relational compromise. Spano and Lamont have proposed a model that explains these findings;[13] chronic dyspareunia results in anticipatory anxiety (due to the distress from painful sexual encounters), which then leads to poor arousal and tense pelvic-floor muscles. Poor arousal and tense muscles maintains painful intercourse, resulting in increased dyspareunia and, ultimately, in negative feelings about intimacy. Thus, it is not surprising that treating the psychosexual distress that is inherent in PLV improves sexual outcomes and reduces pain. A number of studies support sexual counseling as a crucial step that finally enables women with PLV to resume full sexual activity without pain, even when other treatments such as vestibulectomy and pelvic floor rehabilitation have been completed.

So how do you proceed to manage your patient and support her as she navigates this complex and emotionally challenging diagnosis? Validating and naming this condition for women who often feel embarrassed and isolated in their pain is the first step toward beginning treatment. Vulvar pain conditions don't develop overnight, so the expectation for a quick cure is naïve. PLV is associated with localized pain in the vulvar vestibule, psychosexual dysfunction, and tender pelvic-floor muscles, and each contributes significantly to compromise quality of life, sexual function, and psychological well-being. Although there is no single treatment option that consistently provides a cure for PLV, studies support that a multidisciplinary treatment plan offers the most promising hope of alleviating all aspects of pain.

Caring for these patients provides a great opportunity to be a clinician. The challenge of working through a complex diagnosis and managing a condition that requires skill in office practice, a thoughtful approach to medical and surgical therapy, and a cognitive-behavioral approach to psychosocial distress brings out the best in the obstetrician gynecologist. Educate physical therapists and mental health providers in your area about PLV so that you can confidently refer your patient for supportive care. Initiating therapy in any of the three domains (pain triad) of PLV will likely improve your patient's pain. These strategies will allow forward strides in the care for the woman with provoked localized vulvodynia. ■

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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 Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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. You will no longer have to wait to receive your credit letter!

CME Questions

1. Data from the Danish National Database study of Lidegaard showed that the risk of venous thrombosis in reproductive age women was:
   a. 2.1 per 10,0000 women-years in users of hormonal contraception.
   b. increased with the use of the LNG IUS.
   c. lower among users of vaginal ring contraception.
   d. increased in users of the contraceptive implant.

2. Assuming each study is well-designed, conducted rigorously, and analyzed correctly, which is most likely to provide a true assessment of risk of thrombosis with a hormonal contraceptive method?
   a. An open-label, Phase 3 efficacy study
   b. A Phase 4 multicenter prospective cohort study
   c. A national registry study
   d. A Phase 2 study assessing pharmacokinetics, pharmacodynamics, and surrogate markers of thrombosis.

3. In the study by Creanga et al, all of the following were associated with prenatal drug exposure *except*:
   a. no prenatal care.
   b. older age of the woman.
   c. public health insurance.
   d. higher education levels.
   e. being unmarried.

4. Based on California Birth Statistics, which of the following is correct?
   a. In general, GDMs have a higher rate of stillbirth than non-diabetics.
   b. At every gestational age there was a significant difference in perinatal death when comparing expectant management with immediate delivery.
   c. The largest difference in stillbirth between groups occurred at 38 weeks.
   d. The data show a clear trend toward better outcome at every gestational age with immediate rather than expectant management.

5. The data from this study show a clear benefit of delivering patients with GDM by 38 weeks.
   a. True
   b. False

6. Which is a problem with the Rosenstein study?
   a. There were no data on the adequacy of diabetic control.
   b. There was no information on antenatal testing.
   c. No data were available on neonatal morbidity.
   d. There were no specifics on the deliveries themselves.
   e. All of the above

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.*

Does Azithromycin Cause Cardiovascular Death?

In this issue: Azithromycin and cardiac risk; warfarin and heart failure; aspirin and VTE; effectiveness of long-acting contraceptives; and FDA actions.

New study finds increased risk

Is azithromycin proarrhythmic? Macrolide antibiotics are associated with an increased risk of sudden cardiac death, but azithromycin (Zithromax), the popular "Z pack" macrolide, has been considered safe. That may change based on the results of a new study from Vanderbilt. Researchers reviewed the records of patients in the Tennessee Medicaid cohort to detect an increased risk of death related to short-term cardiac effects of azithromycin and several control antibiotics. Patients with serious noncardiovascular illness and hospitalized patients were excluded. Over the study period, there were almost 350,000 patients who took azithromycin, 1.35 million patients who took amoxicillin, 265,000 patients who took ciprofloxacin, nearly 200,000 patients who took levofloxacin, and nearly 1.4 million control patients. Five days of therapy with azithromycin compared to no antibiotics significantly increased the risk of cardiovascular death (hazard ratio [HR] 2.88, confidence interval [CI], 1.79 to 4.63; $P < 0.001$) and death from any cause (HR 1.85; 95% CI, 1.25 to 2.75; $P = 0.002$). Use of amoxicillin was not associated with increased risk of death. Relative to amoxicillin patients, patients taking azithromycin were at 2.5 times higher risk of cardiovascular death and 2 times higher risk of death from any cause, although the absolute risk was low with an estimated 47 additional cardiovascular deaths per million courses. Patients at risk for cardiovascular disease were at higher risk, with an estimated 245 additional cardiovascular deaths per 1 million courses. Cardiovascular death risk was higher with azithromycin compared to ciprofloxacin, but the death rate from levofloxacin was roughly the same. The authors conclude that 5 days of azithromycin was associated with a small but absolute increased risk of cardiovascular death, which was most pronounced in patients with a high baseline risk for cardiovascular disease (*N Engl J Med* 2012;366:1881-1890). Soon after this study was published, the FDA issued a statement urging patients to continue taking azithromycin unless instructed otherwise by their health care professional. The FDA will review the results of the study and will communicate any new information on azithromycin, including the potential risk of QT interval prolongation, to health care professionals and the public. Health care professionals are urged to report any adverse effects related to the use of azithromycin to the FDA's MedWatch Safety program. ■

Warfarin doesn't prevent death

Warfarin is no more effective than aspirin in preventing mortality in patients with heart failure who are not in atrial fibrillation (AF), according to a new study. More than 2300 patients with a left ventricular ejection fraction less than 35% (average 25%) and a mean age of 61 years were randomized to warfarin with a target INR of 2.0-3.5 or

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aspirin 325 mg per day. The primary outcome was ischemic stroke, intracerebral hemorrhage, or death from any cause. Patients were followed for up to 6 years with a mean follow-up of 3.5 years. There was no difference in the primary outcome (7.47 events per 100 patient years for warfarin, 7.93 for aspirin; HR with warfarin 0.93, CI, 0.79 to 1.10, $P = 0.40$). Warfarin was associated with a significant reduction in the rate of ischemic stroke but was associated with a higher rate of hemorrhage. The authors conclude that among patients with heart failure who are in sinus rhythm, there was no difference in outcome between warfarin and aspirin, but note that since warfarin was associated with a lower risk of ischemic stroke, the choice between the two drugs should be individualized (*N Engl J Med* 2012;366:1859-1869). An accompanying editorial asks, "Could there be some patients with heart failure who would benefit from warfarin?" Those with AF, a history of cardioembolic stroke, history of left ventricular thrombus, and perhaps those with atherothrombotic coronary artery disease may benefit, but in general, warfarin cannot be recommended for patients with heart failure who are not in AF (*N Engl J Med* 2012;366:1936-1938). ■

Aspirin and venous thromboembolism

Aspirin may be protective in patients who have had an unprovoked venous thromboembolism (VTE) to prevent recurrence after they finish oral anticoagulant therapy. In a double-blind study, patients with first-ever unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment were randomly assigned to aspirin 100 mg daily or placebo for 2 years. The primary endpoint was recurrent VTE with major bleeding being the primary safety outcome. Recurrent VTE occurred in 6.6% of patients on aspirin and 11.2% of patients on placebo (HR 0.58; 95% CI, 0.36 to 0.93). One patient in each group had a major bleeding episode. The authors conclude that aspirin reduces the risk of recurrence in patients with unprovoked VTE after they have finished anticoagulant therapy, with no apparent increase in risk of major bleeding (*N Engl J Med* 2012;366:1959-1967). This study is important because about 20% of patients with unprovoked VTE have a recurrence within 2 years. It also shows that taking low-dose aspirin safely reduces that risk by nearly half. An accompanying editorial points out that a similar but larger study is currently ongoing in Australia and New Zealand with results due later this year (*N Engl J Med* 2012;366:2028-2030). ■

Long-acting contraceptives are better

Long-acting contraceptives, such as IUDs and implants, are up to 20 times more effective than oral contraceptives and other short-acting contraceptive methods, according to a new study. In a large, prospective cohort study, women participants were provided with the reversible contraception of their choice at no cost for 3 years. The endpoint was failure of long-acting reversible contraception (IUDs and implants) compared with commonly prescribed contraceptive methods, including oral contraceptive pills, transdermal patches, contraceptive vaginal rings, and depot medroxyprogesterone acetate injection (DMPA). In the nearly 7500 women participants, there were 334 unintended pregnancies. The failure rate among participants who used pills, patch, or ring was 4.55 per 100 participants years as compared with 0.27 among participants using long-acting reversible contraception (HR after adjustment for age, educational level, and history with respect to unintended pregnancy 21.8; 95% CI, 13.7 to 34.9). The rate for DMPA was also low at 0.22. Younger women (< 21 years) who used a short-acting contraceptive had a pregnancy rate almost twice as high as older participants. The pregnancy rate among women who used DMPA, an IUD, or implant were similarly low regardless of age. The authors conclude that the effectiveness of long-acting reversible contraception is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents or young woman (*N Engl J Med* 2012;366:1998-2007). This study not only points out the reliability of long-acting contraceptives, but also the surprisingly high failure rate of short-acting contaceptives, especially in young women. ■

FDA actions

In the biggest generic launch since last year's atorvastatin (Lipitor), the FDA has approved generic clopidogrel (Plavix). The popular antiplatelet drug, with sales of more than $9 billion last year, will be available from seven generic manufacturers in the 75 mg strength and four manufacturers in the 300 mg strengths. The immediate "multisource" status of the generic approval should result in dramatic cost reductions for patients, from an average of $200 per month to about $40 per month. The drug is approved for treatment of acute coronary syndrome and prevention of thrombotic events in patients who have had a recent myocardial infarction, recent stroke, or peripheral artery disease. ■