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INSIDE

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Recognizing Placenta Accreta Before Delivery

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Patients with submucous fibroids and history of hysteroscopic procedures might benefit from an ultrasound evaluation to look for signs of placenta accreta.*

Source: Al-Serehi A, et al. An association with fibroids and Ascherman syndrome. *J Ultrasound Med* 2008;27:1623-1628.

PLACENTA ACCRETA CAN REPRESENT A REAL CLINICAL CONUNDRUM, especially if it is unrecognized before delivery. Therefore, clinicians have been justifiably sensitized to its possible presence in patients who have the greatest risk for it — those who have had a previous cesarean section. However, in this recent report, two cases were presented that represent two variations on the placenta accreta theme.

The first case involved a 40-year-old woman who had had a myoma resected, as well as lysis of adhesions, by hysteroscopy. The patient had had one previous cesarean section. She became pregnant through in vitro fertilization with donor eggs from a 30-year-old. Not surprisingly, she was found early on to have twins. Two more 2 cm fibroids were noted in the anterior wall of the uterus at the time of her first examination. However, the placenta was on the posterior wall. At 34 weeks she had severe vaginal bleeding requiring an emergency cesarean section. After delivery of the baby, a supracervical hysterectomy was done to stop the bleeding. Pathology showed a complete placenta accreta. With the benefit of hindsight, the authors re-evaluated the last ultrasound scan at 32 weeks and found none of the typical criteria for this condition.

The second case involved a patient who was noted at 18 weeks to have a complex mass in the base of the placenta with low resistance

flow around it. At first, it was contiguous with the uterine wall, but later this was not clear. It did not grow, and the pregnancy continued uneventfully until term, when she delivered spontaneously without problems. The "tumor" came out intact with the placenta. Pathology showed it to be a submucous fibroid and the trophoblast had worked its way around the base of the fibroid to completely separate it from the uterine wall.

■ COMMENTARY

These two cases show us that there may be other predisposing factors to placenta accreta, in addition to a previous cesarean section with placenta previa — namely, previous hysteroscopic surgery and fibroids.

First, since the best way to avoid disaster is to be forewarned, let's touch upon the typical ultrasound findings with accreta and the accuracy with which ultrasound techniques can predict this condition. Finberg first described criteria correlating with accreta, which included thinning of the interface between the bladder and the uterine wall and a loss of the "clear space" between the placenta in the uterine wall.[1] He also described what we have found to be the most consistent predictor of accreta, a Swiss cheese-appearing tissue near the basal plate, with swirling lacunar flow within the echo-spared areas. Comstock recently has added the presence of color Doppler flow in the affected area, "beating" at a fetal rate.[2] Using these criteria, in perhaps the largest accumulation of cases, Warshak et al found the diagnostic sensitivity of ultrasound to be 82%, with a specificity of 96%.[3]

MRI has also been used to diagnose this condition, and the results have been no better than with ultrasound. However, this method has been found to be helpful in patients with equivocal ultrasound findings. Our experience is that ultrasound has outperformed MRI, since the results with the MRI often are not definitive.

An interesting, but little-known fact is that 50% of accretas are associated with elevations of second trimester maternal serum alpha-fetoprotein (MSAFP) well above 2.0 MoM.

Fibroids are becoming a more common accompaniment to pregnancy because more patients of advanced maternal age are now becoming pregnant. However, it is unclear what real effect they have on pregnancy. There are two studies showing a modest increase in seemingly every complication known to pregnancy. However, although I have not been able to quantify this, my feeling is that the overwhelming majority of patients with fibroids sail through pregnancy without a hint of a problem. We do know that they grow most rapidly in the first trimester and taper off thereafter to a point where they rarely increase in size after 20 weeks. Also, they never win a competition for the blood supply to the fetus.

The two cases above should not cause us to adjust our management of patients with fibroids to include, for example, an expensive MRI. However, here are some suggestions to diminish the chances of being blindsided by placenta accreta.

Patients at greatest risk include:

1. Those with a previous cesarean section with a portion of the placenta over the old scar.
2. Those with a placenta previa, straying close to or over the old scar.

Those whose risk is on a lower scale include:

3. Those with a history of uterine surgery with incisions through the entire uterine wall.
4. Those with a history of uterine adhesions.
5. Those with submucous fibroids — only when the placenta is over the fibroid.

If the patient has either criteria 1 or 2, and, theoretically, 3, she would benefit, at least, from a special ultrasound scan after 32 weeks to look for signs of accreta, and if the results are equivocal, an MRI could be useful. With criteria 4 and 5, a comprehensive ultrasound evaluation of the placental interface would only be in order for patients with elevated MSAFP.[4,5]

(Addendum: Although the aim of this review is to deal with the diagnosis of placenta accreta, there is now a trend in some centers to adopt an approach of watchful waiting in patients wishing to preserve reproductive function, by leaving the placenta intact. There is no con-

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Questions & Comments
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sensus as to whether to use methotrexate to shrink the tissue, but one can use Doppler flow studies of the uterine cavity to determine the ideal time for later removal of the tissue by D&C.) ■

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Discontinuing Bisphosphonate Therapy

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Follow-up of a cohort of new bisphosphonate users documents an increase in hip fractures in noncompliant women within 1 year after discontinuation, but no increase in compliant women.*

Source: Curtis JR, et al. Risk of hip fracture after bisphosphonate discontinuation: Implications for a drug holiday. *Osteoporosis Int* 2008;19:1613-1620.

CURTIS AND COLLEAGUES FROM THE UNIVERSITY OF Alabama at Birmingham measured the rate of hip fracture among women who discontinued bisphosphonate therapy compared with women who remained on treatment. A cohort of women ages 60-78 who were new users of bisphosphonates were identified from a U.S. health care organization that covers more than 25 million people in the United States. The study group consisted of 9063 users who had been compliant for at least 2 years. The hip fracture rate about doubled in the women who discontinued treatment compared with those who did not. The incidence of hip fractures during treatment was lower compared with non-treated individuals. After discontinuation for a year or longer, the risk of hip fracture increased by 9 months in women with lower compliance rates. In women with high compliance rates for 2 or 3 years, there were no significant differences in fracture risk after discontinuation for up to 1 year later.

■ COMMENTARY

Bisphosphonates are known to have such a high binding affinity for bone that inhibition of bone resorption persists after discontinuation. In addition, the remodeling of bone releases bound bisphosphonates to act again, creating the potential of adding to a treatment regimen to produce relatively high-dose exposure. For these reasons, many supported limiting the duration of bisphosphonate treatment because of the possibility of oversuppression of bone turnover eventually weakening bone strength. Now we have to add to our thinking the latest reports of serious side effects.

Bisphosphonate treatment has been linked with atrial fibrillation. A meta-analysis, presented at the meeting of the American College of Chest Physicians in October 2008, estimated that atrial fibrillation is observed in 2.5%-3% of treated individuals, and that 1%-2% experience hospitalization or death. A case-control study concluded that 3% of bisphosphonate users developed atrial fibrillation.[1] In a Letter to the Editor in the Jan. 1, 2009, issue of the *New England Journal of Medicine*, the FDA reported 23 cases (8 fatal) of esophageal cancer in patients being treated with alendronate.[2] A total of 31 cases of esophageal cancer have been collected in Europe and Japan associated with alendronate, risedronate, ibandronate, and etidronate. Although this is a small number of cases with drugs that have been used for 13 years by millions of people, the concern has added credibility because of the well-recognized side effect of esophagitis with oral bisphosphonates.

The risk of osteomyelitis and osteonecrosis of the jaw and face has been recognized for several years, but continues to be controversial. To be sure, most of the cases have been in cancer patients, usually treated with intravenous high doses, but this complication has been reported in patients receiving oral bisphosphonate treatment for osteoporosis, with no history or evidence of malignancy.[3,4] Experts in the field point out that many clinicians specializing in osteoporosis have never seen a case; the incidence is somewhere between 1 in 10,000 and 1 in 100,000. They further argue that a true cause-and-effect relationship would require appropriate controlled studies, and apparently 2 are ongoing. But I would argue that one cannot delay clinical decision making until data are

available, and it is by no means certain that the ongoing trials will yield definitive results on such a rare event.

We previously reviewed a follow-up report from the alendronate fracture intervention trial.[5] The results indicated a lingering residual positive effect on bone of alendronate that was present for more than 5 years. This is a marked contrast to estrogen treatment where bone loss resumes immediately after discontinuation. It is important to emphasize that in alendronate-treated women who had bone density measurements in the osteoporotic range at discontinuation, the rate of nonvertebral fractures increased after discontinuation. This new report further strengthens the conclusion that protection against bone resorption persists for a period of time after discontinuing treatment. But remember that a good response to bisphosphonate treatment requires the intake of 1000 mg calcium and 800-1000 IU of vitamin D daily.

It seems to me that duration of exposure to bisphosphonate should be limited, avoiding high local dosage secondary to the liberation of tightly bound bisphosphonate combined with ongoing treatment. Many clinicians recommend discontinuation after 5 years with resumption of treatment when bone loss is demonstrated. But be sure that the bone density is no longer in the osteoporotic range before discontinuation. The follow-up data indicate that it is worthwhile to obtain a bone density measurement at a point 2-4 years after initiating bisphosphonate treatment. If the density is not in the osteoporotic range, discontinuation of treatment is recommended with annual follow-up bone density measurements. Treatment should be resumed if a bone loss of 5%-10% can be documented.

Two other cautionary points are worth remembering. Avoid combining two antiresorptive agents (even though there may be a small additional gain in bone density, there is no evidence that an additional benefit on fracture risk is achieved). Think twice before treating young postmenopausal women with a bisphosphonate. ■

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Visual Estimation and Calculated Blood Loss After Delivery

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Synopsis: *These researchers propose new methods for calculating blood loss during delivery.*

Source: Stafford I, et al. Visually estimated and calculated blood loss and vaginal and cesarean delivery. *Am J Obstet Gynecol* 2008;199:519.e1-519.e7.

A FEW STUDIES HAVE SUGGESTED THAT WE TEND TO underestimate blood loss during deliveries and cesarean sections. A group from Louisiana State University has addressed this issue again in a very clever way.

Between Jan. 1, 2005, and Sept. 2, 2005, when hurricane Katrina cut the study short, complete data were available on 671 women, none having a blood transfusion. Two hundred and thirty one (34%) mothers had cesarean sections, 421 had spontaneous deliveries (62.2%), and 25 patients (3.7%) had operative vaginal deliveries. Each patient had a subjective clinical estimation of blood loss during and after her delivery, which was paired with the calculated blood volume loss by an accepted set of formulas. First, the maternal blood volume was calculated in the following way: $0.75 \times$ [(maternal height in inches $\times$ 50) + (maternal weight in pounds $\times$ 25)]. Then the blood loss was computed by multiplying the maternal blood volume by the percent of blood volume lost, the latter being quantified by the equation: [(pre-delivery Hct − post-delivery Hct)/pre-delivery Hct]. (I have included these formulas for those wanting to more accurately determine blood loss in their patients.)

The median estimated blood loss (EBL) by visual assessment was 250 cc, 300 cc, and 800 cc for normal spontaneous delivery, operative delivery, and cesarean delivery, respectively. The same median figures for calculated blood loss were 575 cc, 728 cc, and 818 cc. The median difference between the two methods was 306 cc for normal spontaneous delivery, 469 cc for operative

delivery, and 75 cc (a surprise) for cesarean sections. However, when blood loss during cesarean section exceeded 1000 cc, then there was a significant underestimation by the visual method. Last, as expected, there was an impressive increase in blood loss with each successive degree of perineal laceration. For example, the calculated blood loss (by the above formulas) was 519 cc, 604 cc, 764 cc, and 932 cc for no laceration, first degree, second degree, and third/fourth degree lacerations, respectively. The visual estimations undershot the calculated value in each category by 200-580 cc.

■ **COMMENTARY**

This study shows we are not very good at ballparking blood loss. Perhaps wishful thinking plays a role in our estimates, but it seems that in every category there was a major underestimation of true blood loss. Review of records of pregnancies ending in maternal mortality (13 per 100,000) or severe maternal morbidity has shown a tendency to miscalculate the seriousness of these patients' clinical conditions. Since maternal hemorrhage plays a major role in most of these complications, early blood replacement could be extremely important in preventing the rapid deterioration of these patients' conditions.

This tendency to underestimate blood loss by a factor of two might possibly be something that happens only in New Orleans, but I seriously doubt it. It might be useful for us to try the above formula ourselves on a few patients to see how close we come to the EBL. However, reading this may well bias our subjective estimates. ■

Hormone Therapy Improves Quality of Life in Older Women

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A randomized trial similar to the WHI reported improvements in quality-of-life measurements after 1 year of hormone therapy.*

Source: Welton AJ, et al. Health related quality of life after combined hormone replacement therapy: Randomised controlled trial. *BMJ* 2008;337:a1190; doi:10.1136/bmj.a1190.

THE WOMEN'S INTERNATIONAL STUDY OF LONG Duration Oestrogen after the Menopause (WISDOM) trial was a randomized, controlled trial in the United Kingdom, Australia, and New Zealand, of 3721 women aged 50-69 treated with either combined 0.625 mg conjugated estrogens and 2.5/5.0 mg medroxyprogesterone, or placebo. The original plan was to randomize 22,300 women to the study that would last 10 years. The study was canceled in October 2002, in reaction to the initial reports from the WHI. Unfortunately, the premature cancellation precludes the possibility of any long-term data from WISDOM. This report summarizes the effect on 2130 women who completed 1 year on a collection of symptoms that relate to quality of life. There were statistically significant improvements among the treated women in the categories of vasomotor, sexual, and sleep symptoms. Treated women reported a reduction in aching joints and muscles, night sweats, insomnia, and vaginal dryness. The treated group reported more breast tenderness, but the percentages were notably low (16% in the treated group and 7% in the placebo group). There was no difference in scores related to depression.

■ **COMMENTARY**

The WISDOM trial claims that small effects on quality of life reported by the WHI and HERS can be attributed to the insensitive measurement tools used in those clinical trials. The WISDOM trial used a survey tool specifically designed to assess postmenopausal physical and emotional well-being, plus a validated, generic questionnaire, the European quality of life instrument (EuroQol). Only the specific questionnaire detected significant changes; the European generic tool did not. This emphasizes the importance of using the appropriate study tool to investigate this area of postmenopausal health. Similar results with vasomotor symptoms, sleep, and joint complaints were actually reported by the WHI, but with a smaller difference between treated and placebo groups. The WHI survey had only one question devoted to sexuality.

Both WISDOM and WHI reported no effects on the reporting of depression. This is consistent with the studies in perimenopausal women documenting a significant increase in risk of new depressive symptoms only in women with a history of adverse life events (the events are not defined or specified in the reports).[1,2] The results of these two cohort studies support the argument that there is a vulnerable group of perimenopausal women who are responsible for the increase of new depression observed during the perimenopausal transition. In randomized trials of older postmenopausal women, these women should be present in equal numbers in the treated and placebo groups, and, therefore, the trials cannot assess the impact of hormone therapy on depression.

The results of the WISDOM trial are not surprising; they reflect what all clinicians have observed in their own practices. But it is good to add the statistical significance of a clinical trial to clinical experience. The most important point to be made is this: The WISDOM, WHI, and HERS trials were all similar in that they enrolled postmenopausal women heavily tilted towards the oldest age group without symptoms. It is a simple and logical conclusion that hormone therapy in a younger, symptomatic group of postmenopausal women would produce greater quality-of-life benefits than that quantified in the clinical trials. The backlash of the WHI negatively influenced clinicians and patients to hesitate in promoting hormone therapy for symptomatic postmenopausal women. Thankfully, we are now seeing a swing back to hormone therapy for symptomatic women. The WISDOM trial supports this position, but all 3 clinical trials underestimated the beneficial impact because of the age and symptom status of their participants.

There is another important lesson in the WISDOM trial. Even older postmenopausal women who are symptomatic benefit from hormone therapy. Age should not be the sole guiding factor in decision making. ■

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Special Feature

On the Origin of Ovarian Cancer … Is It the Ovary?

By Robert L. Coleman, MD

Professor, University of Texas;
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Dr. Coleman reports that he is a consultant to GlaxoSmithKline, Eli Lilly Co., Abbot Laboratories, Sanofi-Aventis, and Pfizer; and serves on the speakers bureau of OrthoBiotech.

ONE OF THE MOST COMMON AND POIGNANT QUESTIONS an ovarian cancer patient asks upon learning of her diagnosis is, "How did I get this? … Where did it come from?" The answer, unsatisfactory to both, is usually of the form, "… it's not exactly clear … but it likely comes from disregulated growth at the surface of the ovary." The pacifying (maybe just temporizing) statement of fact is supported by epidemiological data focusing on the ovulatory axis, where risk association is highest in nulliparous women and women with early menarche and late menopause, and lowest in those with multiple live births and those with a history of prolonged oral contraceptive use.[1] The observational data support a contention that functional mutations arise in the repetitive breaking and repairing of the ovarian coelomic surface, leading over time and under the influence of various molecular promoters, to development of cancer.[2] Evidence of surface epithelia-lined inclusion cysts are usually pointed to as the germinal culprit, where, in the event of malignant transformation, access to the surface and peritoneal cavity is the principal pathway to metastatic spread.[3] This "incessant ovulation" theory is presented in nearly every contemporary textbook on the subject and data from interventional studies, such as the documented risk reduction by hormonal contraception or bilateral salpingo-oophorectomy in high-risk women (because of either family history or BRCA mutation), support the contention.[4,5] Yet what is undeveloped in most accounts is the controversy that lies at the true core of the question posed by our patient — the origin of disease.

Ovarian cancer is a rare condition diagnosed in fewer than 25,000 patients annually. The constellation of disease termed "ovarian" frequently includes morphologically similar processes arising in the peritoneal cavity (so called primary peritoneal cancer) or fallopian tubes (fallopian tube cancer). Molecular studies have demonstrated the similarity of these conditions[6] and investigational treatment studies frequently allow all three, although criteria to separate their origin are available. For instance, a peritoneal malignancy can only be classified as primary if: 1) both ovaries are normal in size or enlarged by a benign process, 2) the involvement in the extra-ovarian sites is greater than the involvement on the surface of either ovary, or 3) the ovarian tumor involvement is either nonexistent, confined to the ovarian surface epithelium without stromal invasion, or involving the cortical stroma with tumor size less than 5×5 mm.[7] Nevertheless, it is troublesome that the histological spectrum that makes up "ovarian" cancer in the ovary consists of cells that are not native to this organ. Serous cancer, the most common type, is composed of cells morphologically resembling the epithelial lining of the fallopian tube; mucinous cancer, resembling those of the endocervix; and endometrioid cancer, resembling those of the uterine glandular lining. According to the coelomic origin theory, the development of these cell types

comes from the metaplastic differentiation of the ovarian (or peritoneal) mesothelium, which then de-differentiate in inclusion cysts to become cancer. The differentiation and de-differentiation process, while explicative, is counterintuitive to our current understanding of malignant progression. Further, the elusive intermediary step, in situ or pre-cancer, has yet to be described, and represents a problematic distraction of this theory.

An alternative hypothesis on the origins of "ovarian" cancer has resurfaced, and now armed with provocative molecular findings, deserves closer examination.[8-10] Binding the histological elements of cancers called "ovarian" is their origin, the Müllerian system. Embryological development of the upper vagina, cervix, uterus, and fallopian tube comes from the paramesonephric ducts, which in the absence of Müllerian inhibiting substance (MIS), fuse distally to make the midline structures, and remain unfused proximately to form the fallopian tubes. The undifferentiated gonad that becomes the ovary (in the absence of MIS) is unrelated to this tract, yet malignancy attributed to the ovary comes from cells that describe the Müllerian system, namely fallopian tube, uterus, and endocervix. Beyond morphology though, evidence has recently surfaced that molecularly links ovarian cancer histology and cells of the Müllerian tract.[11] The HOX family of homeobox genes controls the normal developmental pattern along the anterior-posterior axis. These genes uniquely appear to specify morphological identity through their spatially and temporally restricted expression. The discovery that specific HOX genes responsible for the formation cells of the fallopian tube, endometrial glands, and endocervix could produce ovarian cancers of serous, endometrioid, and mucinous variety, respectively, lends credence to the hypothesis that ovarian cancers could arise from cells of the Müllerian tract. Mixed tumors may be explained in the differential expression of more than one of these genes.

Further support comes from the identification of an in situ lesion in the fallopian tube, first discovered through serial sectioning in specimens retrieved from women with BRCA germline mutations undergoing risk-reducing prophylactic bilateral salpingo-oophorectomy.[12] The so-called "serous tubal intraepithelial carcinoma," or STIC, was also identified in nearly one-half of tumors designated as primary peritoneal (based on the definition presented above), which was typically fimbrial and unifocal.[13-17] However, in cases where primary and distant STIC was found, the p53 signature was identical in all, harboring the same p53 mutation.[18]

The data are clearly provocative, but don't explain the origin of disease in women in whom the uterus, tubes, and ovaries are removed. Proponents of the theory point to the existence of a secondary Müllerian system, which includes vestigial remnants of the oviducts and cystic inclusions lined with Müllerian epithelium along the paratubal and paraovarian tissues.[8] These extra-Müllerian lesions, termed endosalpingiosis, endometriosis, and endocervicosis, reflect their source organ histologically. They are found throughout the peritoneal cavity and extraperitoneally, and have been documented with benign, low malignant potential (borderline), low-grade serous, and carcinomatous elements. Given the high prevalence of these types of cystic inclusions, it is not surprising that multifocal (peritoneal) disease is commonly described when cancer is diagnosed. More study of this phenomenon is indicated.

The principal and ultimate impact of understanding the origin and biology of disease is to develop effective and acceptable prevention strategies. It is well documented that more than three-quarters of women presenting with ovarian cancer have advanced disease, and while many will enjoy a good response to surgery and chemotherapy, recurrence is both common and deadly. Describing the molecular events leading to a precursor lesion (e.g., STIC) or identification of its presence is an initial step forward. The recent discovery of circulating nucleic acids, circulating tumor cells, and microRNA (miRNA) cells offer new opportunities to meet this challenge.[19-21] ■

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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.

CME Questions

50. Which of the following represents the highest risk for accreta?
a. Posterior placenta with a previous section
b. Anterior low-lying placenta over the old scar
c. A fibroid with an MSAFP of 2.0 MoM
d. Anterior placenta without a previous cesarean section

51. How much does visual EBL underestimate calculated EBL?
a. 2-fold
b. 3-fold
c. No difference
d. Only slightly

52. The following statements are true regarding hormone therapy and quality-of-life measurements *except*:
a. Hormone therapy does not benefit women with depression.
b. Joint complaints are improved by hormone therapy.
c. Vasomotor symptoms impair quality of life.
d. Sleep is improved by hormone therapy.

Answers: 50. b, 51. a, 52. a.

In Future Issues:

Long-acting Contraception for Pain Control in Patients with Endometriosis

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*.

Warning Regarding Topical Anesthetics

In this issue: FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

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the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; P = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■