Effects of Temperature on Amnioinfusion

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: A recent study suggests that it may be possible to lower the chances of neurological injury in fetuses vulnerable to hypoxia by dropping intrauterine temperatures through amnioinfusion of room temperature saline.


EVERY SO OFTEN, ONE RUNS ACROSS A PAPER THAT IS SOMEWHAT OFFBEAT, but could have some beneficial clinical implications. One such article appeared recently in the British Journal of Obstetrics and Gynecology that dealt with a way to possibly counter the fetal effects of maternal hyperthermia and even protect the brains of fetuses/infants against potential hypoxic insult during labor.

Tomlinson et al recruited 20 laboring women who had had intrauterine catheters inserted to assess uterine contractions (controls). Another 14 patients having amnioinfusion (AI) for repetitive variable decelerations were recruited (the AI group). Every patient had a temperature probe inserted into the uterine cavity through the already-inserted catheter so that continuous intrauterine temperatures could be monitored. The patients having AI had room temperature sterile saline infused at a rate of 10 mL/minute for the first hour and 3 mL/minute thereafter. Ambient temperatures in the patients’ rooms were recorded during the infusion and maternal oral temperatures were taken every 15 minutes. Neonatal rectal temperatures were assessed as soon as possible after delivery (within 90 seconds). All but three patients in the
The authors' null hypothesis was that infusion of room temperature saline would not lower intrauterine temperatures, and, as the authors hoped, it was rejected. The mean average intrauterine temperatures were 0.5°C warmer than the maternal oral temperatures in the control group. However, the infused group had mean intrauterine temperatures that were 0.2°C cooler than mean maternal temperatures. When comparing average intrauterine temperatures between AI and controls in the total populations studied, AI mean temperature was 36.4°C vs 37.4°C in controls, representing a 1°C difference. In a subgroup of patients who were afebrile throughout the study, the AI lowered intrauterine temperatures by 1.5°C (35.8°C vs 37.3°C), and if an epidural was in place for 3 hours or less, the AI group’s average intrauterine temperature was 1.7°C cooler (35.5°C vs 37.2°C). The above results were statistically significant.

Regarding neonatal temperatures, the infants tested had rectal temperatures immediately after birth that were, on average, 1.0°C higher than their moms’ oral temperatures, suggesting that after a while the infusion could not neutralize elevated intrauterine temperatures.

The greatest benefit might be in clinical situations where the fetus is most vulnerable to hypoxia such as fetal growth restriction, fetal tracing with late decelerations, fetal tracing with decreased beat-to-beat variability, or any fetal tracing with non-reassuring fetal heart rate pattern. This could perhaps be done even while preparing for an emergency cesarean section. This paper can act as a springboard to further study, which obviously is necessary since this intriguing concept is great for chin stroking, but, as of now, is simply conjecture.

References
5. Dietrich WD, et al. Intraischemic but not postischemic

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Endometriosis Implicated Again in Histological Variants of Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: Self-reported personal history of endometriosis was associated with an increased risk of ovarian cancer. Further, it was differentially associated with clear cell, endometrioid, and low-grade serous ovarian carcinoma in this pooled analysis. No relationship appeared between endometriosis and high-grade serous or mucinous ovarian cancer, or borderline variants of these two histologies. The results suggest further work is necessary to understand whether endometriosis plays a strategic precursor role in certain ovarian cancer histological subtypes.


Several studies have implicated endometriosis as a risk factor for the subsequent development of invasive epithelial ovarian cancer. However, while some histological subtypes, such as clear cell and endometrioid, have been associated, little is known of the other subtypes (e.g., serous and mucinous). To address the hypothesis, members of the Ovarian Cancer Association Consortium (OCAC) pooled data from 13 predominately population-based case-control studies conducted in Australia (1), Europe (3), and the United States (9), assessing risk factors for the development of ovarian malignancy. The data cohort included 23,144 women; 7911 (34%) with invasive epithelial ovarian cancer, 1907 (8%) with borderline tumors, and 13,326 (58%) controls. Controlled confounding variables were age, ethnic origin, oral contraceptive use, parity, breastfeeding, weight, height, BMI, tubal ligation, and family history. Serous histology was reclassified by WHO grade with grade I representing “low-grade” serous (LGSOC) and all others as “high-grade” serous (HGSOc). A history of endometriosis was found in 9.3% of women diagnosed with invasive ovarian cancer compared to 6.2% of controls (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.31-1.63); in addition, among the five histological subtypes considered, the association was strongest for clear cell carcinoma (OR 3.05, 95% CI 2.43-3.84), compared to endometrioid (OR 2.04, 95% CI 1.67-2.48) or LGSOC (OR 2.11, 95% CI 1.39-3.20). No relationship was observed between endometriosis and invasive HGSOc or mucinous cancer, or of borderline serous and mucinous histology. The effects were upheld in a sensitivity analysis, which considered the time between endometriosis diagnosis and the diagnosis of cancer. The authors conclude that the association should raise awareness in treating clinicians and spark investigation into mechanistic processes driving malignant progression.

COMMENTARY

This article is by far the largest collection of retrospective data to address the relationship between endometriosis and ovarian cancer. The strength of the pooled analysis is that it provides the ability to delve further into histological association, which has been done only to a limited degree and only for certain subtypes. The provocative data do raise the hypothesis that, albeit uncommon, a malignant ovarian phenotype occurs to a greater degree in women with a personal history of endometriosis than those without, particularly for clear cell and endometrioid tumors (previously known) and LGSOC (previously unknown). The relationships are compelling, but as is the case with retrospective studies cannot be inferred as causal, and we must consider several confounding issues and procedural assumptions that could affect the strength of association.

First, all the data regarding the diagnosis of endometriosis in this study are self-reported. There was no attempt to confirm that, indeed, patients had the disease (e.g., a site audit). In two sites where central registries are maintained, the diagnosis was confirmed by review of discharge summaries, but even in these cases it is unknown if these are histologically based or an inferred diagnosis for pelvic symptoms. The authors acknowledge this limitation but state it would unlikely affect the differential association among the subtypes. However, it is plausible that since women with clear cell, endometrioid, and LGSOC are diagnosed at a younger age, bona fide endometriosis may be differentially recognized by a higher frequency of surgical procedures and confirmatory histology. Second, the histological criteria by which clear cell carcinoma and LGSOC is made are not clearly provided. This has been a significant issue in treatment studies where adjudication of the pathology must be made prior to registration. For
instance, it is unclear how cases of mixed clear cell and serous carcinoma were handled. Third, ethnic differences were considered in the confounding variables, which is appropriate given the substantially higher frequency of clear cell carcinoma in Asian-Pacific Islanders; however, it is not clear that endometriosis is similarly increased in this cohort. The higher prevalence of clear cell cancer in this population could significantly attenuate the association. Fourth, the one truly novel finding of the study, the association of endometriosis to LGSOC, was based on reclassification of the WHO grading criteria and not on pathological review. A recent study has found that this methodology misclassifies about 5% of cases, predominately WHO grade 2 (HGSOC) patients being more appropriately identified with LGSOC. Since the frequency of each WHO grade was not given and pathology was not reviewed for consistency, it is difficult to know how to interpret this association.

Nevertheless, the recent discovery of ARID1A mutations in clear cell and endometrioid cancers and the association of these tumors to endometriosis provide sufficient rationale to investigate the underlying biology. In addition, microarray interrogation of HGSOC has identified an inflammatory-like signature for some cases. It would be of interest to know if these cases too had an association with endometriosis, which is well recognized to induce stromal alterations and an inflammatory response.

References

How Truthful are Patients with Their Physicians?

**Abstract & Commentary**

**By Frank W. Ling, MD**

Patients who received treatment for depression within a year were identified in a Japanese database of more than 323,000 patients. The investigators asked 2354 patients to complete a questionnaire on depression with a specific focus on patient-physician relationships. Only 2020 patients successfully completed the survey, with 70.2% reporting that they had withheld the truth from their physician. There was significant correlation with being female, younger age, and having a lower degree of satisfaction with communication with their physician. Information about “daily activities” and “symptoms” was withheld in 69.2% and 52.6% of patients, respectively. Female patients were more likely to be untruthful regarding “adherence to prescribed medication” and “figures such as body temperature and weight.” A little over 32% of patients had discontinued treatment without consulting the physician, which correlated more with being female, young, and unsatisfied with their communication with their physician.
pain. The findings also suggest that a younger age is a contributing factor to withholding the truth, which is of particular importance to us because of the obstetric population that we serve.

Several reasons that patients gave for acting as they did reminded me of patients in my own practice. Any practitioner in the women’s health arena has heard comments that were cited in the article for noncompliance with medications, such as “...my symptoms did not improve even though I received treatment,” “...my symptoms got better,” “I was afraid of getting hooked on prescribed medications,” or “I experienced side effects.” We should all pay close attention to the troubling finding that the second most common reason for discontinuing medication was “I did not get along well with my physician.” Since this is not something that a patient is likely to tell us directly, it appears that we need to remain vigilant in all patients. Since it is the patient who is “ill,” the responsibility of maximizing the doctor-patient alliance falls squarely on our shoulders.

There are certainly obvious aspects of the study that leave it vulnerable to criticism, e.g., it involves only Japanese patients, it includes only depressed patients, the patients essentially self-selected themselves into the study, etc. Nevertheless, the core message remains a strong one: If you suspect noncompliance in your patients, you just might be correct.

The Etonogestrel Contraceptive Implant and Obesity

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: In this large, prospective cohort study, the etonogestrel contraceptive implant was equally effective in normal, overweight, and obese women.


The etonogestrel subdermal implant was approved for use in the United States in 2006 and provides contraception for up to 3 years. The contraceptive efficacy of the implant rivals that of IUDs and sterilization with a 0.05% failure rate.¹ The original trials for approval, however, only included women who were normal weight (women > 130% of their ideal body weight were excluded). Therefore, until this study, there were few data on implant effectiveness in overweight and obese women.²

This study alleviates any confusion surrounding implant use in the overweight and obese population. Although we already know that IUDs are unaffected by weight, we can now counsel women that the efficacy of the implant will not be influenced by their weight.
United States, the unintended pregnancy rate currently stands at 49% and is a major public health problem. At the same time, the obesity rate is rising dramatically with 30% of the U.S. population now being considered obese. This report will help providers encourage the use of long-acting reversible contraception (LARC) such as IUDs and implants in overweight and obese women. LARC, due to its high efficacy and continuation rates, is considered in the top tier of contraceptive options. The advantages of LARC also include few contraindications and cost-effectiveness.

Irregular vaginal bleeding, a common side effect of progestin-only contraceptives, is the most frequent reason cited for implant removal. In the clinical trial for approval in the United States, 11% of participants discontinued the implant due to irregular bleeding. Counseling women about what to expect prior to implant use is critical to prevent premature discontinuations. On average, women using the implant will have no more bleeding over a 90-day period than they would have had with three menstrual periods. However, the bleeding and spotting are unpredictable and remain that way for the entire 3 years of use. I tell my patients that they will not have regular menstrual periods and to expect episodes of unpredictable bleeding or no bleeding at all. Studies show that in any given 90-day period, 22.2% of women will have amenorrhea, 33.6% will have infrequent bleeding, 6.7% will have frequent bleeding, and 17.7% will have prolonged bleeding.

I also reassure my patients that the amount of bleeding they may have is not dangerous. There is limited evidence that increased weight does increase bleeding days in women using the implant but more studies need to be done to clarify this issue. For women complaining of persistent or prolonged vaginal bleeding, we don’t have a proven long-term treatment. However, for temporary relief, there is a small amount of anecdotal evidence that oral estrogen alone or in the form of combined oral contraceptives for 1 to 3 months can help some women with this complaint. A shorter option for treatment is a short course of NSAIDs, such as mefenamic acid 500 mg three times daily for 5 days. I think it is worth offering some intervention if it will encourage women to continue with the implant given the benefits of LARC. Despite our best efforts at counseling and treatment of irregular bleeding, some women will ultimately decide to remove the implant. We can counsel them in that case about IUDs if they still desire long-term contraception.

References


High-dose Vitamin D Reduces Fracture Risk

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: A reanalysis of 11 double-blind, randomized, controlled trials demonstrated that high-dose vitamin D supplementation (≥ 800 IU daily) was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older.


Results of primary studies on and meta-analyses of the effects of vitamin D therapy on fracture risk have failed to conclusively demonstrate benefit. To help clarify this relationship, the authors conducted a reanalysis of recent randomized controlled trials. They obtained participant-level data from 11 double-blind, randomized, controlled trials of oral vitamin D supplementation (daily, weekly, or every 4 months), with or without calcium, as compared with placebo or calcium alone in persons 65 years of age or older and pooled the data to examine the primary endpoints of hip and any nonvertebral fractures incidence according to Cox regression analyses, and adjusted these outcomes for age group, gender, type of dwelling, and study. Their primary aim was to compare data from quartiles of actual intake of vitamin D (including treatment adherence and supplement use outside the study protocol). The analysis group included 31,022 per-
sons (mean age, 76 years; 91% women) with 1111 incident hip fractures and 3770 nonvertebral fractures. Overall, participants who received vitamin D had clinically unimportant reductions in fracture: A nonsignificant 10% reduction in the risk of hip fracture (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.80 to 1.01) and a statistically significant 7% reduction in the risk of nonvertebral fracture (HR, 0.93; 95% CI, 0.87 to 0.99). However, when risk was analyzed by quartiles of actual intake, a 30% reduction in the risk of hip fracture (HR, 0.70; 95% CI, 0.58 to 0.86) and a 14% reduction in the risk of any nonvertebral fracture (HR, 0.86; 95% CI, 0.76 to 0.96) was seen at the highest vitamin D intake level (median, 800 IU daily; range, 792 to 2000), and the benefits at this level of intake were consistent across subgroups such as age, type of dwelling, baseline 25-hydroxyvitamin D level, and additional calcium intake.

■ COMMENTARY

The risk of fracture in women accelerates after menopause. Although reduction in fracture risk is well established with estrogen therapy, some women have contraindications to estrogen use, and others prefer not to use it. However, in the absence of estrogen, accelerated bone turnover occurs in early menopause. With this turnover, serum levels of calcium are high and calcium excretion is increased. With all of the pressure moving calcium away from bone, it is not surprising that the role of calcium supplementation is somewhat controversial. I think of it like throwing a 5-pound bag of salt into the ocean. More substantively, among women in the placebo group of the Early Postmenopausal Interventional Cohort study (a clinical trial of alendronate) whose total calcium intake was > 1333 mg/d (the highest tertile of total calcium intake), a decline in bone mineral density of almost 2% was observed, and this was similar to declines observed in the lower two tertiles of total calcium intake.1 So calcium supplementation alone is insufficient to prevent bone de-mineralization.

Vitamin D deficiency is common, and at menopause the effect of inadequate nutrition and low exposure to sunlight is amplified by an age-related decrease in the ability of tissues to convert the major circulating form of vitamin D (25-hydroxyvitamin D) to the active form of vitamin D (1,25 dihydroxyvitamin D).2 Active vitamin D binds with high affinity to the nuclear vitamin D receptor (VDR) to orchestrate biologic effects in the intestine, bone, skin/hair follicle, and other VDR-containing tissues.3 A dequate vitamin D replacement appears to be more important than calcium replacement. Unfortunately, the available literature on vitamin D and bone health has been inconsistent.

The paper by Bischoff-Ferrari and colleagues helps to unravel some of the mystery surrounding the vitamin D literature. The technique of reanalysis is much more powerful than simple meta-analysis, as the primary original data are analyzed as a new study, rather than simply combining outcomes to improve statistical power. Since the majority of subjects were women, this applies to our practice.

The most important contribution of this paper is the clear documentation of a dose response. Compliant subjects receiving the higher dose of 800 IU/day had a 30% reduction in hip fracture. Unfortunately, few of the studies included information about actual vitamin D levels. Although giving more vitamin D to someone with already adequate levels will not improve outcomes, it probably makes sense to either replace at the higher levels (1500-2000 IU/day) recommended by the endocrine society or to follow serum levels (to maintain 25-hydroxyvitamin D > 30 ng/mL). To restore very low levels of vitamin D, prescription strength vitamin D3 should be provided (50,000 IU once weekly for 6 months) followed by standard replacement.

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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.

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In Future Issues:

Current Management of Fetal Growth Restriction

CME Questions

1. Regarding the amnioinfusion study, which answer does not fit the results?
   a. Average intrauterine temperatures were about 0.5°C higher than oral temperatures.
   b. Intrauterine temperatures after amnioinfusion in the overall study population were about 1°C lower than control intrauterine temperatures.
   c. In afebrile amnioinfusion patients, the average temperatures were 1.5°C cooler than controls.
   d. In those with epidurals in place for 3 hours or less, the intrauterine temperature difference between amnioinfusion and controls was 1.7°C.
   e. All of the above are correct.

2. It is more important to apply cooling at the time of hypoxic insult, as opposed to later in the process of neurological injury.
   a. True
   b. False

3. Which is correct with regard to the concept of fetal/neonatal cooling?
   a. There is no evidence that it works in neonates or animals.
   b. Infusion of room temperature saline attained the goal of lowering intrauterine temperatures by greater than 2°C.
   c. Intrauterine temperatures on average were about 0.5°C warmer than maternal oral temperatures.
   d. Immediate neonatal rectal temperatures were 2°C warmer than intrauterine temperature readings before delivery.

4. Which of the following is true about the features/results of the Pearce study on endometriosis and ovarian cancer?
   a. It was a retrospective cohort study.
   b. Central histological review was made for the diagnosis of ovarian cancer in centers with registry-based informatics.
   c. Women with epithelial and non-epithelial ovarian cancers were eligible.
   d. All studies included were population-based.
   e. Endometriosis was self-reported.

5. Obese women using the etonogestrel subdermal contraceptive implant are more likely to experience contraceptive failures.
   a. True
   b. False

6. The reanalysis of vitamin D replacement showed that there was:
   a. no difference in fracture risk reduction with low (400 IU) or high (800 IU) therapy.
   b. an increase in kidney stones with very high-dose (50,000 IU) therapy.
   c. a dose response with a 30% reduction in hip fracture seen in compliant subjects who received 800 IU/day.
   d. a reduction in fracture risk only when high-dose vitamin D was provided with 1500 mg of calcium each day.
Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride
Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (J Sex Med published online July 12, 2012).

Pharmaceutical company ruling
Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. The New York Times cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers.

FDA actions
The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous “fen-phen” combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the
FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline’s Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (Arch Intern Med 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech’s ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee’s recommendations and should make a final recommendation later this year. ■