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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Multimodal Stepwise Post-Cesarean Pain Control Reduces Opioid Use

By Camille Hoffman, MD, MSc

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

SOURCE: Smith AM, et al. Multimodal stepwise approach to reducing in-hospital opioid use after cesarean delivery: A quality improvement initiative. *Obstet Gynecol* 2019;133:700-706.

SYNOPSIS: These investigators found that the routine use of acetaminophen alone rather than a combination acetaminophen-opioid significantly reduced overall and daily opioid use. In addition, there was no worse effect on overall pain score or length of stay.

Prescription opioid use, and subsequent misuse, has resulted in a grand public health issue and, unfortunately, is responsible for claiming numerous lives each year. These authors from the Naval Medical Center in Portsmouth, VA, assessed delivery population data before and after a quality improvement (QI) initiative to evaluate a "standardized, structured approach to in-hospital post-cesarean delivery pain management." The main goal of this initiative was to uncouple scheduled acetaminophen prescribing (stop using combination acetaminophen-hydrocodone or acetaminophen-oxycodone) from opioid prescribing in the electronic order set. In addition to scheduling acetaminophen alone, the initiative also included scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and limited opioid use to breakthrough pain after acetaminophen and NSAIDs. A significant drop in overall opioid use — quantified by median morphine milligram equivalents per stay (75% reduction) and per day (77% reduction) — resulted from this subtle yet powerful change. There was no difference in pain score, amount of NSAIDs used, or length of stay. There were significant increases in acetaminophen use and the proportion of patients who used no opioids during their hospital stay (6% pre-QI vs. 19% post-QI).

■ COMMENTARY

Many women experience their first exposure to opioids with cesarean delivery. About 30% of deliveries are by

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cesarean. Of women who are opioid-naïve at the time of delivery, about one in 300 will become persistent opioid users after this first episode of exposure.[1] This is a part of the opioid crisis in which the obstetrician/gynecologist has power and influence.

We are taught to control pain post-cesarean, since undertreatment of postpartum pain has been associated with greater opioid use, delayed recovery of function, persistent pain, and increased rates of postpartum depression.[2] On the other hand, excessive opioid exposure resulting in an opioid use disorder leads to pain, suffering, and increased risk of death. Fortunately, our anesthesiology colleagues provide the greatest "layer" of pain control post-cesarean with long-acting neuraxial opioids; however, oral pain medication also is the rule following cesarean delivery.[3]

In this study, Smith et al sought to evaluate whether the implementation of a simple quality improvement measure would decrease the use of opioids. We learned that not only did the routine use of acetaminophen alone, instead of combination acetaminophen-opioid, significantly reduce overall and daily opioid use, this simple measure also had no worse effect on overall pain score or length of stay. This demonstrates that women did not appear to be suffering more at the "lack" of opioids. Furthermore, there was a significant increase in the percentage of women who used no opioids at all during their stay to almost 20%.

Based on this simple tweak of the electronic medical record's order set, here are some suggestions for minimizing post-cesarean delivery opioid use at your institution AND for minimizing postpartum opioid use in general:

- Make this change in your own electronic medical record's order set, or put in specific orders to uncouple acetaminophen from opioids (combination acetaminophen-hydrocodone or oxycodone).
- Schedule NSAIDs and acetaminophen as first-line treatments for postoperative pain.
- Take scheduled opioids off the menu, and inform patients that they may request additional medications after standing orders for acetaminophen and NSAIDs have been administered.
- Discharge home with fewer opioid pills. In a study assessing post-discharge opioid use after cesarean delivery, 83% of women used opioids for a median of only eight days (interquartile range, six to 13 days), and 75% had unused tablets.[4] ■

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ABSTRACT & COMMENTARY

Does Hormone Therapy Increase the Risk of Alzheimer's Disease?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: A large Finnish case-control study suggests that postmenopausal hormone therapy results in a 9-17% increase in the risk of Alzheimer's disease. However, the small effect size, and likely confounding of use effect, does not provide strong evidence for a causal relationship.

SOURCE: Savolainen-Peltonen H, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: Nationwide case-control study. *BMJ* 2019;364:l665.

A number of case control and other epidemiologic observational studies support a decrease in the risk of Alzheimer's disease (AD) associated with use of postmenopausal hormone replacement therapy (HT). In contrast, the prospective, randomized Women's Health Initiative Memory Study found that both oral conjugated equine estrogens alone, or in combination with medroxyprogesterone acetate, increased the risk of dementia and cognitive decline.[1] Savolainen-Peltonen et al conducted a large

national case-control study that evaluated the relationship between HT and AD among postmenopausal women in Finland. They identified as cases all postmenopausal women in Finland who received an AD diagnosis from a neurologist or geriatrician between 1999 and 2013 to qualify for reimbursement for treatment from national health insurance, a total of 84,739 women. They used the Finnish national population register to identify an equal number of controls, matching by age and hospital district. They used data on HT use available from the Finnish national drug reimbursement register. They calculated odds ratios (OR) and 95% confidence intervals (CI) for AD using conditional logistic regression analysis.

Most (99%) of the cases received the diagnosis of AD at or after 60 years of age, with the majority (56%) diagnosed after the age of 80 years. Compared to never-users of HT, use of estradiol only resulted in a statistically significant overall 9% (OR, 1.09; 95% CI, 1.05-1.14) increase in the risk of AD, and use of combined HT increased the risk by 17% (OR, 1.17; 95% CI, 1.13-1.21). The differences between estrogen-only and combined HT were not significant. Use of vaginal estradiol was not related to risk of AD (OR, 0.99; 95% CI, 0.96-1.01). The use of tibolone, a selective estrogen receptor modulator with estrogenic, androgenic, and progestagenic activities, also was not associated with any increase in risk. The authors found similar associations in women who started HT at < 60 years of age and ≥ 60 years of age. The ORs increased minimally, and inconsistently, with duration of use in both women who started HT at < 60 years of age and ≥ 60 years of age.

Based on these findings, the authors concluded that the long-term use of systemic HT "might be" associated with an overall increased risk of AD. They further concluded that the type of progestogen or the age at initiation of systemic HT does not modify the risk.

■ COMMENTARY

Getting older is not easy. Although a good diet, exercise, and a healthy lifestyle can influence the progressive decline in physical capacity and stamina that comes with aging, all of us have seen cancer and dementia reduce both the quality and length of life. Therefore, it is not surprising that journals and the news media have great interest in reporting findings of studies that suggest a potential risk-modifying factor. Unfortunately, most published studies present more noise than news. As clinicians, we must sort through the mess to help our patients draw reasonable conclusions. How should we evaluate this new study suggesting an association of HT with development of Alzheimer's dementia?

The short answer is that the limitation of the case-control study design does not permit any reasonable conclusion. First, a case-control study can demonstrate association, but cannot show causality. When evaluating a case-control study, the presence of uncontrolled confounding always should be suspected as the explanation for any association. The glaring confounder in this study is diagnosis bias. Women required a diagnosis of AD to qualify for benefits for AD treatment under the Finnish national insurance system. Some of these benefits included medications. One can reasonably assume that those women who presented for medical care for AD also may have been more likely to present for, and have received, medical care for menopause. This would create a prescription bias favoring more HT use among those women diagnosed with AD. Thus, the selection of controls in this study does not appear appropriate for the comparison.

I am always impressed by how large sample size is used to demonstrate the importance of a finding. Journal editors love these large numbers; this study included almost 85,000 cases and 85,000 controls so it must be important, correct? Wrong. Large numbers allow for very precise and narrow CIs but do not influence or increase the significance of the effect size. This provides the frequent problem of a statistically significant and clinically unimportant result. Here, we have very small (9-34%) increase in the odds ratio, (e.g., 1.09-1.34). These are extremely weak associations. In general, we should ignore ORs less than 2.0. The most likely explanation is bias.[2]

In 2017, other Finnish investigators published results from the Kuopio Osteoporosis Risk Factor and Prevention cohort, a population-based cohort followed for 20 years. They reported a history of HT use did not change the risk of AD, but that a trend toward protection emerged with longer duration of self-reported use with an approximately 50% reduction in risk seen in women reporting > 10 years of HT (adjusted hazard ratio [HR], 0.53; 95% CI, 0.31-0.91).[3] This prospective study provides much better evidence, with a more robust estimate of benefit that approaches a moderate effect (HR, 0.5). The Cache County Cohort, a prospective study of incident dementia in men and women residing in a single county in Utah, enrolled an older group of subjects (men and postmenopausal women in their 70s) than the Kuopio cohort (perimenopause to early menopause).[4] In the Cache County study, men and women were equally likely to develop AD up to about the age of 80 years, when the relative risk for women more than doubled. Utah women who reported any use of HT had a reduced risk of AD compared with non-HT users (adjusted HR, 0.59; 95% CI, 0.36-0.96). The reduction in risk showed a strong linear relationship with duration of use becoming significant only among women using HT for more than 10 years. Again, the prospective nature of these studies provides more confidence in the risk estimates, with the magnitude of the protective effect of long-term (> 10 years) HT on AD risk remarkably consistent. However, a heathy user effect could confound these results, so more research is needed.

As I have stated before, cognitive benefits are not an indication for HT. Clinicians should discuss the limitations of the data and the potential risks and benefits of treatment. Bad studies, like this Finnish case control, can reduce the confidence of women to continue treatment, particularly if they are asymptomatic. I feel our best data still support that HT continued for at least 10 years may maximize protection against the development of AD. ■

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ABSTRACT & COMMENTARY

Perioperative Antibiotics in Gynecologic Surgery: The Case for Myomectomy

By Robert W. Rebar, MD

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

SYNOPSIS: The authors of a retrospective cohort study suggest that perioperative antibiotics reduce the risk of surgical site infection in women undergoing myomectomy.

SOURCE: Kim AJ, et al. Perioperative antibiotic use and associated infectious outcomes at the time of myomectomy. *Obstet Gynecol* 2019;133:626-635.

There has been a continuing effort to reduce the number and severity of surgical site infections, defined here as infection occurring within 30 days of surgery and involving the surgical incision(s), organ, or site. Part of that effort has involved the possible use of perioperative antibiotics. Current recommendations from the American College of Obstetricians and Gynecologists suggest the use of perioperative antibiotics in several gynecologic procedures, including laparotomy, but do not recommend use in cases involving diagnostic or operative laparoscopy not involving hysterectomy or a pre-existing infection.[1]

Although an estimated 34,000 myomectomies are performed annually in the United States,[2] there are no good studies examining the use of perioperative antibiotics in these cases. Consequently, investigators at a single medical center in Boston sought to identify patterns of antibiotic use in a cohort of women undergoing myomectomy and to examine associations between antibiotic use and surgical site infections by reviewing data from women undergoing myomectomy at two area hospitals between the years of 2009 and 2016.

A total of 1,211 women undergoing myomectomy were included in the cohort. The most frequent indications for surgery were pelvic pain or pressure or heavy menstrual bleeding. Excluded from analysis were women undergoing vaginal or hysteroscopic myomectomy, those undergoing chromotubation, and those converted to hysterectomy. Almost 93% of the women received perioperative antibiotics, and only 88 women did not receive any antibiotics. Of those patients receiving perioperative antibiotics, 95.6% received a beta-lactam drug, most commonly cefazolin (1 to 3 g) intravenously. It was not possible to determine precisely when the antibiotics were administered. Two-thirds of the cases were performed in a minimally invasive manner, with almost 96% performed by trained subspecialists. Patients receiving antibiotics had longer median operative times (140 minutes vs. 85.5 minutes; $P < 0.001$), greater estimated blood loss (137.5 mL vs. 50 mL; $P < 0.001$), a greater number of myomas removed (7.2 vs. 2.4; $P < 0.001$), greater median myoma weight (255 g vs. 52.9 g; $P < 0.001$), higher frequency of entry into the endometrial cavity (30.1% vs. 13.6%; $P = 0.001$), and longer median length of stay (1 vs. 0 days; $P < 0.001$). Yet, multivariable regression analysis of infectious outcomes, which controlled for age, route of surgery, high-risk factors, any intraoperative complication, myoma weight, and entrance into the endometrial cavity, indicated that surgical site infection occurred almost four-fold more commonly in the absence of antibiotics (6.8% vs. 2.9%; adjusted odds ratio, 3.77; 95% confidence interval, 1.30-10.97; $P = 0.015$).

■ COMMENTARY

A retrospective cohort study from a single institution involving a limited number of surgeons, most with advanced fellowship training in minimally invasive surgery, is far from the ideal way to answer a clinical question. The authors themselves noted that they were unable to tabulate data regarding many perioperative factors that might contribute to surgical site infection, including any type of preoperative abdominal and vaginal wash, hair clipping, type of surgical scrub, method of wound closure, and intraoperative temperature. The authors further noted that the generalizability of their findings might be limited because most patients were white and largely healthy, with low rates of diabetes mellitus and active smoking and an average body mass index of less than 30 kg/m^2.

So why choose this article? Surgical site infections are the second most common reason for unplanned hospital readmission after hysterectomy and result in increased morbidity and healthcare costs.[3] Surgical site infections are a

common cause of morbidity for all gynecologic procedures. Because of the frequency of infections following gynecologic surgery, various groups have attempted to develop consensus patient safety bundles to prevent infection.[4,5] Investigators are reporting in the literature that adherence to such gynecologic-specific bundles is proving effective for hysterectomy. In one recent study, full implementation of a patient safety bundle reduced the site-specific infection rate for hysterectomy from 4.51% to 1.87%.[6] Maintaining low rates will require continued vigilance and adherence to the entire patient safety bundle, including appropriate therapy for medical conditions such as diabetes prior to and during surgery, standardization of a patient wash before admission, preoperative and intraoperative warming, standardized aseptic skin and vaginal preparation, standardized regimens for sterile dressing, standardized antibiotic use, and timely and constructive direct feedback to all members of the healthcare team. In a study examining data from the National Surgical Quality Improvement Program, researchers reported that minimally invasive surgery was associated with reduced rates of surgical site infection for each of four procedures (appendectomy, colectomy, hysterectomy, and radical prostatectomy) examined.[7]

We have an obligation to attempt to reduce surgical site infection for all gynecologic procedures. Myomectomy is becoming more common as women delay childbearing. Kim et al emphasized the need for randomized, controlled trials to document that standardized antibiotic prophylaxis can reduce surgical site infection. We are all aware of circumstances in which randomized trials have failed to replicate findings from retrospective studies. In a review of guideline-based antibiotic prophylaxis for more than 545,000 women undergoing gynecologic surgery for whom antibiotic prophylaxis was recommended (abdominal, vaginal, or laparoscopically assisted vaginal hysterectomy), investigators indicated that 87.1% received appropriate prophylaxis, 2.3% received non-guideline recommended antibiotics, and 10.6% received no prophylaxis.[8] Among more than 490,000 women who had surgery for which antibiotic prophylaxis was not recommended (oophorectomy, cystectomy, tubal ligation, dilation and curettage, and myomectomy), 40.2% received antibiotics.[8] Yet, we all know that giving antibiotics in situations in which the benefit is unproven may have untoward consequences as well.

With regard to myomectomy, the authors of a Cochrane Review concluded that laparoscopic myomectomy is associated with less subjectively reported postoperative pain, lower postoperative fever, and shorter hospital stay compared with all types of open myomectomy.[2] This meta-analysis was unable to address site specific infection, uterine rupture, occurrence rates for thromboembolism, and the need for repeat myomectomy and hysterectomy at a later date. Still, it suggests that minimally invasive surgery is indicated for myomectomy when and where possible. The study by Kim et al strongly suggested that perioperative antibiotics should be used for women undergoing myomectomy by whatever route until such time as we have the definitive answer from needed randomized trials. Accumulating literature further indicates the need for each medical center to develop standardized patient safety bundles for all gynecologic procedures to reduce surgical site infection. I selected this imperfect but informative article for discussion to emphasize this need. Moreover, for the present the article should encourage us all to use perioperative antibiotics when performing myomectomy. ■

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SPECIAL FEATURE

Estrogens Used in Hormonal Therapy

By Jeffrey T. Jensen, MD, MPH, Editor

To practice as a consultant in reproductive medicine, clinicians require a strong background in hormonal therapy. In this feature, we will review the role of steroidal estrogens used in contraceptive and hormone therapy.

First, let's briefly review how steroid hormones work. Most steroid hormones circulate through the blood bound to specific carrier proteins. For example, estrogens and androgens circulate bound to sex hormone binding globulin (SHBG), while glucocorticoids and progesterone bind to cortisol binding globulin (CBG). Albumin binds all steroid hormones with low affinity but high capacity. Only the free (unbound) hormone can exert a biologic response.[1] Route of administration, dose, metabolism, and tissue-specific receptor activity of various natural and synthetic steroid and peptide hormones also influence the biologic response. The

lipid-like nature of steroid hormones allows them to pass through cell membranes easily.

The classical mechanism of steroid action requires hormone binding to a specific hormone receptor. Two nuclear estrogen receptors have been described: ERα and ERβ. Receptor binding leads to dimerization and binding with other regulatory cofactors, followed by interaction with nuclear DNA to stimulate transcription of mRNA. The mRNA is transported to the cytosol and ribosomes for translation to protein.[2] Although there is some evidence that steroid hormones also work through direct (non-nuclear) actions, the take-home point is that classical steroid hormone action takes time (hours to days). In other words, the clinical response following administration of a steroid requires patience.

Estrogen is not a hormone. Rather, the term estrogen encompasses a family of natural and synthetic hormones with activity at estrogen receptors. Four natural estrogens exist in humans: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). These 19-carbon steroids differ by the number of hydroxy (-OH) groups present on the cyclopentanophenanthrene ring steroid backbone, hence the shorthand nomenclature.

E2, the most biologically active of the natural estrogens and the primary estrogen of the reproductive years, is secreted by the ovaries from menarche through menopause. The hypothalamic-pituitary ovarian axis regulates estrogen production by stimulating ovarian follicle development. Theca cells surrounding antral follicles produce androstenedione and testosterone. Granulosa cells then aromatize these androgens to estrone and estradiol. Isomerization of estrone to estradiol occurs through 17b-hydroxysteroid dehydrogenase.

E1, the primary estrogen of menopause, results primarily from the conversion of adrenal androstenedione by aromatase in peripheral fat. E1 is about 12-fold less potent than E2.[3] However, since E1 can undergo isomerization to E2, peripheral conversion in young and old obese women can result in physiologically and clinically important levels of E2.

E3 is the primary estrogen produced by the placenta. E3 is a weak estrogen (80-fold less than E2) that undergoes rapid elimination.[3] Prior to the development of fetal monitoring, obstetricians monitored E3 levels to evaluate fetal well-being. Another pregnancy-related estrogen, E4, is the most recently discovered natural human estrogen. The fetal liver produces E4 beginning in the ninth week of pregnancy and production ceases during the first week after birth. E4 is about 30- to 35-fold less potent than E2.[4] It makes sense that these lower-potency estrogens serve to reduce the effect of the high estrogen environment of pregnancy on the fetus.

When given orally, E1, E2, and E3 undergo rapid hepatic metabolism through conjugation for excretion. Estradiol has a half-life of about 14-16 hours, with estrone and estriol even shorter. The poor oral bioavailability and rapid metabolism of natural estrogens presents a challenge when using these agents for oral therapy. In contrast, E4 undergoes minimal liver metabolism and has a half-life of about 28 hours.[4]

Structural modifications of natural estrogens with polar sidechains designed to improve bioavailability with oral dosing have been synthesized. These can be considered prodrugs. For example, estradiol valerate (E2V) is rapidly hydrolyzed and converted to E2 during absorption in the gastrointestinal tract (1 mg of E2V contains 0.76 mg of E2).[5] Piperazine estrone sulfate undergoes conversion to estrone after oral absorption.[6] Therefore, a lab test for E1 and E2 will detect levels achieved following oral administration. Pregnant mares produce and excrete large volumes of conjugated estrogens in their urine: hence, the name Premarin for these conjugated equine estrogens (CEE). It is important to note that CEE represents a group of biologically active molecules rather than one specific compound and not a prodrug for estradiol. Although some conversion to E2 occurs, serum concentrations of E2 will not reflect the total estrogenicity. Ethinyl estradiol (EE), the form of estrogen used in most combined hormonal contraceptives (pills, patch, ring), also is not a prodrug for estradiol. Laboratory assays for E2 do not detect EE. Like estradiol, EE undergoes hepatic conjugation following oral administration, but unlike estradiol these conjugated forms remain highly potent, stimulating the liver on second pass. Therefore, even when delivered non-orally, EE exerts potent effects on the liver.

The effects of estrogens differ depending on dose, potency, molecule, and route of administration. Oral administration of estrogens exposes the gut and liver to high concentrations of steroid, resulting in extensive first-pass metabolism and hepatic stimulation.[7] This results in the induction of important hepatic globulins involved in coagulation and in lipid and steroid hormone transport pathways.[7] Of major interest is the induction of SHBG by estrogen. The increase in SHBG that occurs in users of combined hormonal contraceptive methods results in a decrease in free androgen levels, an important effect that provides the basis for treatment of androgen-related symptoms, such as acne and hirsutism. The degree of hepatic induction following oral administration of an oral estrogen is dose dependent.[8,9]

The most important clinical consequence of hepatic stimulation with estrogen therapy is the increased risk of venous (VTE) and arterial (ATE) thrombosis. Humans likely evolved this shift to clot formation in response to estrogen as an adaptation to reduce blood loss with pregnancy.[10] Ordinarily, the ovary delivers estradiol directly into the circulation at physiologic levels. Placental production of E2 leads to an increase in the liver production of clotting proteins and an increased risk of blood clots during pregnancy. Numerous studies have documented the increase in thrombosis associated with estrogens used in contraception and menopausal therapy.

Estrogens are eliminated from the body by metabolic conversion to inactive molecules followed by excretion

in the feces and urine. The first step in this metabolism requires hydroxylation catalyzed by cytochrome P450 (CYP) enzymes in the liver.[11] Therefore, drugs that increase or decrease the activity of CYP enzymes will influence the level of circulating estrogens. CYP3A4 and CYP2C9 are the major isoforms contributing to the oxidative metabolism of EE in human liver microsomes.[12] Thus, coadministration of drugs that induce or suppress CYP enzymes may affect the levels of estrogen used therapeutically.

Comparator studies evaluating the effect of ligands on the suppression of FSH and induction of hepatic globulins have demonstrated that the EE is about 100-fold more potent than E2.[6] Since EE passes through the liver on first pass without extensive conjugation, the liver effects of EE remain potent on recirculation. To restate for emphasis, the enhanced effect of EE on induction of hepatic globulins occurs because of greater potency, lack of significant first-pass conjugation, and potent induction on recirculation. This leads to important clinical consequences. E2 undergoes isomerization to E1, a less potent estrogen. This is of particular importance following oral administration.[13] Thus, the stimulation effects of E2 on the liver following oral administration occur primarily as a result of first-pass. Parenteral administration of E2 at physiologic levels does not result in significant hepatic stimulation.[7] In contrast, EE induces potent stimulation regardless of route of administration.

In other words, while oral administration of any estrogen will exert dose- and potency-related increases in hepatic globulins, parenteral administration of natural estrogens at physiologic levels should not increase clot risk. In contrast, parenteral administration of EE does not reduce hepatic impact; hormonal contraception with transdermal or transvaginal administration of EE is associated with a risk of VTE similar to that observed with oral preparations.[14]

Evidence is accumulating that transdermal delivery of estradiol is not associated with an increased risk of VTE during postmenopausal hormonal therapy (HT). Canonico et al performed a case-control study that evaluated the associations of obesity and estrogen use on VTE risk in postmenopausal women in France. They found an increased risk for overweight (adjusted odds ratio [aOR], 2.5; 95% confidence interval [CI], 1.7-3.7; and aOR, 3.9; 95% CI, 2.2-6.9) for obese women compared to normal weight. They also reported that oral estrogen increased the risk four-fold (aOR, 4.5; 95% CI, 2.6-7.7), but found no increase in women using transdermal E2 (aOR, 1.1; 95% CI, 0.7-1.7) compared to nonusers. They reported significant interaction with the combination of oral estrogen use and overweight or obesity (aOR, 10.2; 95% CI, 3.5-30.2; aOR, 20.6; 95% CI, 4.8-88.1, respectively), but no excess risk among overweight and obese users of transdermal E2.[15]

A 2019 publication from the United Kingdom has provided additional evidence supporting these results. Using data from the UK Clinical Practice Research Datalink databases, Vinogradova et al completed a case-control study that compared 80,396 women between 40 and 79 years of age with a primary diagnosis of venous thromboembolism between 1998 and 2017 to a group of 391,494 female controls matched by age, general practice, and index date. They calculated odds ratios and adjusted these for demographics, smoking status, alcohol consumption, comorbidities, recent medical events, and other prescribed drugs. They found an overall increase in VTE with any hormone therapy consistent with other studies, but the risk was confined to oral therapy. Transdermal E2 therapy did not increase the risk of VTE (aOR, 0.93; 95% CI, 0.87-1.01).[16] These results are highly encouraging and are consistent with our biologic understanding of the effects of estrogens on the liver.

These results should inform our use of estrogen therapy in postmenopausal women. Transdermal or vaginal delivery of estradiol should increase cardiovascular safety. Although we do not have evidence that parenteral estradiol reduces the risk of heart attack and stroke, I predict these data will follow.

What about hormonal contraception? Over the last decade, two oral contraceptives based on estradiol have been introduced: E2/nomegestrol acetate (not available in the United States) and E2V/dienogest vaginal rings containing estradiol.[17] A combination of E4 with drospirenone pill[18] is in clinical trials. The estradiol ring is particularly exciting, as we should expect results similar to those observed with transdermal estrogen therapy in postmenopausal women. Estradiol pills still provide hepatic stimulation on first pass, but the effect on hepatic globulin synthesis appears lower than EE.[19,20] While interesting, we cannot rely on unvalidated surrogate markers to predict a clinical benefit.

The INAS-SCORE study investigated the cardiovascular risks associated with the use of the E2V/dienogest pill in women from the United States and Europe.[21] Investigators enrolled 50,203 new COC users, and completed up to 5.5 years of follow-up. Overall, 20% of the cohort used the E2 pill and 80% used EE pills. Compared to all EE COCs, the adjusted hazard ratios for DVT for the E2V/DNG was 0.5 (95% CI, 0.2-1.0). Although the point estimate suggesting a lower risk is intriguing, the confidence interval overlaps 1.0 supporting caution in our enthusiasm.

Estetrol, also appears to have lower impact on hemostatic factors following oral administration.[22] Confirming whether oral contraceptives currently in development using Estetrol or estradiol-containing vaginal rings will have less thrombosis risk than existing CHC products will require similar population-based trials. This new emphasis on approaches to estrogen administration that reduce hepatic stimulation should improve safety of combined hormonal contraception. In my opinion, this represents a major breakthrough. While the differential impact of various progestins have preoccupied us for many years, the overall effect on thrombosis risk appears minimal. In contrast, moving away from ethinyl estradiol should improve outcomes and reduce risk. ■

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CME/CE QUESTIONS

1. The median morphine milligram equivalent per stay was reduced by what percent pre- vs. post-quality improvement intervention?
a. 10%
b. 50%
c. 75%
d. 100%

2. The relationship between hormonal therapy and Alzheimer's dementia seen in the Finnish case-control study demonstrates which of the following?
a. An inverse relationship to duration of use
b. A weak association that is likely a result of confounding
c. A strong relationship to dose of progestogen
d. A moderate risk only in women who smoke more than 10 cigarettes/day

[IN FUTURE ISSUES]

Prophylactic Antibiotics for Miscarriage Surgery
A Conservative Option for Fecal Incontinence
Changes in Cervical Cancer Care