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INSIDE

Menorrhagia, Bleeding Disorders, and the Levonorgestrel IUD

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

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

Synopsis: *In a group of women with inherited bleeding disorders, improvement of menorrhagia and amenorrhea was seen in more than half of the group along with an increase in hemoglobin concentration.*

Source: Kingman CE, et al. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. *BJOG*. 2004;111:1425-1428.

THIS IS A PROSPECTIVE TRIAL IN WHICH THE LEVONORGESTREL-releasing IUD was used in 16 patients who had an inherited bleeding disorder including 13 with von Willebrand's disease and 2 with factor XI deficiency. No pelvic pathology was identified in any patient. All previous therapies had been unsuccessful. The follow-up for patients was for 9 months, with all patients having an improvement in menorrhagia with 56% becoming amenorrheic.

COMMENTARY

I call your attention to a related article that looked at 115 women with menorrhagia, of whom 25 were adolescents, 25 were perimenopausal women, and 65 were reproductive-aged. Hemostatic abnormalities were identified in 47%. Of note, adolescents and perimenopausal patients were as likely to have a clotting abnormality as a reproductive-aged patient.[1]

These 2 articles are an important reminder to a precept that we all learned in medical school. In particular in adolescents first starting their periods, menorrhagia should be a potential symptom of an underlying bleeding disorder. In this age patient, it certainly makes sense since the periods are heavy from the onset of periods, reflecting a heretofore unknown problem. We should not be lulled into a false

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sense of security, however, just because the woman is at reproductive age or even perimenopausal. Bleeding abnormalities appear to be just as likely later on in life when a thorough investigation is initiated.

So let's work our way back to the topic of levonorgestrel-releasing IUD's. With another apparently effective treatment modality for menorrhagia, (in addition to the likes of oral contraceptives, the contraceptive patch, depot-medroxyprogesterone acetate, endometrial ablation and hysterectomy) we shouldn't forget that the underlying work-up to look for the etiology is still of primary importance. Before treatment is initiated, I want to re-emphasize the 4 traditional elements of diagnosis:

1. History—make sure that the patient truly has menorrhagia, ie, are the periods predictable and heavy, otherwise it may well be dysfunctional anovulatory bleeding;
2. Physical—determine if there is any palpable etiology of the heavy bleeding, eg, fibroids;
3. Imaging—utilize cost-effective imaging including transvaginal ultrasound and possibly saline hysterosonography to identify fibroids and/or endometrial polyps, and;
4. Laboratory—obtain baseline blood count as well as clotting studies to rule out a bleeding disorder.

It is with this return to basics of menorrhagia diagnosis, that the most logical treatment options can be offered patients of any age. Certainly it appears that the levonorgestrel-releasing IUD will become one of the options we need to offer our patients. ■

Reference

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Are Fertility-Sparing Procedures Safe for Women with Ovarian Borderline Tumors? Probably.

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston TX

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol Myers Squibb, and Ortho Biotech.

Synopsis: *Fertility-sparing surgery for ovarian LMP tumors is an option for motivated patients. Preservation of the contralateral adnexa increases the risk of recurrence, but surgical resection is usually curative.*

Source: Rao GG, et al. Fertility-sparing surgery for ovarian low malignant potential tumors. *Gynecol Oncol*. 2005;98: 263-266.

It has been well documented that women diagnosed with low malignant potential (LMP) tumors have an excellent prognosis with few recurrences identified in those undergoing definitive resection. However, many of these cases occur in women of childbearing age in whom fertility may be desired. Limited evidence to date has suggested that subtotal resection is not associated with worsening prognosis although recurrence risk is increased. In evaluation of this objective, Rao and colleagues examined

the outcomes of 38 patients with LMP tumors who underwent fertility-sparing operations as primary management of their disease. Most had unilateral oophorectomy; 5 underwent cystectomy only. Although formal staging wasn't obtained in all cases, only 4 were not apparent stage I. No patients received adjuvant therapy. At a median 26 months of follow-up 6 patients had recurred (16%); 5 in a remaining ovary, in which all were cured following subsequent resection. Five women delivered 6-term infants during post-treatment surveillance. Rao and colleagues conclude that given these characteristics, well-informed patients might safely choose surgical therapy which preserves their fertility. Although recurrence may be experienced, surgical resection is generally curable.

COMMENTARY

Most women diagnosed with an ovarian malignancy have invasive, advanced-staged disease requiring aggressive cytoreduction and adjuvant chemotherapy. The track record in successful management for these patients is well described and while improving, is, in general, poor. On the other end of this spectrum, tumors of low malignant potential are characterized by limited extra-ovarian disease at presentation, long periods of disease-free survival and infrequent need for systemic adjuvant therapies. While some of these tumors can be fatal, particularly in those patients in whom inoperable disease attains a progressive or an invasive phenotype, the majority follows a more benign course compared to their invasive counterpart. Surgical staging studies of women with these neoplasms have documented that thorough abdominal and pelvic sampling will upstage approximately 20% of apparent stage I cases.[1-4] However, it has been increasingly documented that re-operating to formally stage a patient with a *surprise* LMP final pathological diagnosis is of little value. Nonetheless, receiving the diagnosis of LMP intraoperatively generally promulgates formal surgical staging as subsequent upgrading to invasive disease can occur in 5-30%. In patients with unstaged invasive lesions the stakes are higher; and the management considerations in this situation are to re-operate for formal staging or empiric multi-agent chemotherapy. With these caveats, a young woman undergoing surgical exploration for adnexal pathology should have a discussion that not only incorporates the possibility of cancer but also the procedures to be undertaken in this situation. For the motivated patient who understands the attendant risks of subtotal resection in the event of LMP, fertility-sparing procedures are an option. Data from the current series as well as others would support this management pathway.[5] Staging biopsies are still obtained but resection of all fertility organs may be omitted. The decision to remove these retained organs after childbearing is less definitive but generally recommended if it is an organ responsible for persistent or recurrent disease.

Advanced reproductive techniques are redefining what "fertility-sparing" entails. A retained uterus without ovaries permits surrogacy, as well as subcutaneously implanted ovarian tissue in the absence of ovaries or a uterus. Such extremes are infrequently encountered but underscore pre-operative counseling necessary for women with adnexal masses in whom, prospective education can maximize options for fertility-desiring women. ■

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Polycystic Ovary Syndrome: Changes in Glucose Tolerance

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Professor of Obstetrics and Gynecology, Oregon Health & Science University, Portland

Synopsis: *Women with polycystic ovaries demonstrate a definite rate of worsening glucose tolerance and conversion to type 2 diabetes mellitus.*

Source: Legro RS, et al. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab*. 2005;90:3236-3242.

LEGRO AND COLLEAGUES FOLLOWED 71 WOMEN WITH polycystic ovary syndrome and 23 normal women

with regular menses for 2 to 3 years. Impaired glucose tolerance increased in prevalence during the follow-up period in the women with polycystic ovaries, from 37% with impaired tolerance and 10% with type 2 diabetes mellitus at baseline to 45% and 15%, respectively. Based on their results, Legro et al affirm the importance of periodic assessment of glucose tolerance, but they question whether this is necessary annually.

COMMENTARY

Although we know that there is a high prevalence of impaired glucose tolerance in adult women with polycystic ovaries, we have not known the rate at which individuals change from normal to abnormal. The changes in the women in this study were not dramatic. For example, the glycohemoglobin levels were in the range of normal in the group with polycystic ovaries, but the levels had increased to the upper range in the relatively short time of the follow-up. Nevertheless, the measurements indicated a worsening and conversion rate of about 2% per year to type 2 diabetes mellitus.

Another useful clinical finding in this study was the fact that fasting glucose levels did not change. Therefore, measurements of fasting glucose and glycohemoglobin levels will not detect the early worsening of insulin resistance and glucose tolerance. The proper method to evaluate insulin resistance and glucose tolerance has been somewhat controversial. Because of the variability, the fasting glucose to fasting insulin ratio is no longer recommended; a 2-hour oral glucose tolerance test is now the preferred method of assessment.

All anovulatory women who are hyperandrogenic should be assessed for glucose tolerance and insulin resistance with measurement of 2-hour glucose and insulin levels after a 75 g glucose load.

In my view, periodic surveillance is necessary in women who continue to manifest this disorder. Until strong evidence emerges to the contrary, I believe an annual assessment with the 2-hour glucose tolerance test is appropriate, especially in women who fail to lose weight. ■

Interpretation of the 2-hour glucose response:	
Normal	less than 140 mg/dL
Impaired	140-199 mg/dL
Noninsulin-dependent diabetes mellitus-	200 mg/dL and higher
Interpretation of the 2-hour insulin response:	
Insulin resistance very likely	100-150 U/mL
Insulin resistance-	151-300 U/mL
Severe insulin resistance	greater than 300 U/mL

Adult Schizophrenia Following Prenatal Exposure to the Chinese Famine of 1959-1961

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA

Dr. Berga is a consultant for Pfizer, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc.

Synopsis: *Prenatal exposure to famine doubles the risk of schizophrenia in later life.*

Source: St Clair D, et al. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. *JAMA*. 2005;294:557-562.

Schizophrenia is a common form of severe mental illness characterized by disordered thoughts processes, hallucinations, delusions, and social withdrawal. The cause has been attributed to many factors, including obstetrical complications, season of birth, maternal stress, prenatal viral exposure, and poor maternal nutrition. However, schizophrenia is increasingly viewed as a neurodevelopmental disorder, with environmental influences during early brain development modifying the risk. The lifetime risk is roughly 1%. It is universally distributed and rates are similar in men and women. In the 1990s, 2 studies found that prenatal exposure to famine during the Dutch Hunger Winter of 1944-1945 roughly doubled the risk of schizophrenia.[1,2] The aim of the present study was to see if this association held in another population exposed to famine.

The current study was done in China. The famine occurred from 1959 to 1961 and was due to immense social and economic upheaval coupled with bad weather. The study was made possible by referral patterns in the region. The Fourth People's Hospital in the only psychiatric hospital in the region where the famine was greatest and records are complete from 1971 to the present. The risk of schizophrenia for each year of birth was measured by the cumulative incidence of outpatient consultation and inpatient admission. More than 97% of the cases with schizophrenia from 1955 to 1965 were born in the region. During the famine, birth rates decreased by 80% and cumulative mortality rates for

children during the famine years roughly doubled to 40%. The odds ratio for schizophrenia was 0.89 in 1959, 2.30 in 1960 ($P < 0.001$), 1.93 in 1961 ($P < 0.001$), and 0.95 in 1962.

COMMENTARY

This study may not seem immediately relevant to our typical population of pregnant women. However, its lessons are worth considering. It has long been assumed that undernutrition in pregnancy carries few fetal consequences, as the fetus is spared at maternal expense. Emerging evidence on several fronts appears to directly challenge this assumption. Most of us have heard of the Barker hypothesis, which posits that maternal undernutrition sufficient to produce infants that are small for gestational age predisposes those same offspring to excess and premature cardiovascular disease in later life. Hansen et al have shown that significant maternal grief in early gestation markedly increases the risk of congenital malformations.[3] Haddow et al have shown that even subclinical hypothyroidism lowers overall intelligence and increases the risk of poor neurodevelopment.[4] Folate deficiency leads to neural tube defects, particularly in predisposed populations. Further, there is a link between severe undernutrition and psychopathology, including schizophrenia, antisocial personality, and schizoid personality disorder. dditionally, the culture conditions for embryos during assisted reproductive techniques may increase the risk for certain congenital disorders attributable to altered fetal genomic imprinting, ie, some aspect of the embryo's culture conditions (nutrition) changes the way that the maternal and paternal alleles are methylated. Methylation patterns, in turn, alter the timing and dosage of gene expression, thus influencing embryo development.

In an accompanying editorial, Neugebauer points out that the most pressing question from a public health and interventionalist perspective is whether the relevant restriction of interest constitutes a global nutritional deficiency or a specific micronutrient deficiency.[5] Our own research on stress-induced anovulation suggests that combined metabolic and psychosocial stress is far more potent in eliciting maternal biochemical perturbations than either nutritional or psychosocial stress alone. Certainly famine constitutes more than nutritional deprivation and thus it was not surprising to read that birth rates during the famine fell by 80%. However, the pregnancies that resulted also were certainly subjected to both extreme undernutrition and severe psychosocial stress, so it is almost surprising to find that the risk of schizophrenia and other neurodevelopmental disorders was not greater. Indeed, the results suggest a degree of adaptation and resilience that one might not have expected given the apparently high fetal susceptibility to subtle perturbations noted above.

Resilience in the face of adversity notwithstanding, we need to know if there are ways to ameliorate the fetal consequences of nutritional deprivation. At least one of the positive answers does not entail achieving an equitable distribution of the world's financial and nutritional resources and ought to be feasible and relatively inexpensive. That answer is to provide our familiar micronutrient and friend of rapidly replicating cells, folate. Neugebauer points out that diet-triggered alterations in DNA methylation patterns may be buffered by having sufficient folate in the microenvironment of the replicating cells. Indeed, the genetic polymorphism methyltetrahydrofolate reductase, C677T, a key enzyme regulating intracellular folate availability, increases the risk of schizophrenia independent of undernutrition. Thus, famine seems to impact the DNA in a manner similar to that associated with embryo culture. Of course, other mechanisms also may be at play in famine and assisted reproduction as well.

The take-home message here is three-fold. First, think folate always, but especially when diet appears to be inadequate. Second, circumstances that combine both undernutrition and psychosocial stress, such as famine, typically result in anovulation and infertility rather than an at-risk pregnancy. Third, the chance that environmental or lifestyle insults will alter fetal imprinting or DNA methylation patterns, augment later cardiovascular risk, or subtly impact neurodevelopment is probably greater when conditions are not so severe as to cause anovulation. In the absence of medical intervention, stress-induced anovulation prevents the worse case scenario. ■

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Hospitalization for Preterm Labor

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

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

Synopsis: *Compared with hospitalization, outpatient management of women with arrested preterm labor and intact membranes had no effect on the rate of preterm birth.*

Source: Yost NP, et al. Hospitalization for women with arrested preterm labor: a randomized trial. *Obstet Gynecol*. 2005;106:14-18.

THERE IS A STRONG TENDENCY TODAY TO CONTINUE TO hospitalize patients diagnosed to have arrested preterm labor. A randomized trial was designed to answer the question of whether this practice was necessary, and the results were recently published in the July issue of *Obstetrics and Gynecology*.

Yost and colleagues randomized 108 women who were admitted with painful preterm contractions at 24 to 33 weeks gestation and with cervical dilation of 2-4 centimeters. All women were given steroids, but not started on tocolytics. One group (54) was discharged with a prescription for decreased activity (but not bedrest). Hospitalization was continued until 34 weeks in the other group.

There was no difference in the time of delivery (36 vs 36.5 weeks), pregnancy prolongation (38.6 days vs 37 days), or percentage that reached 36 weeks (71% vs 70%) between nonhospitalized and hospitalized patients. Interestingly, 15 patients (29%) left the hospital against medical advice after an average of 10 days.

Yost et al's conclusion was that continued hospitalization had no benefit, but they admitted that they stopped the study prior to achieving the statistical power to conclusively demonstrate the lack of efficacy of hospitalization. They terminated the study because:

1. It took 6 years to recruit the patients in the study, and it might take another 4 years to complete the study.
2. There was no difference in outcome.
3. They needed to move on to another study to assess the benefit of progesterone in prolonging pregnancy.

COMMENTARY

In a companion editorial, Robert Goldenberg, one of the leading experts on clinical trials, pointed out that the study was underpowered statistically, and even suggested that it might have been doomed from the start.[1] However, although he indicated that the data should do little "to influence care," he then went on to allude to other evidence that hospitalization, bedrest, and even "intense maternal observation" have failed to demonstrate benefit in other preterm labor studies; and, in one study, the intensely observed patients even had a higher rate of respiratory distress syndrome (compared to the controls).

For years, it was in vogue to restrict the activity of patients with twins, and many practitioners were even advocating bedrest in the latter stages of pregnancy for these patients.[2-4] However, pooled data from randomized trials, pitting hospitalized twin patients' outcomes with those of controls pursuing ad-lib activity, suggest a higher rate of preterm birth and prolonged neonatal stays in twins on bed rest.

Some will question whether adding tocolytics would have made a difference in the study results. However, there has not been a study to demonstrate the benefit of tocolytics, except perhaps to prolong pregnancy long enough to get steroids on board.

What is quite clear is that hospitalization is extremely expensive. In a previous *OB/GYN Clinical Alert*, I indicated that one day of hospitalization on our antepartum service had a baseline cost of about $900.[5] This has now risen to about $1,700. The average stay for the hospitalized patients in the above study was 30 days, so the average total cost of just occupying a bed for those patients would have been $51,000 per patient. Although Dallas Hospital costs may be less than ours, this alone would have been enough to stop the study when Yost et al found no difference in outcome after 6 years.

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Anorexia Nervosa: Treatment of Low Bone Mass

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Body weight is the major determinant of changes in bone density in adolescents with anorexia nervosa.*

Source: Golden NH, et al. *J Clin Endocrinol Metab*. 2005:90:3179-3185.

GOLDEN AND COLLEAGUES COMPARED ALENDRONATE treatment (10 mg daily) with placebo in a randomized clinical trial, in 32 female adolescents with anorexia nervosa. In addition, every participant was supplemented with calcium and vitamin D. Every individual was malnourished and had either primary or secondary amenorrhea. After one year of treatment, bone density in the spine and femoral neck as measured by DEXA increased in the alendronate group compared with no increase in the placebo group, although the difference achieved statistical significance only in the femoral neck. However, both groups gained weight and the bone density response was influenced by individual response in body weight. Those individuals who gained weight had the greatest increases in bone density; however, even though two-thirds of the patients resumed menses, less than a third restored bone mass to the normal range, and 3 experienced fractures.

COMMENTARY

It is well recognized that young women with anorexia nervosa have reduced bone mass. This loss of bone is the result of 2 forces: 1) GnRH suppression resulting in amenorrhea and hypoestrogenism with increased bone resorption, and 2) The deprivation of adequate nutrition and its support of normal physiology such as the dynamic process of bone remodeling, resulting in both increased resorption and decreased bone formation. Although not well documented, there is every reason to believe that the loss of bone at a young age impairs the attainment of normal bone mass, placing anorexic individuals at risk of osteoporosis and fractures. Therefore, bone mass in an anorexic adolescent is an important concern, and it is worthwhile to provide treatment to increase bone accumulation.

Golden et al were encouraged by the response to alendronate, and compared their results to reports in the literature indicating no response to estrogen or oral contraceptives. But the key is not the treatment with alendronate. The important factor is response in body weight because of an improvement in the anorexia. Even the control group in this report gained bone—because most of the individuals, both in the treatment group and the control group, responded to active management of their primary problem, anorexia nervosa.

There is a simple clinical lesson in these results that has been apparent to me for many years from my own experience. Unless there is an improvement in the eating disorder and better nutrition, the bone responds poorly or not at all to antiresorptive agents such as estrogen or bisphosphonates. In patients with eating disorders, the bone response to hormone therapy will be impaired as long as an abnormal weight is maintained. I have taught for many years that a lack of response indicated by repeated bone density measurements is an excellent method to detect an on-going eating disorder that may have been camouflaged by the patient. Because the pubertal gain in bone density is so significant, individuals who fail to experience this adolescent increase may continue to have a deficit in bone mass despite hormone treatment. Reduced menstrual function for any reason early in life (even beyond adolescence) may leave a residual deficit in bone density that cannot be totally retrieved with resumption of menses or with hormone treatment. This is just one of the reasons to focus on the cause of the problem, the eating disorder. Until good nutrition is restored and body weight returns to normal, adjuvant bone treatments don't do much good. ■

CME Questions

5. The following statements are true of anorexia nervosa *except*:
a. Anorexia nervosa is associated with both increased bone resorption and decreased bone formation.
b. Bone anti-resorptive agents are relatively ineffective in malnourished individuals.
c. Estrogen stimulates bone formation.
d. Alendronate inhibits bone resorption.

6. **The following statements are true regarding polycystic ovaries and glucose tolerance *except*:**
   a. A fasting glucose level as part of an annual evaluation is an adequate screen for impaired glucose tolerance.
   b. Active intervention by clinicians can prevent the onset of overt diabetes mellitus in women with polycystic ovaries.
   c. The rate of conversion to type 2 diabetes mellitus in women with polycystic ovaries warrants periodic assessment of glucose tolerance.
   d. Fasting insulin levels reliably establish the presence of insulin resistance.

7. **Which of the following micronutrients has been implicated in risk of schizophrenia?**
   a. Calcium
   b. Trytophan
   c. Vitamin D
   d. Folate
   e. Iron

Answers: 5 (c); 6 (a); 7 (d)

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.

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Beta-Blockers May Be Useful for Noncardiac Surgery

High risk patients benefit from perioperative beta-blockers when undergoing major noncardiac surgery according to new study. Researchers from Tufts University reviewed the records of 782,969 patients in 2000 and 2001 at 329 hospitals throughout the United States. Patients were graded with the Revised Cardiac Risk Index (RCRI), which takes into account high-risk surgery, ischemic heart disease, cerebrovascular disease, renal insufficiency, and diabetes. The RCRI is graded on a 0-5 point scale, with 5 representing the highest risk. High risk surgery included all intrathoracic, intraperitoneal, and superinguinal vascular procedures. Patients with contraindications to beta blocker therapy were excluded. Over 660,000 patients had no contraindications to beta-blockers, and 120,338 patients received beta-blocker treatment during the first 2 hospital days. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk. Patients with an RCRI of 0 or 1 were found to have no benefit from beta-blocker treatment, whereas for patients with an RCRI of 2, 3, or 4, or more the adjusted odds ratio for death in the hospital, were 0.88 (95% CI, 0.80, 0.80-0.98), 0.71 (95% CI, 0.63 - 0.80) and 0.58 (95% CI, 0.50-0.67), respectively. The authors conclude that perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk patients undergoing major noncardiac surgery. They also noted that there was no benefit for low risk patients (Lindenauer PK, et al. Perioperative Beta-Blocker Therapy and Mortality After Major Noncardiac Surgery. *N Engl J Med*. 2005;353:349-361). An accompanying editorial points out that perioperative beta-blocker therapy has been somewhat controversial because of conflicting data in recent years. The current study shows an apparent benefit in high-risk patients, but they also look forward to the results of 2 ongoing randomized trials that will help clarify the role of beta-blockers for low-risk and intermediate-risk patients (Poldermans D, et al. Beta-Blocker Therapy in Noncardiac Surgery. *N Engl J Med*. 2005;353:412-414).

Promising New Weight Loss Drug?

More data shows that topiramate (Topamax) is associated with weight loss and, in this latest study, may also lower blood pressure in obese, hypertensive patients. In a study from Norway, 531 obese patients with hypertension were randomized to placebo, topiramate 96 mg/day, or topiramate 192 mg/day. All patients received the same diet, exercise, and behavioral modification advice. Patients were followed for 28 weeks. Mean weight loss was 1.9% for placebo and 5.9% and 6.5% for the 96 mg and 192 mg doses, respectively ($P < 0.001$ for each compared with placebo). Diastolic blood pressure was reduced 2.1, 5.5, and 6.3 mm Hg, respectively ($P < 0.015$ vs placebo). Systolic blood pressure was reduced 4.9, 8.6, and 9.7 mm Hg, respectively (P = NS). Paresthesia occurred in 33% of the active treat-

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ment group. The authors conclude that topiramate produced clinically relevant effects in reducing body weight and BP, with generally mild to moderate adverse effects (Tonstad S, et al. Efficacy and Safety of Topiramate in the Treatment of Obese Subjects with Essential Hypertension. *Am J Cardiol.* 2005;96:243-251).

Treating Shift-Work Disorder

Modafinil (Provigil) may be of some value for people with excessive sleepiness associated with shift-work sleep disorder. Researchers from Harvard randomized 209 patients with shift-work sleep disorder to receive either 200 mg of modafinil or placebo before the start of each shift. Modafinil resulted in modest improvement in nighttime sleep latency (1.7 ± 0.4 vs 0.3 ± 0.3 minutes, respectively; $P = 0.002$). More patients also had improvement in their clinical symptoms based on multiple objective tests and patients diaries (74% vs 36%, respectively; $P < 0.001$). Patients taking modafinil also had reduction in frequency and duration of lapses in attention during nighttime testing of performance, and proportionally fewer patients reported having had accidents or near accidents while commuting home (both $P < 0.001$). These benefits, however, were mild, and patients treated with modafinil continued to have excessive sleepiness and impaired performance at night. The authors conclude that modafinil 200 mg at the beginning of a shift may improve shift-worker's performance as compared to placebo, although the benefit is modest (Czeisler CA, et al. Modafinil for Excessive Sleepiness Associated with Shift-Work Disorder. *N Engl J Med*. 2005;353:476-486). An accompanying editorial urges caution when interpreting these results and suggests "the current study does not adequately assess the clinical value of this particular drug in shift-work sleep disorder, nor does it justify writing more prescriptions for modafinil." The authors do note that up to 20% of workers in industrialized nations are shift-workers and calls for "further scientific studies to address in a cohesive manner the serious health and safety issues that surround us by virtue of us having become, to a large extent, a shift-working society" (Basner RC. Shift-Work Sleep Disorder--The Glass is More Than Half Empty. *N Engl J Med*. 2005;353:519-521).

Another Flu Vaccine Shortage?

With the flu season looming, Chiron Corp. is again having difficulty with flu vaccine production. Last year the company found contamination at its Liverpool production plant, a situation that cause severe shortages of vaccine in the United States. This year, the company has discovered contamination at a German plant and is stating that it can only provide vaccine for the US market. The German plant was primarily the source of the Begrivac flu vaccine, which was sold on the world market. The company is making "substantial progress" in fixing problems at the Liverpool plant where the US vaccine is made. Meanwhile, Acambis plc is working on a universal flu vaccine that could offer permanent protection against all types of influenza. The company hopes to generate a universal vaccine that would not require annual changes in formulation and would protect against both influenza A and B including avian strains. The company, however, states that it may require years of clinical trials before earning approval. Fears of avian influenza pandemic have prompted the French company Sanofi-Aventis to work on a vaccine for the avian H5N1 strain that has killed millions of birds and 50 people in Asia. Preliminary results are promising, however, full-scale production could take months, according to Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases.

FDA Actions

The FDA has approved the first of the new class of drugs for the treatment of insomnia characterized by difficulty with sleep onset. Takeda Pharmaceutical's ramelteon (Rozerem) is a selective agonist at 2 melatonin receptors in suprachiasmatic nucleus, receptors that are thought to regulate circadian rhythm and sleepiness. Recently marketed sleeping medications target GABA receptors (ambien, lunesta) and, although these drugs are associated with less addiction and sleep latency then benzodiazepines, they are still designated as Schedule IV drugs. Ramelteon has shown no evidence of abuse or dependence potential and will, therefore, be marketed as a unscheduled drug. It is also approved for long-term use and has not been associated with memory impairment or impairment of motor ability. The most common adverse events associated with ramelteon were somnolence, fatigue and dizziness (> 2% over placebo).

Plan B, Barr Pharmaceutical's "morning-after pill" is being considered for over-the-counter approval by the FDA. The issue has become a political hot potato, and even briefly held up the Senate's confirmation of Lester Crawford, MD, as Commissioner of the FDA. It is expected that decision will be made by September. ■