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INSIDE

Cesareans for All?

SPECIAL REPORT

By John C. Hobbins, MD

Cesarean Section Rate Trends

IT IS CLEAR THAT THE UNITED STATES' CESAREAN SECTION RATE (CSR), while tailing off in the late 1990's, is now again rapidly heading upward. For example, the CSR in 1988 reached 24.7% after rising steadily from 1980 when it was 16.6%. Then, probably through various attempts to control the numbers of Cesarean sections, the rate dropped slowly to 20.8% in 1997. However, for reasons stated below, the percentage of C-sections in the United States in 2002 rose to 26%, representing a 20% increase. Data from Latin America indicate a very rapid rise in CSR in some countries but not others. For example, in 1997 the CSR in Chile was 40% while in Peru it was only 7%. In some cities in Asia, such a Taipei, the rate is 32%.

What Should be the Ideal CSR?

In 1985, a WHO document noted that "there is no justification for any region to have a rate higher than 10-15%." However, this opinion was simply that—an opinion—which, whether valid or not, was not really based on any compelling data. Rates do vary among various populations and depend upon attitudes, resources, and policies. Undoubtedly, biases play a major role but, of late, there is no general agreement on what the CSR should be.

Why the Recent Rise in CSR?

1. **A lack of enthusiasm for vaginal birth after Cesarean (VBAC's)**

In 2 years, the VBAC rate in the United States dropped from 26% attempted in 1998 to 20% in 2000 while the CSR rose in those same years. Now, figures from 2002 indicate a rate of only 12.7% in those eligible for this option.

Among many reasons for this trend, a *New England Journal of Medicine* randomized controlled trial (RCT) quantifying the risk of uterine rupture got the attention of many providers already gun-shy of the legal implications of this complication, no matter how low the

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risk. The American College of Obstetricians and Gynecologists (ACOG) even drafted VBAC guidelines that required providers to be "immediately available" when a patient choosing a VBAC was laboring.

As long as prostaglandins are not used for cervical ripening in these patients, the incidence of true uterine rupture in VBAC is, at most 1%, and fetal oxygen deprivation would occur in less than 10% of those, thus resulting in a risk of 1 in 1000 of fetal compromise in VBAC.

Nevertheless, once a trend like this starts, it gains momentum when the process has liability and logistic ramifications.

2. **Increased rate of inductions**

The rate of inductions in the United States (NCHS statistics) from discharge data rose from 9% of all deliveries in 1990 to 21% in 2002. Again, there are a variety of reasons for this which have to do with patient and provider convenience, as well as the over-diagnosis of impending fetal jeopardy.

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EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
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As indicated in a previous Clinical Alert, induction of labor is associated with a doubling of Cesarean sections. Yet Kaufman et al have shown induction to not be associated with overall cost savings.

3. **Changing management of breeches**

A much discussed RCT in the *New England Journal of Medicine* showed a higher rate of fetal mortality and morbidity with vaginal delivery of breeches compared with elective Cesarean section. Although the absolute numbers of adverse fetal outcomes were small, the difference was enough to make many providers abandon this option for patients.

Even the practice of external versions for breeches has lost momentum of late because of the possibility of fetal bradycardia during version attempts.

4. **The plummeting use of forceps**

There is recent evidence that forceps deliveries are associated with higher rates of maternal pelvic and fetal complications. Although both may be due to the reasons why the forceps were used (long labors, maternal exhaustion, CPD, and fetal distress), rather than to the forceps themselves, this trend away from forceps is certainly understandable.

There is no way that this tendency will reverse itself in the near future because so few practitioners are being trained in the nuances of the techniques. For example, obstetrical residents in the United States do an average of 28 forceps deliveries, (only a very small percentage of which are mid-forceps) during their 4 years of training and soon there will be nobody willing or able to train our upcoming residents.

Given the apparent risk of mid-forceps delivery, it probably is good that this is a dying art, but it is likely that there will always be a need for low forceps or vacuum extraction, hopefully performed by competently trained practitioners.

5. **More patients of Advanced Maternal Age**

CDC-P data indicate that in 1975 the birth rate of mothers 35-39 years was 20/1000 and 30-34 years to be 50/1000. These rates increased to 40/1000 in 2000 for the former group and 90/1000 for the latter. In just one year (1999 to 2000), the birth rate rose 5% in women 30-34 years and those 35-39 years. Interestingly, this rate went from 7.5 to 7.9/1000 in those 40-44 years and 0.4 to 0.5/1000 in those 45-54 years. For a variety of reasons, these patients have a very high CSR.

Patient-Requested Cesarean Section

We recently were visited by an obstetrician who trained in the United States and now practices in his city of birth, Teheran. He indicated that he did the vast majority of his deliveries by elective Cesarean because

of patient preference and his convenience.

In a private practice setting in Mexico City, the elective CSR exceeds 75%. A professor from our university visiting Mexico City was told that most private patients wish to avoid pelvic morbidity caused by a vaginal delivery.

In the 1985 WHO report noted above, this quote reflects the feeling at that time about patient-request Cesareans ". . . maternal request is not on its own an indication for Cesarean section and specific reasons for the request should be explored, discussed, and recorded." It further indicates that if there is no identifiable reason for a Cesarean section, the clinician has the right to decline the women's decision, but should offer referral for a second opinion.

Because of the increasing demand for Cesarean section, the ACOG Ethics Committee was pressed into action. In a news release from ACOG on October 31, 2003, the following statements were made: "If the physician believes that Cesarean delivery promotes the overall health and welfare of the mother and fetus more than a vaginal birth, he or she is ethically justified in performing a Cesarean delivery."

On the other hand, "if the physician believes that a Cesarean would be detrimental. . . he or she is ethically obliged to refrain from performing the surgery."

Also, "physicians are under no obligation to initiate discussions regarding elective Cesarean—when not considered medically acceptable to the physician."

In other words, it is ethically acceptable for the provider either to do the Cesarean section or to refuse to do it, but the provider need not bring it up as an option.

Let's explore the pluses and minuses of patient-requested elective Cesarean section:

1. **Pelvic relaxation and incontinence.** Perhaps the best study comparing Cesarean section with vaginal delivery comes from Norway. Rortreit et al surveyed 15,307 women younger than 65 years of age. They found the prevalence in the entire population of any incontinence was 20.7%. The difference between never pregnant individuals, those having had Cesarean section, and those having had vaginal deliveries involved stress incontinence only. Nullips had stress incontinence in 4.6%. Cesareans were associated with stress incontinence in 7% and vaginal deliveries (age corrected) in 12.2% (OR, 2.2).

In another study, Buchsbaum found the incidence of stress incontinence in parous individuals to be roughly similar to nulliparous post-menopausal women. Other studies have had similar results to the Norwegian study indicating that vaginal delivery was not associated with any increase in any type of incontinence (anal, urge incontinence) other than stress incontinence, and pregnancy, in general, had the greatest effect on pelvic organ instability.

2. **Complications with Cesarean delivery vs vaginal delivery**

Maternal death with Cesarean section	4/10,000
Maternal death with all vaginal births	1/10,000
Maternal death with elective Cesarean section	2/10,000
Maternal death with normal vaginal birth	0.5/10,000

3. **The following represents an itemized summary of various complications from vaginal and Cesarean delivery based on a review of the literature. Data on elective Cesarean delivery alone are difficult to come by.**

Increased with Cesarean Delivery	No Difference	Reduced with Cesarean Delivery
bladder injury	hemorrhage	perineal pain
ureteral damage	infection	urinary incontinence
hysterectomy	fecal incompetence	prolapse
thromboembolic abnormality	dyspareunia	
length of stay	postnatal depression	
re-admission to hospital	intra-cranial hemorrhage	
maternal death	brachial plexus injuries	
uterine rupture	cerebral palsy	
later infertility		
placenta previa		

Adopted from the National Institute for Clinical Excellence

Who's Most Apt to Either Offer or Comply with Patient-Requested Cesarean Section?

Two recent studies from The Netherlands and the United States involving provider surveys indicate that the more compliant caregivers were: older, more experienced, and more often practicing in an academic center. The sex of the practitioner was not a factor. In the New York study, 13% of physicians offered elective Cesarean sections and 8.8% of patients requested it without indication.

The Cost of Elective Cesarean Section

One British study specifically addressed the cost of requested Cesarean sections. Based on data from England and Wales, the authors indicated that 7% of all Cesarean sections in the year 2001 were done for maternal request only. The authors calculated that, based on UK cost figures, this represented an extra £1257 ($2,255) per individual section over vaginal delivery. They also figured that if these operations were not undertaken, a total of £11 million (approximately $19.7 million) could be saved in England and Wales per year.

One can imagine that dollar figure in the United States where there are 4 million births per year, compared with half a million births in the United Kingdom.

Conclusion

The increasing demand for elective Cesarean section represents an ethical and logistic dilemma. On one hand, all providers should respect patient autonomy (the major reason in the Dutch study that providers granted their patients' wishes for Cesarean section). On the other hand, Cesarean section is still a "major" operation that is not devoid of maternal and fetal complications. It puts stress on today's available resources and is downright costly.

Autonomy is based on informed choice and it is extremely important for patients to know that the most common rationale used for avoiding a vaginal delivery is flawed. Stress incontinence happens even in nuns. Clearly, pregnancy alone has an effect in those pre-disposed to it, but the difference between the modes of delivery is very small when one excludes those with difficult forceps deliveries and excessively long second stages of labor. Wilkes et al have suggested that in some cases a clinical backdrop will evolve in which a vaginal delivery is destined to fail. However, in the majority of situations where there is no clinical indication for Cesarean section, it would seem preferable to set guidelines with the patient for "bail out," thereby avoiding prolonged labor and instrumental delivery. This would seem preferable to sectioning everyone at the front end. ■

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YKL-40 and Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *YKL-40 may represent a novel marker for the detection of early-stage ovarian cancer. YKL-40 levels in early stage patients may also predict disease recurrence and survival. The use of YKL-40 in detection of early stage ovarian cancer deserves further investigation.*

Source: Dupont J, et al. *J Clin Oncol*. 2004;22: 3330-3339.

THE QUEST TO IDENTIFY ACCURATE SERUM BIOMARKers for ovarian cancer has been problematic owing to their insensitivity and poor specificity as a decision tool and technological challenges facing the newer proteomic algorithms. Addressing this problem, Dupont and colleagues evaluated a new biomarker, YKL-40, in the diagnosis and prognosis of ovarian cancer. The biomarker was compared against CA-125 and CA 15-3—two known markers of ovarian pathology. To do this, YKL-40 levels were evaluated among 42 patients diagnosed with stages I to IV ovarian, fallopian tube, and primary peritoneal cancer, and 8 patients with recurrent disease, as well as 46 normal controls, 19 patients without prior cancer seen in a high-risk ovarian screening clinic, 42 patients in the same clinic with a history of cancer, and 33 patients with benign gynecologic disorders. Serum values for YKL-40 and CA-125 were obtained for all cohorts. An abnormal value was established from normal controls as greater than or equal to 62 ng/mL. Among the 4 patient cohorts without ovarian cancer, YKL-40 values were not significantly different and were within the normal limits. Patients with ovarian

cancer recorded significantly higher mean levels of all their biomarkers compared to normal controls.

However, YKL-40 values appeared to be stage-discriminant, that is, higher with advancing stage and tumor burden. In addition, YKL-40 values were abnormal among all histologies, and a value above 80 ng/mL was prognostic for poor outcome. Compared with CA-125, YKL-40 was appropriately abnormal significantly more often in cancer patients and normal significantly more often in normal controls and patients with benign disease. Dupont et al conclude that these characteristics, along with the test's availability and technical facility, make YKL-40 and important ovarian cancer biomarker that should be evaluated in large prospective trials.

COMMENT BY ROBERT L. COLEMAN, MD

Most clinicians are well aware of the ovarian cancer survival track record. However, patients with early stage ovarian cancer are most often cured of their malignancy—some by surgery alone. Finding these patients, heretofore, has been largely serendipitous; usually identified during exploration for a pelvic mass. Nonetheless, improving our ability to either identify these patients and those at risk for malignancy fuels the labor to develop an effective screening program. If the current 1 in 4 ratio of early to late stage patients could be improved to just one in 3 the median overall survival would increase to about 5 years. Imagine if the ratios were reversed entirely!

In the current study, Dupont et al introduce a new, readily available serum biomarker, YKL-40, in an attempt to improve upon the current best, CA-125. Little is known about this marker's function but it appears to express in conditions of extracelluar matrix degeneration and angiogenesis. The third marker in this study, CA 15-3, although not widely used, has been recently shown to add significantly to a predictive model, along with CA125, in patients with pelvic masses. Given the insensitivity of CA-125 alone, most efforts in the line of biomarker development have turned to cocktails of markers in the hope of improving accuracy of diagnosis. Although most trials have shown some increase in predictive power with this strategy, the varied prevalence of cancer in the study cohorts may more strongly affect the predictive capacity than biomarker performance. In addition, with more tests comes more cost limiting the generalization of practice.

There are several noteworthy findings about YKL-40 that supports Dupont et al's recommendation to study this marker more fully. First, this is one of the few biomarkers which demonstrates abnormal levels in both mucinous and non-mucinous neoplasms. Although CA 19-9, a gastrointestinal marker, has been evaluated in mucinous neoplasms it is usually done once the diagnosis is made limiting it as a preoperative tool. Second, nearly two-thirds of stage I/II ovarian cancers had elevation of the marker. Historically, approximately 50% of stage I/II ovarian cancers are CA-125 negative (in the current report it was 35%). Third, the marker was rarely positive in benign disease or among normal controls. This may have been aided by patient selection as those with inflammatory conditions were screened out in some of the normal control cohorts. Lastly, the marker appears to be prognostic on a number of levels: stage/tumor burden, survival, and predisposition for disease. With regard to this latter point, 3 high risk but without disease patients with falsely elevated YKL-40 values were subsequently diagnosed with cancer with the following 18 months. It is important to recall that an association between false-positive elevation and subsequent ovarian cancer diagnosis accompanied the early work with CA-125. Although, subsequent studies confirmed that CA-125 alone was too insensitive to act as a screening tool, further prospective evaluation with YKL-40 in much larger cohorts is warranted. In addition, studies to identify this protein's function may aid in construction of targeted therapy.

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Assessing Blood Estradiol Levels

ABSTRACT & COMMENTARY

Synopsis: *Topical estradiol application can be associated with falsely high blood estradiol measurements.*

Source: Vihtamaki T, et al. *Maturitas*. 2004;48: 347-353.

Vihtamaki and colleagues from Finland measured the circulating levels of estradiol 12 hours after the topical, percutaneous, evening administration of 1.5 mg estradiol (EstroGel) in 10 women who had been using this method of hormone therapy for at least 2 years. The gel was applied with a plastic gloved hand to an area as large as possible (per standard directions for use) on the thigh for 2 weeks followed by application on

the arm for 2 weeks. This was followed by the same schedule but this time using a bare right hand for the application. The blood samples were collected from both cubital veins. The major finding was remarkably higher estradiol concentrations when the gel was applied to the left arm or the thigh with a bare right hand. Therefore, skin contamination by topical estradiol can distort blood estradiol measurements.

COMMENT BY LEON SPEROFF, MD

Estradiol delivery can be accomplished by the daily application of a gel (EstroGel, Estreva) or a lotion (Estrasorb) to the skin, usually over the upper arms and shoulders or the abdomen and thighs.1,2 The gel preparation produces blood levels of estradiol of approximately 95-125 pg/mL, levels that are both higher and more variable than the standard oral regimens.3,4 EstroGel and Estreve are supplied in a pump that delivers 0.75 mg estradiol with each dose of EstroGel and 0.5 mg with Estreva. Estrasorb is packaged in foil pouches; the contents of 2 pouches applied daily produce systemic levels similar to those achieved with a 50 µg gestradiol patch method.

Studies with topical estradiol have indicated that blood estradiol measurements vary from individual to individual. The differences between individuals reflect differences in percutaneous absorption, variations in estradiol metabolism, retention time in the skin, and surface area of the application. Because of these differences, the same dose will not have the same clinical efficacy in all individuals. Within one individual, the blood levels are relatively constant; and for this reason, monitoring the estradiol level when clinically indicated is worthwhile. When a topical estradiol method is being used, care must be taken to obtain the blood sample from an arm that has not received estrogen application and that is opposite to the drug-applying hand. Unfortunately with the percutaneous method, accuracy requires the use of a gloved hand and leaving one arm untouched for 2 weeks.

Why measure the blood estradiol at all? Because of the variability from individual to individual in metabolism, it makes sense that the same dose will not provide clinical efficacy in all patients. The problem is that we are limited by having only one objective assessment of efficacy: bone density measurements. For this reason, it is worthwhile to measure the bone density in treated women when they are in their late 60s to detect poor responders. On the average, about 10-15% of women lose bone despite being prescribed hormone therapy. A Finnish 5-year clinical trial reported a prevalence of poor response based on bone density of 11% for spinal bone and 26% for the hip.[5] As expected, smoking and low body weight were common findings among the poor responders, but the most impressive characteristics were lower estradiol and higher FSH levels. It is only logical that there exists a group of women who metabolize and clear administered estrogens at a greater rate, and thus require a higher dose to sustain a protective effect on bone. Indeed, considerable variation in estradiol levels has been documented in individuals receiving both oral and transdermal hormone therapy.[6,7] Marketing presentations by the pharmaceutical companies provide mean levels, suggesting stable and smooth maintenance of blood levels; however, the ranges, which are wide, are not revealed. An aim of individualizing hormone therapy is to determine the appropriate dose for the intended objective; in the case of bone, the minimal estradiol level should be 40-60 pg/mL, and a practical range for a blood sample derived during office hours from a patient taking her medication at night is 50-100 pg/mL.

Monitoring the estradiol blood level in postmenopausal women receiving hormone therapy is not as straightforward as it would seem. There are 2 primary difficulties. First, the clinical assays available differ considerably in their technique and quality (laboratory and antibody variations). Second, the various commercial products represent a diverse collection of estrogenic compounds, ranging from estradiol to unique equine estrogens. Although the body interconverts various estrogens into estrone and estradiol, is this process relatively consistent within and between individuals? For example, a highly specific assay for estradiol will detect very low levels of estradiol in women receiving 0.625 mg conjugated equine estrogens; nevertheless, most clinical assays will report a level of 40-100 pg/mL in these women. I find measurement of blood estradiol levels very useful in selected patients, such as the patient who requests ever-increasing doses of estrogen for the treatment of symptoms, which in the presence of very high blood levels of estradiol can be confidently diagnosed as psychosomatic. What each clinician must do is learn what blood level of estradiol as performed by the local laboratory is associated with the standard doses of hormone therapy (0.625 conjugated estrogens, 1 mg estradiol, 50 µg transdermal estradiol) and consistently use the same laboratory. In our laboratory this range is 40-100 pg/mL estradiol when the estrogen is taken the evening before the office visit (with transdermal administration, blood sampling should be obtained the day before new patch placement); the range reflects individual variation including the variability from peak to nadir values. Remember that because FSH is regulated by a factor

other than estrogen (ie, inhibin), FSH levels cannot be used to monitor estrogen dosage. Postmenopausal hormone therapy will produce only a 10-20% decrease in FSH and LH, and there is great individual variability in the responses.[8]

Products containing ethinyl estradiol will not affect the circulating estradiol level. Ethinyl estradiol circulates without being changed, and the antibodies in the immunoassays for estradiol will not recognize it. It is for this reason that women on oral contraceptives have very low measurements of estradiol. This problem for the postmenopausal use of ethinyl estradiol is not a major handicap because ethinyl estradiol is slowly metabolized, and blood levels are relatively stable with less variation from individual to individual compared with the other estrogen formulations.

As clinicians and the pharmaceutical industry promote lower doses of estrogen with the attractive notion that less is safer, a greater rate of poor response as measured by bone density can be expected. In my view, once a poor responder is detected by measurement of bone density, titering of estrogen dose is indicated, using the blood concentration of estradiol. I would further emphasize that appropriate detection and investigation will confirm that a relatively low blood estradiol level is the cause of most cases of poor bone response (in the presence of appropriate calcium and vitamin D supplementation). Measurement of vaginal pH from the lateral vaginal wall is very simple and inexpensive. It has been impressive in our experience and that of others how an acidic pH (less than 4.5) correlates with estrogen administration.[9,10] This may be the best method to assess the adequacy of estrogen therapy. Assessing vaginal cytology is not useful. The vaginal mucosa is too sensitive to estrogen to allow dose-response titering. ■

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Surgical Staging Of Ovarian Low Malignant Potential Tumors

ABSTRACT & COMMENTARY

Synopsis: *Routine pelvic and para-aortic lymph node dissection is not necessary in the majority of women with ovarian low malignant potential tumors.*

Source: Rao GG, et al. *Obstet Gynecol*. 2004. 104: 261-266.

Patients with ovarian tumors of low malignant potential have an excellent prognosis and few require adjuvant therapy. Although it is commonly preferred that patients identified intraoperatively with this neoplasm undergo formal surgical staging, the benefit of these additional procedures has been questioned given that few patients are treated on the basis of these biopsies. Rao and colleagues in a retrospective, multi-institutional study of borderline ovarian malignancies reviewed the outcomes of 248 women with ovarian tumors of low malignant potential in order to evaluate the benefits of surgical staging. Consecutive cases over a 20-year period were accessioned. Formal staging procedures were performed on approximately three-quarters of patients including 72% who had no visible intraperitoneal disease. Upstaging on the basis of these procedures occurred in 28% including a small fraction (6%) with retroperitoneal disease (all pelvic). None of the 314 paraortic nodes sampled contained disease.

After a median follow-up of more than 2 years, all but 15 (6%) patients are disease-free. No difference in recurrence rates were observed between those staged and those not staged. In addition, analysis of patterns of recurrence suggested no difference whether surgical staging was performed nor was there a difference in recurrence among stage III cases whether they received adjuvant chemotherapy or not. In a multivariate analysis of recurrence risks only 2 factors were independently predictive: lower gravidity and stage category (I vs II-IV). In addition, none of the 57 mucinous borderline tumors recurred or were upstaged. Rao et al conclude that survival of this class of neoplasms is excellent and routine pelvic and paraortic lymphadenectomy is unwarranted in the majority of patients.

■ **COMMENT BY ROBERT L. COLEMAN, MD**

Surgical staging for all non-benign ovarian neo-

plasms is a practice endorsed by gynecologic oncologists throughout the world. A recent survey from the Society of Gynecologic Oncologists documented that 97% of respondents recommended formal surgical staging for all patients with ovarian tumors of low malignant potential (LMP). Although mounting data from retrospective and prospective trials suggest patients with these tumors do very well, a common reason to promote the additional surgery at the time of extirpation is to not miss staging an occult invasive tumor—a finding that may be underappreciated in frozen section analysis of a large pelvic mass. Indeed, recent studies of frozen section report qualifications found invasive disease in 6 to 28% of cases of LMP tumors. The likelihood appears to be higher when an at least LMP was used to qualify the diagnosis compared to a rule out LMP. The current report, however, cannot provide confidence that staging is not required when the diagnosis is returned intraoperatively. Failure to gather that information in patients subsequently identified with bona fide invasive disease heralds the dilemma to either subject the patient to another operation or administer adjuvant chemotherapy to someone who may not need it. The report does confirm that in the majority of cases, LMP will be the final diagnosis for which surgical staging will add little except more blood loss and longer hospitalization. This is relevant in the not infrequent situation where a seemingly benign intraoperative ovarian masses was resected and LMP is returned on the final pathology report. While details of the pathology, wishes for future fertility along with intraoperative findings will be important in considering whether additional surgical staging is recommended, the current study would suggest most patients would benefit little from re-operation, particularly mucinous neoplasms. In all, it is prudent to preoperatively counsel patients with pelvic masses for the possibility of staging and to have appropriate consultation with a gynecologic oncologist when the diagnosis is returned intraoperatively. ■

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CME Questions

6. The following statements are true regarding measuring blood estradiol levels in women receiving hormone therapy except:

a. Differences among individuals in the metabolism of estrogen accounts for variability in clinical response to a single dose of therapy.
b. All patients receiving postmenopausal hormone therapy demonstrate an increase in bone density.
c. Topical estrogen administration may produce more variability in circulating estradiol levels than other methods of administration.
d. Vaginal pH is a sensitive indicator of circulating estradiol levels.

7. The following statements are true regarding cesarean sections *except*:

a. The percentage of cesarean sections in the United States is at an all-time high.
b. Vaginal deliveries are an established cause of stress incontinence.
c. The American College of Obstetricians and Gynecologists has stated that clinicians are not obligated to present the option of elective cesarean section
d. In recent statistics, the oldest mothers had lower rates of cesarean section.

8. The following statements are true regarding ovarian cancer *except*:

a. No single serum screening test is effective, but a combination of biomarkers may prove to be of value.
b. Re-operation for surgical staging of low malignant potential tumors is not necessary.
c. Surgical staging of low malignant potential tumors is not necessary during the initial surgical procedure.
d. A frozen section during the initial surgical procedure may miss an occult invasive tumor.

Answers: 6 (b); 7 (b); 8 (c)

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Linking COX-2 Inhibitors and Cardiovascular Event Risk

A new, and as of yet unpublished study, has raised increased concern about the relationship between rofecoxib (Vioxx), Merck's blockbuster COX-2 inhibitor, and cardiovascular events. The study, which was presented at a meeting in Bordeaux France, was financed by the FDA in collaboration with California's HMO giant Kaiser Permanente. The study was designed to determine if celecoxib, rofecoxib, ibuprofen, naproxen, or other NSAIDs increase the risk of acute myocardial infarction (AMI) or sudden cardiac death (SCD). Utilizing the 6-million member California database for Kaiser Permanente, all patients ages 18-84 who had taken a COX-2 inhibitor or nonselective NSAIDs between January 1999 and December 2001 were entered into the cohort. Controls were a risk-set match 4:1 on event date, birth year, gender, and health plan region. There were 8199 acute cardiac events within the study cohort (6675 AMI, 1524 SCD). The data revealed that rofecoxib use at > 25 mg per day increased the risk of acute cardiac events 3.15 fold (OR, 3.15 [1.14-8.75]). Rofecoxib at a dose < 25 mg resulted in an odds ratio of 1.29 (0.93-1.79), which was not statistically significant. When comparing low-dose rofecoxib to celecoxib (Celebrex), the risk of AMI and SCD was higher with rofecoxib (P= 0.04). Other NSAIDs, including naproxen, indomethacin, and possibly diclofenac, also increased the risk of AMI and SCD. These data will be presented in this country in October at the American College of Rheumatology. Concern about the relationship between rofecoxib and cardiac events was first raised with the publication of the VIGOR trial (*N Engl J Med.* 2000;343:1520-1528) which showed a relative risk of cardiac events associated with rofecoxib of 2.38 (95% CI, 1.39-4.00; P= .002). Dr. Eric Topol and colleagues from the Cleveland clinic subsequently reevaluated these data along with data from other studies and raised the concern of prothrombotic potential of COX-2 inhibitors, especially rofecoxib (*JAMA.* 2001;286:954-959). Their concern centered on the tendency for COX-2 inhibitors to block production of prostacyclin—thus blocking antiaggregatory and vasodilatory effects, while having no effect on thromboxane, which is responsible for platelet aggregation. Blockage of thomboxane is a COX-1 effect and accounts for the majority of the cardioprotective effects of aspirin and other NSAIDs. Rofecoxib, the most COX-2 specific of the drugs tested, may unbalance thromboxane and prostacycline accounting for the cardiovascular risk.

Some have considered a strategy of adding aspirin to a COX-2 inhibitor, but a new study suggests that aspirin negates the GI benefits of the COX-2 inhibitor, the primary benefit of COX-2 inhibitors over nonselective NSAIDs.

Researchers from USC performed a double-blind trial of rofecoxib, rofecoxib plus low-dose

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

aspirin, ibuprofen, or placebo in patients without ulcers or erosive esophagitis. Endoscopies were performed at baseline, 6 weeks, and 12 weeks. At 12 weeks, the cumulative index of ulcers was placebo 5.8%, aspirin 7.3%, rofecoxib plus aspirin 16.1%, and ibuprofen 17.1% ($P < 0.001$ for rofecoxib plus aspirin and for ibuprofen vs each of placebo and aspirin). Over the same time, rofecoxib plus aspirin and ibuprofen both significantly increased the number of erosions (both $P < 0.001$ vs aspirin and placebo). The authors conclude that low-dose aspirin does not significantly increase ulcer recurrence, but that the addition of a COX-2 inhibitor with aspirin increases the rate of ulceration to a rate that is similar to a nonselective NSAIDs (*Gastroenterology.* 2004;127:395-402).

Viagra: Maximum Capacity at High-Altitudes?

High-altitude hikers may soon be requesting sildenafil (Viagra) prescriptions based on the results of a new study. The drug, which is a phosphodiesterase-5 inhibitor, is known to cause pulmonary vasodilation. German researchers postulated that such an effect may increase exercise capacity during induced hypoxemia at low altitudes and at Mount Everest base camp. Fourteen healthy mountaineers and trekkers were assessed with measurements of systolic pulmonary artery pressure, cardiac output, and peripheral arterial oxygen saturation at rest and during assessment of maximal exercise capacity on cycle ergometry while breathing a hypoxic gas mixture at low altitude, and retested at high-altitude at the Mount Everest base camp. Sildenafil 50 mg significantly increased arterial oxygen saturation during exercise ($P = 0.005$), reduced systolic pulmonary artery pressure at rest ($P < 0.001$), and during exercise ($P = 0.031$). Sildenafil also increased maximum workload and maximum cardiac output compared with placebo. At high-altitude, the drug had no effect on arterial oxygen saturation at rest nor during exercise compared with placebo, however, the sildenafil reduced systolic pulmonary artery pressure at rest ($P = 0.003$), during exercise ($P = 0.021$), increased maximum workload ($P = 0.002$), and cardiac output ($P= 0.015$). Two patients noted worsening headache at high-altitude with the drug. The authors conclude that sildenafil is the first drug to increase exercise capacity during severe hypoxia both at sea level and at high-altitude (*Ann Intern Med.* 2004;141:169-177). An accompanying editorial suggests that sildenafil is not a substitute for acclimatization to high-altitude and suggests that the findings of the study are compelling and that further research into a phosphodiesterase inhibitors in the treatment of pulmonary vascular disease is needed (*Ann Intern Med.* 2004;141:233-235).

FDA Actions

Eli Lilly has received FDA approval to market duloxetine (Cymbalta) for the treatment of major depression. The drug is a serotonin and norepinephrine reuptake inhibitor (SNRI), similar to venlafaxine (Effexor-Wyeth). The drug is also being studied for the treatment of stress urinary incontinence and diabetic neuropathic pain. Lilly, and the drug approval process for duloxetine, came under scrutiny earlier this year when a 19-year-old female volunteer committed suicide after discontinuing the drug during clinical trials. The patient had no history of depression prior to the study.

Shire Pharmaceuticals has received expanded indication for its mixed amphetamine product Adderall XR for the treatment of adults with attention deficit hyperactivity disorder (ADHD). The drug is a one-a-day preparation that has been widely used in children since 2001.

The FDA and Genentech have issued a warning to physicians regarding the risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). The drug is an angiogenesis inhibitor, a novel antineoplastic used to treat metastatic colon cancer and other solid tumors. Reports of cerebral infarctions, myocardial infarctions, transient ischemic attacks, and angina have all been associated with use of the drug.

The FDA has approved an orally disintegrating form of carbidopa/levodopa for the treatment of Parkinson's disease. The preparation dissolves rapidly in the mouth without the need for water, allowing for dosing even when patients are rigid or suffering from "off periods," when producing can be problematic. It will be marketed under the trade name Parcopa and will be available in 10/100 tabs, 25/100 tabs, and 25/250 tabs, similar to brand name Sinemet levodopa/carbadopa.