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INSIDE

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Latest National Estimates of Contraceptive Failure

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The latest estimates of contraceptive failure from the 2002 National Survey of Family Growth fail to demonstrate an improvement.*

Source: Kost K, et al. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception.* 2008;77:10-21.

Kost and colleagues provide updated contraceptive failure rates derived from the 2002 National Survey of Family Growth.[1] The objective was to see if the effectiveness with which American women used contraception has improved. The results reflect the typical use of a method in a general population, not the efficacy when a method is used perfectly. There were 7643 women, ages 15-44, surveyed in this national sample. Sixty-two percent (38.1 million) of American women in reproductive age in 2002 were using some method of contraception. It is well-recognized that induced abortions are underreported by respondents; therefore the results were corrected for the number of abortions resulting from contraceptive failure. The estimated failure rates after one year of use were as follows:

	Typical Use	Perfect Use
Injectable methods	6.7%	0.3%
Pill	8.7%	0.3%
Male condom	17.4%	2.0%
Withdrawal	18.4%	4.0%
Rhythm methods	25.3%	5.0%
All methods	12.4%	

The current estimates of failure were not significantly different compared with the previous estimates from the 1995 national survey. Women over the age of 30 are less likely to experience failure than young women; teens are more than twice as likely to

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experience a failure than older women. Hispanic women and even more so, Black women, experience higher failure rates. Groups that were less likely to experience contraceptive failure were women who did not intend to have a subsequent birth and women who had no previous births. Married women experienced the lowest failure rates and cohabiting women the highest. The most important determinants of pill failure, therefore, were: age, intention toward a future birth, parity, and marital status. Interestingly, once these factors were accounted for, duration of use, race, ethnicity, and poverty status no longer affected the risk of pill failure. The same factors influence condom use, but when corrected for these factors, race, ethnicity, and poverty affected the risk of condom failure.

COMMENTARY

This is a subject of great interest because the rate of unintended pregnancies in the U.S. continues to be high. About one-half (3.1 million) of all pregnancies in the U.S. are unintended, and nearly half of those occur in women using a method of contraception. Here is a more striking statistic: one of every two American women aged 15-44 has experienced an unintended pregnancy.

An important piece of good news was the fact that women at each end of the economic spectrum, the poorest and the wealthiest, experienced a decrease in failure rates from 1995 to 2002, although the poorest women continued to have a higher failure rate than did the better-off women. Also, although the overall failure rate was not statistically significant comparing 1995 and 2002, there was about a 2.5% improvement; this missed mathematical significance but it may reflect a meaningful change in our population. This change is probably due to an increase in pill and injectable methods and a decrease in condom use during this period of time. It will be of great interest in the next survey to see if the newly marketed patch, vaginal ring, and implant favorably affect these statistics.

Women living in poverty who must rely on condoms or withdrawal (male-dependent methods) have about a two-fold increase in failure rates, but if they can use the pill, their failure rates are the same as better-off women. The message is clear: we need to make the more effective methods available for low-income women.

There is an alarming message in this report. Overall use of contraception among women at risk of unintended pregnancy decreased from 92.5% in 1995 to 89.3% in 2002. The use of contraception among low-income women at risk of pregnancy decreased from 92.1% in 1995 to 86.3% in 2002. I think this indicates an American problem; women are having more difficulty obtaining effective contraception.

What do women have to overcome to achieve good contraceptive efficacy, and if they are already using a method, to switch to a more effective one? Choices must be available for various methods. The technique of using a method must be compatible with an individual and her lifestyle. Some methods require partner cooperation. Once chosen and obtained, the individual must exert dedication to its use. The failure to substantially improve contraceptive failure rates from 1995 to 2002 indicates that we are not making enough progress with each of these variables.

It is not enough to say the obvious—that we need greater education—but we need to learn where and when education is most effective, where is money best spent, and how to maximize the choices available for all women. This isn't a task just for professional health care providers; it is a widespread social problem that requires policy and budgeting decisions. Trussell and Wynn, in an excellent editorial that accompanies the article, point out that technological achievements are not enough.[2] The problems are more sociologic, such as cost and insurance coverage (and I would add the ridiculous practice of providing pills only one month at a time). These are

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Questions & Comments

Please call **Iris Young**, Managing Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

reasons why other countries have lower percentages of women at risk for unintended pregnancies. In my view, this requires governmental action at both the federal level and the state level. So, whom are you voting for? ■

References

1. Kost K, et al. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception.* 2008;77:10-21.

2. Trussell J, Wynn LL. Reducing unintended pregnancy in the United States. *Contraception.* 2008;77:1-5.

More Can Be Dangerous: Computed Tomography and Radiation Exposure

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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

Synopsis: *The radiation dose received in one typical CT scan slightly increases the lifetime risk of death from cancer. The risk is age and site-dependent as children and digestive organs are more radiosensitive.*

Source: Brenner DJ, Hall, EJ. Computed Tomography—An Increasing Source of Radiation Exposure. *NEJM.* 2007;357:2277-2284.

OF NOTE, THIS PUBLICATION IS A REVIEW ARTICLE and not original science. The use of and possible indications for Computed Tomography (CT) scans have been rapidly growing since its introduction, particularly in the area of adult screening (ie, virtual colonoscopy, CT whole-body screening). Drs. Brenner and Hall have written a comprehensive and very understandable (even to medical specialties outside of radiology!) review article on everything you ever wanted to know regarding CT scans.[1] Although CT scans are quick, user-friendly (for both the physician and the patient), and noninvasive, they impart a significant amount of ionizing radiation (10mGy for one abdominal/pelvic CT scan but often more scans are needed to complete one study). Epidemiologic studies have shown that exposure to an average of 20-50mGy of ionizing radiation increases the risk of cancer. The risk is age and site-dependent as children and digestive organs are more radiosensitive.

■ COMMENTARY

I often have difficulty articulating to my family, friends and patients why more isn't always better and can be, at times, dangerous especially in regard to screening for cancers. Although advancements in science and technology have been a boon to the field of medicine, we aren't there yet with the use of CT scans for cancer screening.

How accurate is the test? Does early diagnosis lead to improved survival or quality of life? Will we do more good than harm? What is the severity and frequency of the disease? Costs of the test, the disease treated or untreated? These are the questions that we as medical professionals should be asking prior to adding a screening test to our current screening armamentarium.[2,3] Unfortunately, this is not the same approach our patients use and who can blame them? When offered a choice between a noninvasive test vs a scope up their "nether regions" or testing "#2", what choice would anyone make? But I think we can still make our argument that "more isn't better" with the following:

1. One must still undergo a complete bowel preparation with virtual colonoscopy.

2. The colon does not does not virtually inflate with air. The colon needs to be insufflated prior to a virtual colonoscopy (use your imagination).

3. If something is found on a virtual colonoscopy, a standard colonoscopy is necessary.

4. You are increasing your risk of death from cancer by screening for it with a virtual colonoscopy through exposure to ionizing radiation.

Now, not to use scare tactics, let me explain this risk of cancer further. The overall risk of cancer and the risk of death from cancer due to exposure to ionizing radiation with a CT scan exists but it is small. The risk is dependent on the average lifetime exposure, the age when exposed, and the body part exposed. For example, exposure to one typical abdominal/pelvic CT scan at age 25 increases your

lifetime risk of death from cancer by 0.06%, but that same exposure as a neonate would be 0.14%.[1] It is also important to note that the article only gives estimated risks for death from cancer and not the risk of cancer, which would be even higher. These are also estimates based on the exposure to only one typical CT scan. Using CT scans for screening purposes would mean a series of CT scans during an individual's lifetime, not to mention CT scans needed for unplanned diagnostic purposes (car accidents, etc). Personally, I am going to save my lifetime limit of ionizing radiation until I am really going to need it (hopefully, never!). ■

References

1. Brenner DJ, Hall, EJ. Computed Tomography—An Increasing Source of Radiation Exposure. *NEJM*. 2007;357:2277-2284.
2. Evidence-based Medicine. How to practice and teach EBM. Sackett D, et al. 2nd Edition. Churchhill Livingstone, NY, NY. 2000.
3. Clinical Epidemiology. Weiss, N. 2nd Edition. Oxford University Press, NY, NY. 1996.

Induced and Spontaneous Abortion and Breast Cancer Risk

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The Nurses' Health Study reports no association between the incidence of breast cancer and induced or spontaneous abortions.*

Source: Michels KB, et al. Induced and spontaneous abortion and incidence of breast cancer among young women. A prospective cohort study. *Arch Intern Med.* 2007;167:814-820.

Michels and colleagues from the Nurses' Health Study searched for a link between the incidence of breast cancer and either induced or spontaneous abortions in their prospective cohort of 105,716 women.[1] During the 14 years of follow-up, there were 1458 newly diagnosed cases of invasive breast cancer. The important hazard ratios (relative risks) after adjustment for breast cancer risk factors are the following:

Induced abortion	HR=1.01 (CI=0.88-1.17)
Spontaneous abortion	HR=0.89 (CI=0.78-1.01)

No trend was observed with number of induced or spontaneous abortions or age at first induced or spontaneous abortion. No association was found with parity. The authors concluded that neither spontaneous nor induced abortions were associated with the incidence of breast cancer, predominantly premenopausal breast cancer in this population.

■ COMMENTARY

This subject has been controversial for more than a decade because of opposite findings reported in over 20 epidemiologic studies. Why is it plausible that abortion might increase the risk of breast cancer? The argument goes like this. A full-term pregnancy before age 35 reduces the lifetime risk of breast cancer. It is believed that the exposure to the high levels of estrogen and progesterone for the length of a normal pregnancy produces a full differentiation of breast cells conferring protection against malignant transformation. A pregnancy that is terminated early, either spontaneously or by induced abortion, results in a hormonal exposure that is harmful because it only produces stimulation and does not persist long enough to produce the beneficial differentiation.

A meta-analysis in 1996 of the world's literature on this subject concluded that induced abortion increased the risk of breast cancer, largely in premenopausal women.[2] This meta-analysis is still referred to today. After the publication of this meta-analysis, responsible epidemiologists re-considered this subject and raised the real possibility that the healthy control women in the case-control studies were reluctant to reveal that they had induced abortions. Subsequently, studies that avoided this recall bias by deriving data from national registries instead of personal interviews failed to find an increased risk of breast cancer associated with induced abortions.[3-5] This was followed by more carefully conducted case-control studies that also failed to find a link between abortions and breast cancer risk.[6, 7] Similarly, newer prospective cohort studies yielded reassuringly negative results.[6, 8]

The Nurses' Health Study investigators point out that it is difficult to control for all breast cancer risk

factors in retrospective studies. They criticize the prospective studies as having insufficient data collection (eg, information on abortion was obtained only once at baseline). Hence, the value of the Nurses' Health Study with updated data-gathering throughout the follow-up. Although the women in this prospective cohort were predominantly premenopausal, 34% were postmenopausal. The Danish cohort study found no association across both premenopausal and postmenopausal age groups.[4]

This study adds to the impressive list of epidemiologic reports that fail to find an association between induced or spontaneous abortions and the risk of breast cancer. A link has been reported only in some studies that collected data retrospectively by personal interviews. The misleading findings in the retrospective studies almost assuredly resulted from the inclination of women who developed breast cancer to disclose previous induced abortions more frequently than the healthy women in the control group. This is also another great example of how a meta-analysis of observational data can produce incorrect conclusions. ■

References

1. Michels KB, et al. Induced and spontaneous abortion and incidence of breast cancer among young women. A prospective cohort study. *Arch Intern Med.* 2007;167:814-820.
2. Brind J, et al. Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis. *J Epidemiol Community Health.* 1996;50:481-496.
3. Rookus MA, Van Leeuwen FE. Induced abortion and risk for breast cancer: reporting (recall) bias in a Dutch case-control study. *J Natl Cancer Inst.* 1996;88:1759-1764.
4. Melbye M, et al. Induced abortion and the risk of breast cancer. *N Engl J Med.* 1997;336:81-85.
5. Erlandsson G, et al. Abortions and breast cancer: record-based case-control study. *Int J Cancer.* 2003;103:676-679.
6. Ye Z, et al. Breast cancer in relation to induced abortion in a cohort of Chinese women. *Br J Cancer.* 2002;87:977-981.
7. Mahue-Giangreco M, et al. Induced abortion, miscarriage, and breast cancer of young women. *Cancer Epidemiol Biomarkers Prev.* 2003;12:209-214.
8. Reeves GK, et al. Breast cancer risk in relation to abortion: results from the EPIC study. *Int J Cancer.* 2006;119:1741-1745.

Relationship between hysterectomy and urinary incontinence

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

Synopsis: *Previous hysterectomy does not appear to be a factor in the development or remission of incontinence.*

Source: Neumann GA, et al. Incidence and remission of urinary incontinence after hysterectomy—a 3-year follow-up study. *Int Urogynecol J.* 2007;18:379-382.

In this Danish study, 415 women who had undergone hysterectomy between 1998 and 2000 responded to the same questionnaire related to incontinence both in September 2001 and also in January 2005. A group of 97 women who had laparoscopic cholecystectomy in 1999 or 2000 served as the control group as they were asked to respond to the same questionnaire at the same time intervals. Stress incontinence was found in 30% of the hysterectomy group in 2005, compared to 28% in 2001. Urge incontinence was reported in 15% and 13%. Interestingly, stress incontinence was found more often at both times in patients who had subtotal hysterectomy.

Within the similar prevalences of incontinence in 2001 and 2005 are the findings that 16% of women who had previously undergone hysterectomy changed from continent in 2001 to stress incontinent in 2005 while 32% changed from stress incontinent to continent. In patients with urge incontinence, these changes were 8% and 35%.

■ COMMENTARY

This study adds another facet to the complicated relationship between the bladder and the uterus. In fact, the natural history of urinary incontinence is not well-understood. Long ago, ie, when I was a resident, it was felt that once a patient was incontinent, the natural course would be that the woman would remain incontinent. Studies since then have demonstrated that it is not uncommon for patients to go back and forth between

continence and incontinence. That would increase the importance for those of us who do hysterectomies to ask the questions about continence before we embark upon the surgery, if, for nothing else, to serve as a baseline determination. This is similar to the importance of us asking about depression and sexual functioning prior to hysterectomy. "Way back when," it was suggested that there is more depression and more sexual dysfunction after hysterectomy. More careful research has determined that this is not the case. Apparently, incontinence falls into that same category.

The finding that subtotal hysterectomy was more associated with subsequent incontinence than total hysterectomy calls into question whether the dissecting of the bladder flap off the cervix truly adversely affects innervation of the bladder as has been suggested by some.

By no means is this the final answer on this topic. My bet is that each of the readers has been queried by surgical candidates about hysterectomy and subsequent incontinence. I know I have. I've also been asked about the risks and benefits of subtotal hysterectomy. I'm sure you have. I admit, though, that I've not suggested to the patients that subtotal hysterectomy is associated with more incontinence. I won't start saying that because I feel that more data are needed, but it certainly appears to me that subtotal hysterectomy benefits do not include prevention of incontinence. Let's all wait and see. ■

Special Feature

Progesterone and the Prevention of 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.

Progesterone in Patients With a History of Preterm Labor (PTL)

YEARS AGO INVESTIGATORS ATTEMPTED TO USE A form of progesterone—delalutin—to prevent PTL. However, since there was no real proof of its benefit, progesterone was relegated to the "been there, done that" bin for many years until the concept was resurrected in the seminal paper published in 2003 by Meis et al.[1] In this collaborative, randomized study of 463 women, undertaken by the NICHD perinatal network, the investigators found that weekly intramuscular injections of 17 alpha-hydroxyprogesterone caproate (17P) diminished the rate of preterm birth (PTB) by 40%. This, and another study from Brazil in patients with a history of PTB showing similar results with vaginal progesterone, stimulated a flurry of new studies, each addressing the permutations of progesterone as a uterine quieting agent.

Progesterone in Patients With Short Cervical Length (CL)

Ever since Iams et al[2] demonstrated the relationship between short CL and PTB, many papers have emerged showing that CL's, obtained by transvaginal ultrasound between 20 and 24 weeks, can give the clinician a reasonable idea of who is at the greatest risk for repeat PTB and, just as importantly, who is at the least risk. It was a logical next step for investigators to fold CL into their preterm treatment protocols as a criterion for entry. For example, in one recent randomized trial, Fonseca et al[3] showed that patients with CL's < 1.6 cm who were given daily progesterone vaginal suppositories had a PTL rate (at < 33 weeks) of 19% vs 34% in those given placebos, which translated into a reduced risk of about 50%.

In another randomized study from Italy,[4] the investigators found that daily administration of vaginal progesterone diminished the rate of incremental cervical shortening in patients initially admitted in preterm labor for tocolysis and later followed up with serial CL's.

The last two enlightening papers[5,6] were published back-to-back in the October 2007 issue of *Ultrasound Obstet Gynecol* by a multinational group of investigators. Six hundred and fifty-nine (659) patients with a history of having had spontaneous PTL ending in delivery prior to 36 weeks were randomized to having daily progesterone gel inserted vaginally (332) or placebo (327), starting from 18 to 20 weeks. Using the endpoint of delivery prior to 33 weeks, there were no statistically significant differences in outcomes between the placebo group (11.3%) and the progesterone group (10%). However, the most interesting finding emerged from a secondary analysis of data from a subset of patients in the same study with CL of <2.8 cm. In this group of patients whose CLs were performed at the time of entry, there was a significant difference in PTB

before 33 weeks (0% in the progesterone group and 29.6 % in the placebo group). This would suggest that CL is a more powerful predictor of PTB, and a much better indicator of whom to treat with progesterone (than using history alone).

COMMENTARY

Many years ago, it was noted that progesterone-primed *in vitro* uterine muscle would not contract when subjected to electrical stimulation. Also, based on earlier studies in the sheep model demonstrating a drop in progesterone levels prior to labor, the concept of a "progesterone block" emerged in which progesterone was cast in the role of protector against preterm labor. Unfortunately, there had to be more to the story since, later, progesterone levels were not found to be decreased prior to labor in humans. However, corticotropin-releasing hormone (CRH) was noted to be elevated in pre-laboring patients. So progesterone's role had to be more subtle, and, therefore, investigation was then channeled to address its ability to bind to progesterone receptors, or to stimulate enhanced gene expression, or, alternatively, to compete with CRH for glucocorticoid receptors (thereby elevating circulating CRH levels). With this in mind, a study[7] surfaced last month in which both natural progesterone and 17P were found to be weak binders to progesterone and glucocorticoid receptors and poor activators of gene expression. Therefore, it seems that investigators will have to search further to find how these agents work.

In the meantime, whatever mechanism is involved, the studies with 17P and vaginal progesterone have now clearly shown that either can diminish the potential for preterm birth, especially in those with a combination of a history of prior preterm birth and a short cervix. Also, a recent study[8] has shown that even if 17P is given later in pregnancy (21-27 weeks) than is generally recommended, there seems to be similar benefit.

For reference, the weekly dosage of 17 alpha-hydroxyprogesterone in the Meis study was 250 mg and vaginal capsules of 200 mg of progesterone were used in the Fonseca study. In the DeFranco paper, 90 mg of progesterone gel was delivered daily with a vaginal applicator.

Key Points

1. Randomized trials show that both weekly intramuscular 17P and daily vaginal progesterone can diminish the rate of PTB in those with a history of PTB together with a short CL.
2. One randomized trial shows a decrease in PTB with 17P in patients with a history of PTB alone.
3. Another (non-randomized) study suggests the benefit of 17P, even when initiated late, at 21 to 27 weeks.
4. As yet, no study has addressed the benefit of either 17P or vaginal progesterone in those with an inadvertent finding of a short CL alone.
5. One study has shown no benefit from 17P in multiple gestations.[9]

References

1. Meis PJ, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med.* 2003;348:2379-2385.
2. Iams JD, et al. The length of the cervix and the risk of spontaneous preterm delivery. *N Engl J Med.* 1996; 334:567-572.
3. Fonseca EB, et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med.* 2007;357:462-469.
4. Facchinetti F, et al. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol.* 2007; 196:453.e1-453.e4.
5. O'Brien JM, et al. Progesterone vaginal gel for reduction of recurrent preterm birth: primary results from a randomized double-blind placebo controlled trial. *Ultrasound Obstet Gynecol.* 2007;30:687-696.
6. DeFranco EA, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improve neonatal outcome in women with a short cervix: a secondary analysis from a randomized double-blind placebo-controlled trial. *Ultrasound Obstet Gynecol.* 2007;30:697-705.
7. Attardi BJ, et al. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17 alpha hydroxyprogesterone caproate, and related progestins. *Am J Obstet Gynecol.* 2007;197:599.e1-599-e7.
8. How HY, et al. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? *Am J Obstet Gynecol.* 197:260.e1-260.e4.
9. Caritis S, et al. A randomized controlled trial of 17-hydroxyprogesterone caproate (17-OHPC) for the prevention of preterm birth in twins. *Am J Obstet Gynecol.* 2006; 195 (Suppl 1): S2.

CME Questions

37. The following statements regarding effective contraception are true except:

a. There is a substantial difference between a method's perfect use and the failure rate in general use.
b. The U.S. has one of the highest rates of unintended pregnancies in contraceptive users.
c. Contraceptive methods requiring male cooperation have the highest failure rates.
d. Over a 7-year period, family planning services in the U.S. increased their impact.

38. One adult abdominal CT scan imparts how much ionizing radiation?

a. 3mGy
b. 0.1mGy
c. 30mGy
d. 10mGy

39. One typical adult abdominal CT study imparts how much ionizing radiation?

a. 10mGy
b. 20mGy
c. 30mGy
d. 40mGy

40. The following statements are true regarding abortions and breast cancer except:

a. An induced abortion before the age of 20 does not increase the risk of breast cancer.
b. The number of induced or spontaneous abortions had no association with the risk of breast cancer.
c. Nulliparous women who have induced abortions have a slightly increased risk of breast cancer.
d. There has been evidence that either premenopausal or postmenopausal breast cancer risk is associated with abortions.

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.

41. Which of the following is not correct:

a. In the study using vaginal progesterone gel, there was a decrease in PTB compared with placebo in patients with a history of PTB.
b. IM 17P has been shown in the Meis study to decrease the rate of PTB in those with a history of prior PTB.
c. A CL <1.6 cm is associated with a high risk for PTB.
d. 17P blunts the incremental shortening of CL.

42. Which are the following is correct

Definitive data show that progesterone, IM or vaginally applied:

a. decreases the rate of PTB in twins.
b. decreases the rate of PTB in patients with short CL but no history of PTB.
c. decreases the rate of PTB in patients with a history of PTB and who also have a short CL.

Answers: 37 (d); 38 (d); 39 (c); 40 (c); 41 (a) 42 (c)

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Another Study Implicates Avandia

In this issue: *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

THE HANDWRITING MAY BE ON THE WALL FOR GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

Prilosec and Nexium Cleared

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."

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Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■