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Evaluating the Role of D&C vs Methotrexate in Ectopic or Non-viable Intrauterine Pregnancy

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: More than 25% of stable women with elevated levels of hCG and no visible intrauterine pregnancy on ultrasound will have a non-viable intrauterine pregnancy, and not an ectopic.

Source: Chung K, et al. Reevaluating the role of dilation and curettage in the diagnosis of pregnancy of unknown location. *Fertil Steril* 2011;96:659-662.

THE AUTHORS PERFORMED A RETROSPECTIVE COHORT STUDY TO EVALUATE the clinical utility of dilation and curettage (D&C) in diagnosing ectopic pregnancy (EP). They enrolled 321 clinically stable women with early pregnancies considered to be at risk for EP. The cohort included women with: 1) no visible intrauterine pregnancy (IUP) with hCG > 2,000 mIU/mL; 2) abnormal rise in hCG level, defined as < 50% increase in 2 days; or 3) abnormal fall in hCG level, defined as < 20% decline in 2 days that showed either no visible IUP on transvaginal ultrasound or an abnormal hCG trend. If clinical suspicion of EP warranted immediate intervention, only a single hCG value was done. Ultrasound impressions were designated as "suspicious for ectopic pregnancy" in the presence of free fluid, thin endometrial echo complex (EEC); mass without gestational sac; or "probable IUP" when an intrauterine sac was seen without a yolk sac or fetal pole. All ultrasounds were performed at the bedside by gynecology residents.

In the entire cohort, 10.6% had an ultrasound impression of "probable IUP;" 28.7% were "suspicious for ectopic pregnancy," and 60.7% were "nondiagnostic." All 321 women underwent a diagnostic D&C under conscious sedation and a diagnosis of EP or IUP was made by final pathologic review. Overall, 73.2% of the patients were ultimately diagnosed with an EP and 26.8% were found to have a non-viable IUP. Women with EP had significantly lower initial hCGs (mean 731 mIU/mL, range 11-39,836) than those with nonviable IUPs (mean

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2806.5 mIU/mL, range 47–48,810) and were more likely to have had a history of a prior EP, but there was no single level of hCG that excluded IUP. The authors concluded that D&C remains a valuable tool to differentiate EP from nonviable IUP and to avoid misdiagnosis and unnecessary exposure to methotrexate. Although low initial hCG values and ultrasound findings, such as a thin endometrial echo complex and the presence of free fluid, are associated with EP, they are not diagnostic.

■ COMMENTARY

As I sit writing this late on a Friday afternoon, I know that around the country many gynecologists are having the uncomfortable experience of needing to follow a stable patient with an abnormal early pregnancy over the weekend. This paper from Kurt Barnhart's group provides useful information on this old problem. Too often, I see women referred from the emergency department or from a primary care colleague with an abnormal pregnancy that has been followed with several ultrasound examinations or a series of quantitative hCG evaluations. Sometimes patients undergo multiple sets of both studies. Few providers consider evaluation of the endometrium to be an important step in diagnosis and treatment.

No one likes to give bad news about a desired early pregnancy, but our job is to be realistic and provide care in the most cost-effective and straightforward fashion. Those of us old enough to remember diagnosing EP in the emergency room with a culdocentesis understand the significance of early diagnosis. Serial determination of quan-

titative hCG coupled with ultrasound allow us to follow the at-risk pregnancy and offer early intervention for EP before rupture. The use of methotrexate to treat EP medically was another major advance; most early EPs now are managed successfully without surgery. Many providers quickly jump to methotrexate when a diagnosis of EP is suspected because the results with this therapy are best when hCG levels are lowest.¹ However, it is important to remember that methotrexate is a potent chemotherapeutic agent with potential for serious complications. Approximately 30% of patients who receive single-dose therapy and 40% of those who receive multidose therapy will experience some type of side effect.² Methotrexate administration also may result in stomatitis and conjunctivitis, and very rarely bone marrow suppression. Although these complications are rare, the treatment is not without risk.

High-resolution vaginal ultrasound is now commonly available in the office and emergency room setting. The combined use of ultrasound and quantitative hCG can provide great clarity in diagnosis of abnormal pregnancy. I use an hCG threshold of 1000 IU/L as the discriminatory zone for detecting an IUP. In a detailed study by Condous et al,³ the sensitivity and specificity of an hCG level of > 1000 IU/L to detect EP were 21.7% and 87.3%, respectively; for an hCG level of > 1500 IU/L these values were 15.2% and 93.4%, respectively, and for an hCG level of > 2000 IU/L they were 10.9% and 95.2%, so not much is gained by going to a higher level of hCG. If there is an hCG > 1000 and no evidence of an IUP, a diagnosis of EP is more likely. If the value is above 3000, one should always see some evidence of an IUP. The ultrasound finding combined with a single hCG should allow a clinician to rapidly triage a patient into a low- or high-risk group. In this paper, more than 50% of EPs and IUPs were identified on the initial evaluation.

Although this small study was retrospective, it provides some important information about patient management. Even with an apparently normal uterine cavity on ultrasound, an IUP cannot be ruled out. Furthermore, empirically treating women at risk for EP with methotrexate does not reduce complications or significantly save on cost (a cost analysis reported that diagnostic D&C cost \$173 to \$223 more per patient but had nearly 14% fewer complications with about 6% fewer hospitalizations).¹ In the Chung et al paper, the woman with the second thinnest endometrial thickness in this series had an IUP. If a D&C had not been done, she would have been subject to methotrexate unnecessarily.

Obviously a D&C has the risk of complications and is painful. However, in the management of EP it can provide rapid answers. Once an abnormal pregnancy has been diagnosed, emptying the uterus provides additional information. Not only will histology provide a definitive diagnosis, but the procedure also will remove trophoblastic

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Questions & Comments

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cells and result in a drop in hCG. So consider the stable patient that you are seeing this Friday afternoon. You can treat her with methotrexate today or get another hCG on Sunday and repeat her ultrasound on Monday. Or, you can do an office manual suction evacuation with a small curette and send the tissue to pathology. We do practically all of these with a local anesthetic only. On Monday, you will either have histology or be able to get another quantitative hCG. If the hCG declines by 50% you should feel reassured to await the tissue diagnosis. With this strategy, you will avoid giving methotrexate to about 25% of your patients. ■

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Vaginal Progesterone

ABSTRACT & COMMENTARY

By *John C. Hobbins, MD*

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University of Colorado Health Sciences Center, Denver*

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

Synopsis: *Vaginal progesterone gel treatment reduces preterm birth by 50% in women found to have a short cervical length by transvaginal ultrasound.*

Source: Hassan SS, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: A multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2011;38:18-31.

IN A COMMENTARY ON PRETERM BIRTH (PTB) IN THE APRIL ISSUE of *OB/GYN Clinical Alert*, I mentioned that data are on the horizon that would support the use of vaginal progesterone to reduce the risk of PTB in patients with short cervixes. Well, the study has now been published, and the results may change how PTB is approached. Virtually all

previous PTB studies have focused on patients with a history of PTB, but Hassan et al¹ initiated a screening study in which all pregnant women were enrolled. At 21 centers around the world, 32,091 patients with singleton pregnancies were screened with transvaginal cervical length (CL) between 19 weeks 0 days and 23 weeks 6 days. Of the women screened, 733 patients (2.3%) had a CL between 1.0 cm and 2.0 cm. The authors further concentrated on this high-risk group. After appropriate exclusions were applied, the remaining 458 (458/733) patients were randomly assigned to placebo (n = 223) or to treatment (n = 235). Both groups were given packs of vaginal applicators containing either 90 mg of 8% progesterone gel or placebo. The product used in the study was Prochieve[®] 8%, also known as Crinone[®] 8%.

Progesterone gel performed superiorly. For example, 21 patients treated with progesterone gel (8.9%) delivered before 33 weeks compared to 36 placebo patients (16.1%) (relative risk [RR] of 0.52, 95% confidence interval [CI] 0.31-0.91). A difference also was found in those having PTB < 28 weeks (5.1% vs. 10.3%, RR 0.50; 95% CI 0.25-0.97). In addition, statistically significant differences were found in the rate of respiratory distress syndrome (3.0% vs 7.6%, RR 0.39), neonatal morbidity and mortality (7.7% vs 13.5%; RR 0.57), and birth weight below 1500 g (6.4% vs 13.6%; RR 0.47).

The authors concluded that giving vaginal progesterone to those with CL of 1.0 cm to 2.0 cm decreased PTB before 33 weeks by 45% and improved neonatal outcome by 50%.

■ COMMENTARY

There are two very important up-shots from the study:

1. Daily vaginal progesterone can work as well as weekly IM 17-alpha hydroxyprogesterone caproate (17P) in preventing preterm birth, with the caveat that 17P mainly has been studied in those with a history of previous PTB.

2. Outcomes were improved in everyone with a short cervix, whether or not they had a history of prior PTB.

In a study published in 2007, Fonseca et al showed a very similar reduction in PTB with vaginal suppositories.² Ever since the well-known Meis et al study surfaced demonstrating the efficacy of IM progesterone in those with a history of PTB,³ many practitioners have begun using 17P for prophylaxis of PTB. However, this new study adds another major facet to the mix — the concept of screening everyone between 19 and 24 weeks with transvaginal assessments of CL.

In a separate article in the same issue of *Ultrasound in Obstetrics and Gynecology*, Werner et al⁴ evaluated the cost-effectiveness of universal screening with CL, followed by treating those with progesterone who have short

cervices. They estimated that for every 100,000 patients screened, \$12 million could be saved and “423.9 quality-adjusted life years could be gained” However, if the cost of the ultrasound exam exceeded \$187, or if there was less than a 20% reduction in PTB, then the economic efficacy of screening everyone diminished appreciably.

Interestingly, I could find no figures in the Werner study regarding the cost of vaginal progesterone. We have had trouble finding a product that is not expensive and has the same makeup as the product used in the above clinical trial. Crinone 8% costs about \$15 per application or \$450 per month. The contentious product history regarding 17P has been instructive. At first, compound pharmacies charged modest prices for 17P. However, one company garnered official approval from the FDA to make a branded 17P (Makena™), and the compound pharmacies were warned off. When it was announced that Makena was priced at \$1500 per injection, this triggered an uproar from some official bodies, causing the company to reduce the price of Makena to \$600 an injection. This still could represent a total outlay of up to \$12,000 per pregnancy. Hopefully, this story will not repeat itself with vaginal progesterone.

The concept of screening each of the more than 4 million pregnant women in the United States is daunting. According to the Werner et al study, the charge of a CL exam must not exceed \$187 if this is to remain cost effective. This should be attainable, but in this land of opportunity the motivation for profit is difficult to blunt. A way to accomplish this screening process with less cost would be to tack the CL exam on to the usual 18- to 20-week fetal anatomy survey that most patients receive as standard of care in pregnancy. It is clear that measuring the cervix transabdominally is not as precise as the transvaginal approach. However, although I have reservations about this as a screening compromise, the transabdominal approach may represent a less expensive and logistically easier way to go. It should be emphasized that the transvaginal exam should always be a first-line approach for those with a history of PTB, and should be used for confirmation in those who seem to have a short cervix on a transabdominal scan. ■

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The Rapalogs: New Class of Therapy for Women with Endometrial Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Dr. Coleman reports that he receives research funding from Novartis, which makes an mTOR inhibitor (everolimus).

Synopsis: *Temsirolimus, an inhibitor of mTOR, demonstrates activity in patients with advanced or recurrent endometrial cancer. Its clinical activity appears to be strongly influenced by prior chemotherapy exposure but not by histology or aberration in the PI3K pathway.*

Source: Oza AM, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: A trial of the NCIC Clinical Trials Group. *J Clin Oncol* 2011;29:3278-3285.

PHOSPHATASE AND TENSIN HOMOLOG (PTEN) IS A TUMOR SUPPRESSOR gene that is commonly mutated in endometrial and other cancers. Loss of PTEN causes deregulation of the phosphatidylinositol-3 kinase/serine-threonine kinase/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway, and provides a selective survival advantage to cancer cells via angiogenesis augmentation, protein translation, and cell cycle progression. Temsirolimus, an ester derivative of rapamycin, inhibits mTOR and was evaluated as a single agent (25 mg weekly intravenously, 4-week cycles) in sequential Phase 2 studies of women with recurrent or metastatic chemotherapy-naïve (Group A) or chemotherapy-treated (Group B) endometrial cancer. In Group A, 33 patients received a median of four cycles (range: 1 to 23 cycles). Of the 29 patients who were evaluable for response, four (14%) had an independently confirmed partial response and 20 (69%) had stable disease as best response, with a median duration of 5.1 months and 9.7 months, respectively. Only five patients (18%) had progressive disease. In Group B, 27 patients received a median of three cycles (range: 1 to 6 cycles),

and of the 25 patients evaluable for response, one (4%) had an independently confirmed partial response, and 12 patients (48%) had stable disease, with a median duration of 4.3 months and 3.7 months, respectively. PTEN loss (immunohistochemistry and mutational analysis) and molecular markers of PI3K/Akt/mTOR pathway did not correlate with the clinical outcome. mTOR inhibition with temsirolimus has encouraging single-agent activity in endometrial cancer, which is higher in chemotherapy-naïve than in chemotherapy-treated patients and is independent of PTEN status.

■ COMMENTARY

It is well-appreciated in the obstetrics and gynecology community that endometrial cancer is a gynecological malignancy increasing in incidence. More than one in five new cases of the disease will prove fatal — a proportion that is increasing with the epidemic of obesity. Adipose tissue produces potent extrinsic mediators for cellular growth, leading to an increased likelihood for events promoting carcinogenesis.¹ One of the most interesting and prevalent events is activation of the PI3K pathway, which is “turned on” by a number of growth factors, including epidermal growth factor, fibroblast growth factor, and insulin growth factor.² A principal regulator of this pathway is PTEN, a tumor suppressor gene. When this gene is knocked out in mice, endometrial hyperplasia forms, demonstrating the important role this gene has on the checks and balance of cellular growth in the uterus. In humans, PTEN can become mutated or down-regulated by other genes (such as src), losing its ability to suppress signaling under ligand stimulation. In addition, the pathway can be activated by gain-of-function mutations in PI3K itself or in downstream effectors, such as Akt, even if PTEN is functioning normally.³ One downstream effector of the PI3K pathway is mTOR (mammalian target of rapamycin).

In recent years, several compounds have been developed to inhibit activation of mTOR. As a class, these agents are called “rapalogs,” as they are derivatives of rapamycin, an immunosuppressive agent used in transplant patients. Several rapalogs are now available and are entering the clinical sphere of endometrial cancer therapy.⁴

Temsirolimus, the focus of this study, is one of the first to report activity as a single agent in women with measurable endometrial cancer. The reason this study is noteworthy is that it describes the clinical activity of an agent that is specifically targeted to a protein, which is believed to drive the cancer process. This is very distinct from chemotherapy, which generally exerts its effect by inducing indiscriminant cell death of rapidly dividing cells (cancer and otherwise). As such, the side-effect profile of these new targeted medicines is much different than chemo-

therapy and could provide new avenues of therapy for this disease. The fact that prior chemotherapy had such a profound effect on the clinical response to temsirolimus suggests that other pathways (“workarounds”) may be activated as disease progresses. Indeed, it has been recognized that a parallel pathway (the ras/raf/MEK) can drive carcinogenesis even with PI3K pathway silencing. Fortunately, several available compounds target the work-around pathway, leading to new trial designs where one or both pathways are targeted in drug combinations or as sequential therapy. The important tenet of these studies is that pathway activation can be measured in tumor prospectively, allowing specific treatment allocation based on this tumor profiling. It is hoped that such a strategy will optimize individual patient care; an important goal as there currently are no FDA-approved non-hormonal agents for this endometrial cancer. ■

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SPECIAL FEATURE

What the Reproductive Specialist Should Know about Detecting Thyroidal Conditions

By Sarah L. Berga, MD

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

THYROID DYSFUNCTION AND DISEASE MAY PRESENT AS REPRODUCTIVE compromise including oligomenorrhea, infertility, and miscarriage. Thyroid dysfunction and dis-

ease may complicate pregnancy and lead to compromised fetal neurodevelopment and preterm labor. Infertility procedures, particularly controlled ovarian hyperstimulation and ovulation induction with gonadotropins, increase the thyroxine requirement before the establishment of pregnancy. As such, the detection of thyroidal conditions may fall to any physician who cares for women, but particularly obstetricians and gynecologists. Although we think of thyroid disease as a simple condition in which thyroxine is given when the thyroid-stimulating hormone (TSH) level is elevated and then TSH levels are monitored to see if the patient is getting the correct amount, it is a bit more complex than that. Indeed, the American Thyroid Association released a 45-page document titled “Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum,” which contains 76 separate recommendations.¹ The document was endorsed by the American Congress of Obstetricians and Gynecologists among other groups.

The introduction highlights a few key points. During pregnancy, the thyroid gland increases 10%-20% in size and the production of thyroxine (T4) and triiodothyronine (T3) increases by 50% along with a 50% increase in the daily iodine requirement. The range of TSH is decreased throughout pregnancy because of the actions of hCG, and thus the upper and lower limits of TSH must be adjusted to detect and treat thyroidal disease. Approximately 10%-20% of pregnant women have antibodies to the thyroid gland during the first trimester and therefore are at high risk of developing overt hypothyroidism during pregnancy. I would add that it long has been known that symptoms such as fatigue are not a good way to screen for thyroid disease in the non-pregnant state, but fatigue is the sine qua non of pregnancy, so the only way to know if a pregnant patient's fatigue is partly related to subclinical or overt hypothyroidism is to screen.

Some of the recommendations of the report are highlighted below:

- Recommendation 2 states that “If trimester-specific reference ranges for TSH are not available, the following reference ranges are recommended: first trimester 0.1-2.5 mIU/L; second trimester 0.2-3.0 mIU/L; and third trimester 0.3-3.0 mIU/L.
- Recommendations 4 and 5 make the point that the wide variation in free T4 methodologies renders TSH a more reliable indicator of thyroidal status during pregnancy than FT4.
- Recommendation 6 is straightforward. Overt hypothyroidism should be treated in pregnancy using the TSH ranges above as guidance for how much thyroxine to give.
- Recommendations 8 and 9 grapple with the gray

area of subclinical hypothyroidism (SCH), noting that SCH has been associated with adverse maternal and fetal outcomes. There is insufficient evidence from randomized controlled trials (RCTs) to recommend for or against universal levo-thyroxine replacement (LT4) in thyroid antibody negative women with SCH. However, women with SCH who are thyroid antibody positive should be treated with LT4.

- Treated hypothyroid patients already receiving LT4 who are newly pregnant should independently increase their dose of LT4 by 25%-30% immediately upon missed menses or positive home pregnancy test. There is great inter-individual variation in the amount of LT4 needed to maintain TSH below 2.5 mIU/L in the first trimester. (Recommendations 13 to 15).
- Euthyroid women who are thyroid antibody positive and not treated with LT4 should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation (Recommendation 20).
- Recommendation 63 advises that women with postpartum depression should be evaluated for autoimmune thyroiditis with TSH, FT4, and thyroid peroxidase antibodies (TPOAb).
- Recommendation 72 states that there is insufficient evidence to recommend for or against universal screening with TSH during the first trimester. However, recommendation 76 suggests that serum TSH be evaluated early in pregnancy to screen for those at high risk for overt hypothyroidism. High-risk factors include: history of thyroid dysfunction or prior thyroid surgery, age > 30 years, symptoms, goiter, TPOAb positive, type 1 diabetes, any autoimmune disorder, history of miscarriage or preterm delivery, history of head or neck radiation, family history of thyroid dysfunction, obesity > 39 kg/m², use of amiodarone, lithium, recent iodinated radiologic contrast, infertility, and residing in an area of moderate to severe iodine insufficiency.

It would seem that all but the most straightforward of patients should be considered at risk and therefore screened. I suspect that by recommendation 72, you were already feeling that the detection and treatment of thyroidal conditions had morphed into a complicated topic. However, if recommendations 1 through 75 were not enough to convince you that this is not an entirely straightforward topic, then reading the rather long list of who is considered high risk and therefore eligible for screening probably was the drop that caused the flood. If all women > 30 years are at high risk, then it is starting to look far simpler and less time intensive to screen. TSH, with or without FT4, is

inexpensive, particularly when compared to some of the screening tests we already perform universally. Also, as I noted earlier, if symptoms such as fatigue and goiter are used as criteria to determine who should be screened, then we are pushed even closer toward universal screening because which pregnant woman is not fatigued and which does not have an increase in thyroid size?

I remember an adage that a mind is a terrible resource to waste. What we know about fetal neurodevelopment and its dependence on appropriate maternal thyroxine supply shifts us in favor of accurate detection. Although we may lack sufficient evidence from RCTs to make a strong recommendation for universal screening, there is a lot of other evidence from the molecular and cellular investigations and even screening trials² to suggest that fetal neurodevelopment depends critically on appropriate maternal thyroxine. Let us not forget that the mother is the sole source of fetal thyroxine during the first trimester and the predominant source even in the second and third trimesters. Finally, I would be remiss to not mention another article released in July 2011 showing that the development of fetal goiter in mothers on antithyroid drugs for Grave's hyperthyroidism responds better to intra-amniotic thyroxine than discontinuing the anti-thyroid drugs.³ The authors suggest that centralized care of pregnant women with Grave's disease is urgently needed to maintain optimal fetal development

Screening guidelines are helpful, but they are a work in progress. When routine screening was conducted, 2%-3% of pregnant women had an elevated serum TSH. Also, if subclinical maternal HYPERTHYROIDISM is not associated with adverse maternal or fetal outcomes⁴ and maternal hypothyroidism is, then it would seem generally better to err on the side of too much thyroxine to the fetus than too little. Not only is TSH a relatively inexpensive test, thyroxine is a relatively inexpensive medication. ■

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Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Instructions

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CME Questions

1. A 26-year-old gravida one presents with painless first trimester bleeding. The pregnancy is desired. Her ultrasound shows no evidence of an intrauterine pregnancy or of ectopic pregnancy. The hCG level is 1100 mIU/mL. All of the following points are true *except*:
 - a. the pregnancy could be ectopic.
 - b. the pregnancy could be intrauterine and abnormal.
 - c. the pregnancy could be intrauterine and normal.
 - d. the patient should be offered immediate uterine evacuation by suction curettage.
2. A 32-year-old G2 P1 presents with painless first trimester bleeding. The pregnancy is desired. Her ultrasound shows no evidence of an intrauterine pregnancy or ectopic pregnancy. The hCG level is 2450 mIU/mL today, and was 1986 mIU/mL two days earlier. All of the following points are true *except*:
 - a. the pregnancy could be ectopic.
 - b. there is a 25% chance that the pregnancy could be intrauterine and abnormal.
 - c. the pregnancy could be intrauterine and normal.
 - d. the patient should be offered immediate uterine evacuation by suction curettage.
3. Which of the following is *false* regarding universal screening with transvaginal sonography?
 - a. The Hassan study shows that screening and treating those with short cervixes with vaginal progesterone can reduce PTB at < 33 weeks by half.
 - b. The Hassan study did not show a reduction in early PTB (< 28 weeks) when those with a short CL are treated with vaginal progesterone.
 - c. There was a reduction in the treated group in combined neonatal morbidity.
 - d. There was also a reduction in days spent in RDS.
4. A universal screening program with transvaginal CL was cost effective if the price of the scan was held to under \$187.
 - a. True
 - b. False
5. Which of the following is *true* regarding current information concerning the prevention of PTB?
 - a. For universal CL screening to be cost-effective, the protocol would have to reduce the PTB rate by 50%.
 - b. Intramuscular 17P has only been studied in those with a history of PROM.
 - c. Intramuscular 17P is easy to obtain and now is inexpensive.
 - d. IM 17P has been tested mostly in those with a history of PTB.
6. Which of the following factors predicted response to temsirolimus in the Oza study?
 - a. Prior chemotherapy use
 - b. Presence of non-measurable disease
 - c. Loss of expression of PTEN
 - d. Uterine serous histology

PHARMACOLOGY WATCH



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

Medication Poisonings Are Increasing in Children

In this issue: Medication poisonings in children; rosuvastatin vs atorvastatin for atherosclerosis; saw palmetto for prostate symptoms; using atypical antipsychotics for off-label indications in adults; and FDA actions.

More medications, more poisonings

Medication poisonings among young children have increased in frequency in recent years despite safety measures to prevent them, according to a new study from *Pediatrics*. Researchers used patient records of more than 450,000 children 5 years old or younger from 2001-2008. The rate of poisoning increased by about a third during this time span compared to the prior decade. Child self-exposure was responsible 95% of the time with ingestion of prescription drugs causing more than half of the poisonings and more than 70% of significant injuries. The most dangerous drugs were opioids, sedative-hypnotics, and cardiovascular agents. The authors conclude that the number of children visiting emergency departments after medication exposure is increasing, with the majority of ingestions caused by children finding and ingesting medications by themselves. They suggest that efforts at poison-proofing homes with young children “may be a good, but insufficient, strategy.” They further suggest that the increase in poisonings is in part due to the rise in number of medications in the environments of young children, with the number of adults taking medications, especially opioid medications, rising dramatically in the last 10 years. Other possible explanations include more siblings on medications, especially ADHD meds, as well as exposure to grandparents’ homes where child-

proofing may not be as rigorous. They further conclude that current preventive efforts are inadequate and new measures, such as efforts targeting home medication safety (including storage of medications and child-resistant closures) and repackaging (such as blister packs and flow restrictors on liquid medications), should be considered. (*Pediatrics* published online September 16, 2011.) ■

Rosuvastatin no better than atorvastatin

Rosuvastatin is no better than atorvastatin in slowing progression of coronary atheroma, according to AstraZeneca, the manufacturer of rosuvastatin and sponsor of the study. Researchers compared rosuvastatin 40 mg to atorvastatin 80 mg in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN) trial. The primary efficacy endpoint was change from baseline in percent atheroma volume in a targeted coronary artery as assessed by intravascular ultrasound. After 104 weeks of treatment in some 1300 patients, there was a numerical greater reduction in favor of rosuvastatin, but the reduction did not reach statistical significance (astrazeneca.com/Media/Press-releases). The full results will be presented at the American Heart Association meeting in

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November. The results come as a blow to the manufacturer of rosuvastatin (Crestor) who had hoped to gain a marketing advantage before the introduction of low-cost generic atorvastatin into the market, slated for December. ■

Saw palmetto for prostate symptoms

Saw palmetto is ineffective for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH), even at higher doses, according to a new study. Previous studies have shown no benefit from saw palmetto, but researchers in this current study set out to test the efficacy of 2-3 times the normal daily dose on men over the age of 45 with significant LUTS. The main outcome was the difference in American Urologic Association Symptom Index score between baseline and week 72. Both saw palmetto and placebo led to an improvement in symptoms with a favorability toward placebo regardless of the dose of saw palmetto. Doses tested were a single 320 mg tablet per day with dose escalation to 2, then 3, tablets per day. The authors conclude that increasing doses of saw palmetto root extract did not lower LUTS more than placebo in men with BPH (*JAMA* 2011;306:1344-1351). This is the second rigorously controlled trial after the Saw Palmetto Treatment for Enlarged Prostates study (*N Engl J Med* 2006;354:557-566) to show no benefit from the supplement on LUTS in men with BPH. ■

Off-label use of atypical antipsychotics

Controversy surrounds the use of atypical antipsychotics for off-label indications in adults, especially the elderly with dementia. A new meta-analysis reviews the evidence of efficacy of these drugs for various off-label uses. Of more than 12,000 studies considered, 162 were included in the analysis. Drugs reviewed included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega). For elderly patients with dementia, a small but statistically significant improvement in symptoms such as psychosis, mood alterations, and aggression were seen with aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, quetiapine was the most effective, while for obsessive-compulsive disorder, risperidone was associated with a 3.9 greater likelihood of favorable response, compared with placebo when used

with antidepressants. There was no benefit seen with any of the drugs used in treating eating disorders, substance abuse, or insomnia, and only marginal benefit in personality disorders or post-traumatic stress disorder. All of these drugs have a boxed warning regarding increased mortality in elderly patients with dementia and increased risk of suicidality. Increased risk of death was seen in elderly patients with a number needed to harm (NNH) of 87. Also noted was increased risk of stroke, especially with risperidone (NNH = 53), extrapyramidal symptoms (NNH = 10 for olanzapine, NNH = 20 for risperidone), and urinary tract symptoms (NNH range = 16-36). Weight gain was also a problem in non-elderly adults, particularly with olanzapine (incidence of more than 40%), while akathisia was more common with aripiprazole. Other common side effects included fatigue, sedation, and extrapyramidal symptoms. (*JAMA* 2011;306:1359-1369). ■

FDA actions

The FDA has issued a warning regarding the potential for arrhythmia associated with the anti-nausea drug ondansetron (Zofran). The drug should be avoided in patients with QT prolongation as they are at particular risk of developing torsade de pointes. Ondansetron should be used with caution in patients with congestive heart failure, bradyarrhythmias, those predisposed to low potassium or magnesium, and in those taking drugs that cause QT prolongation. These patients should have electrocardiogram monitoring if ondansetron is indicated. The FDA is requiring new labeling changes to reflect these warnings.

The FDA is reminding physicians and patients that epinephrine inhaler (Primatene Mist), the only over-the-counter inhaler for asthma, will be removed from the market on December 31. The withdrawal is due to an international ban on chlorofluorocarbon propellant. The FDA is recommending that physicians ask their patients with asthma if they use Primatene Mist and talk to them about prescription alternatives.

The FDA has approved infliximab (Remicade) to treat moderate-to-severe ulcerative colitis (UC) in children 6 years and older who have had inadequate response to conventional therapy. The drug is already approved for adults with UC. The approval was based on a randomized, open-label trial of 60 children ages 6 to 17 with moderate-to-severe UC. The drug carries a boxed warning for serious infections and cancer. Infliximab is manufactured by Janssen Biotech. ■