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Preventing Preterm Birth in Twins

SPECIAL FEATURE

By John C. Hobbins, MD

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

Synopsis: *A recent review of the literature evaluating methods to decrease preterm birth in twins has shown little or no benefit of bed rest, cerclage, or 17 alpha-hydroxy progesterone, but there is some promise for vaginal progesterone in pessaries in women with twin pregnancies and short cervices.*

THROUGH THE YEARS, THE FORMAT FOR VIRTUALLY ALL *OB/GYN CLINICAL Alert* articles has involved a review of a recent article followed by a comment on the meaning and impact of the study's results. This month I am straying from this ritual because a review of the recent literature regarding the prevention of preterm birth (PTB) in twins, which appeared in the August issue of *Obstetrics and Gynecology*, provides extremely important information on the management of multiple gestation, now occurring in at least one of every 40 pregnancies in the United States.

Zork et al objectively summarize recent data in the literature addressing a variety of methods that have been used to prevent twins from delivering even earlier than their now average gestational age of 35 1/2 weeks.[1] One method in particular is very intriguing and I will save that for last.

Bed Rest

The lack of benefit of bed rest in pregnancy, in general, was covered in a recent article,[2] but in twins, specifically, data from a Cochrane database showed no effect of bed rest in twins, in general, and in those patients with twins and short cervices, in particular.

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Progesterone

Progesterone has the ability to quiet smooth muscle in vitro, but recently the rationale for its prevention of PTB has gravitated toward its anti-inflammatory effect. Nevertheless, in twins there are many other factors that could be put into play. For example, the overstretching of the uterus could lead to release of cytokines that may soften the cervix. In addition, the over-distention can trigger the production of prostaglandins, which can cause the uterus to contract. Thus far, attempts to prevent PTB have involved delivery of progesterone through either of two pathways, employed so far mostly in singletons.

17 Alpha-hydroxy Progesterone Caproate

The seminal study by Meiss et al[3] created a wave of enthusiasm over its ability to decrease the chances of early delivery in patients with a history of PTB. Recently, a few studies have specifically addressed its use in twins. A 661-patient, randomized, clinical trial (RCT) from the Maternal-Fetal Medicine network did not demonstrate benefit from 17 alpha-hydroxy progesterone caproate (17P) in preventing PTB in twins,[4] and a subanalysis of these data showed no benefit even in patients with short cervices (< 25th percentile).[5] Another study from the Obstetrix Collaborative Research Network involving 240 twin pregnancies showed no greater ability to prolong pregnancy with 17P.[6] Of some concern was the fact that a separate RCT very recently suggested that 17P actually seemed to increase the rate of PTB prior to 32 weeks in patients with twins whose cervices were < 2.5 cm.[7]

Vaginal Progesterone

Although no recent RCTs have shown the ability of daily vaginal progesterone to significantly drop the rate of PTB in twins, Romero, using a meta-analysis of twin pregnancies separated out from five RCTs, found a significant decrease in composite perinatal morbidity and mortality in those treated with vaginal progesterone, as well as a trend (albeit non-significant) toward a decrease in PTB before 33 weeks (30.4% vs 44.8%).[8]

Cerclage

In one study specifically addressing elective cerclage in twin pregnancies, 22 patients randomly chosen to have cerclage had no improvement in average gestational age compared with 23 controls.[9] Interestingly, in a much quoted meta-analysis, Berghella found that in singleton pregnancies with short cervices (< 2.5 cm) there was benefit from cerclage, but in twins the procedure actually doubled the risk of PTB (relative risk, 2.15; 95% confidence interval [CI], 1.15-4.01).[10]

Pessary

A few small studies emerged from Europe suggesting the benefit of pessaries in women with singletons and short cervices, but data in twins have been difficult to come by until a paper was recently presented at this year's Society for Maternal-Fetal Medicine meeting in San Francisco.[11] In this study, 813 twins were randomly assigned either to having a pessary or no treatment, and the overall outcomes were no different between groups. However, when they broke out patients with cervical lengths that were < 3.8 cm in the second trimester, there was a halving of PTB birth prior to 32 weeks in the pessary group (odds ratio [OR], 0.43; 95% CI, 0.21-0.89).

■ COMMENTARY

Most studies evaluating methods to prevent PTB in twins have yielded results that could be put in the "bummer" category. Bed rest, intramuscular progesterone, and vaginal progesterone do not seem to work in general, and cerclage may even make things worse. However, there is a hint that vaginal progesterone may help in those twin pregnancy patients with short cervices and there is even greater hope that pessaries could be of benefit in preventing PTB in these patients.

Prior to 2003, there has been only a sprinkling of case reports or small series where pessaries have been used to prevent PTB, mostly in singletons. Then Arabin published a pilot study in which none of the 12 patients with singletons and 23 patients with twins and short cervices delivered prior to 32 weeks when they were given pessaries (18-22 weeks).[12]

In an RCT, known as the PECEP study, involving 385

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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

women with singletons and short cervices (< 2.5 cm), Goya et al reported a remarkable drop in PTB prior to 34 weeks (OR, 0.18; 95% CI, 0.08-0.37) and premature rupture of membranes (OR, 0.16; 95% CI, 0.03-0.58) in those with Arabin devices (a silicon cup-type pessary) compared with expectant management.[13] When another study with similar design but smaller numbers (n = 108) did not show benefit of these pessaries in a Chinese population,[14] some questions arose regarding the seemingly high rate of PTB in the PECEP control group.

It is unclear exactly how a pessary works, but the simplistic (and maybe correct) idea is that the axis of the lower uterine segment is changed so that the angle of the downward pressure vector is directed toward the posterior wall of the uterus, rather than at the cervix itself. In a clinical situation where there is strong pressure to do "something" rather than sitting on ones hands, the pessary, although construed as being somewhat intrusive, is far less invasive than a cerclage, and it can be removed and inserted by the patient with little trouble.

Nevertheless, solid proof of its efficacy will have to await the results of studies already in progress in the United States and Europe. ■

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Hormonal Contraception and Breastfeeding

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Infants of women initiating either a combined oral contraceptive, the levonorgestrel IUS, the etonogestrel implant, or a copper IUD at 42 days postpartum ingested similar volumes of breast milk and displayed similar growth. Neither breastfeeding patterns nor continuation were influenced by the type of contraception.*

Source: Bahamondes L, et al. Effect of hormonal contraceptives during breastfeeding on infant's milk ingestion and growth. *Fertil Steril* 2013;100:445-450.

Despite lack of strong evidence of a deleterious effect, many clinicians are reluctant to use combined hormonal contraception (CHC) in breastfeeding women. The concern is that estrogen will reduce breast milk volume and the success of nursing. In fact, the World Health Organization (WHO) Medical Eligibility Criteria (MEC) for contraception lists initiation of combined hormonal methods in breastfeeding women > 6 weeks but < 6 months postpartum as Category 3 (condition where the theoretical or proven risks usually outweigh the advantages of using

the method). Although the Centers for Disease Control and Prevention (CDC) MEC does not restrict use of CHCs in breastfeeding women beyond 4 weeks postpartum, the absence of a definitive, well-designed, randomized trial makes the issue controversial. While the study by Bahamondes and colleagues does not provide this definitive answer, it offers a novel technique to address the question of milk volume and infant growth.

The investigators recruited healthy multiparous women and newborns after a term vaginal delivery at a university hospital. To be eligible, the women needed to have had prior experience with breastfeeding and an interest in exclusively nursing the infant (no supplements) during the study period. The mothers returned to the outpatient clinic on postpartum day 42 to initiate a contraceptive method of their choice; either a combined pill (COC) containing 150 mcg levonorgestrel (LNG) and 30 mcg ethinyl-estradiol (EE) in a 21/7 regimen, the LNG-IUS, the etonogestrel (ENG) implant, or the TCu380A copper IUD. The women were weighed before starting the contraceptive methods. To determine milk intake, the investigators administered deuterium "heavy water" (D_2O) to the mothers. Deuterium is not radioactive and is completely safe. However, the extra proton can be easily detected using mass spectrometry, and the ratio of D_2O to H_2O calculated to determine volume. The investigators used a known initial volume and distribution in the mother to calculate the amount of D_2O in the saliva of the infants and the mothers 30 minutes after a breastfeeding episode on postpartum days 43, 44, 45, 52, 53, 54, 56, 58, 60, and 63 at home. The infants' weights and heights were also measured on postpartum day 42 (baseline) and on days 52 and 63 after delivery.

While there was variation between the groups, when the COC group was compared with the progestin-only (LNG IUS and implant) and copper IUD groups, there was no difference in breast milk intake, infant growth, or success of nursing in the cohort.

■ COMMENTARY

The successful initiation of a contraceptive method postpartum provides a myriad of benefit to families. Repeat pregnancy within 1 year of delivery is associated with poor perinatal outcomes.[1] Barriers to initiation of a method of choice may reduce the uptake of contraception. While it is common practice in the United States to initiate the progestin-only pill (POP) to breastfeeding women, and then switch the pill after 6 months (or when breastfeeding ceases to be the exclusive food source for the infant), there is no strong evidence to support this approach. Women may not call back to change the pill, and since the only POP available in the United States requires meticulous compliance to be most effective, women may be exposed to an increased risk of pregnancy or discontinue the method due to unsatisfactory bleeding.

The elegant study by Bahamondes and colleagues provides additional evidence to support an absence of suppression of normal lactation by combined hormonal methods. Although the sample of women-infant dyads is small for all methods and the allocation of treatment was open label and non-randomized, the resolution of volume measurements made possible through the use of D_2O was excellent. The results provide a supplement to the randomized study of COCs and POP reported by Espey et al last year.[2] Based on these two studies, clinicians should feel comfortable to initiate a combined hormonal method at 4-6 weeks postpartum. For exclusively breastfeeding women, there is no need to initiate a method prior to that time.

But since many women may not follow exclusive breastfeeding rules and also may engage in coital activity prior to the 6-week interval, is it safe to start a combined method earlier than the routine postpartum check-up? The WHO, CDC, and ACOG all say no. The concern is not breastfeeding success but venous thromboembolism (VTE). The recently published CDC MEC for contraceptive use assigns initiation of combined pills before 21 days postpartum as category 4 (unacceptable health risks) and initiation at 21-29 days for women at low risk (e.g., no other risk factors except recent delivery) for thromboembolism is rated category 3 (theoretical or proven risks generally outweigh advantages).[3] The WHO MEC[4] are even more conservative, with a category 4 (unacceptable health risk) for initiation of combined pills within 6 weeks of delivery. While there is no direct evidence examining the risk for VTE among postpartum women using combined pills, this is a high-risk period for VTE independent of CHC use and it makes sense to be cautious. Fortunately, there is no downside to the early use of the implant or an IUD! ■

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Two-step Screening for Ovarian Cancer: A 'Scissor-step' Forward?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *An 11-year prospective screening trial in 4051 menopausal women (age 50-74) demonstrates that the risk of ovarian cancer algorithm probability index, along with ultrasound and gynecologic oncology consultation of "high-risk" cases, produces high specificity and positive predictive value leading to the identification of higher than expected incident early-stage ovarian cancers.*

Source: Lu KH, et al. A 2-stage ovarian cancer screening strategy using the risk of ovarian cancer algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. *Cancer* 2013; Aug 26. Doi: 10.1002/cncr.28183 [Epub ahead of print].

OVARIAN CANCER IS A HIGHLY LETHAL DISEASE OF LOW prevalence in the general population and associated with advanced stage presentation in more than 70% of incident diagnoses. Strategies to identify these clinical features early in the disease process have included a focus on symptomatology, blood-based biomarkers, imaging (predominately ultrasonography), and physical exam with little success.

In this study, a two-stage ovarian cancer screening strategy was evaluated that incorporates change of CA125 levels over time and age to estimate risk of ovarian cancer. Women with high-risk scores were referred for transvaginal ultrasound (TVS). The prospective study included postmenopausal women (age 50-74) with at least one retained ovary, no personal history of ovarian cancer, and no family history of a first- or second-degree relative with breast or ovarian cancer. Patients were also not allowed to have had another malignancy, other than breast cancer, within 5 years of enrollment. Participants underwent an annual CA125 blood test. Based on the Risk of Ovarian Cancer Algorithm (ROCA) result, women were triaged to a subsequent annual CA125 test if deemed low risk, a repeat CA125 test in 3 months if intermediate risk, or TVS and referral to a gynecologic oncologist if high risk. A total of 4051 eligible women participated over 11 years, accounting for 16,832 screen years. The average annual rate of referral to a CA125 test in 3 months was 5.8%, and the average annual referral rate to TVS and review by a gynecologic oncologist was 0.9%. Ten women underwent surgery on the basis of TVS triage, which identified four invasive ovarian cancers (one with stage IA disease, two with stage IC disease, and one with stage IIB disease), two ovarian tumors of low malignant potential (both stage IA), one endometrial cancer (stage I), and three benign ovarian tumors, providing a positive predictive value of 40% (95% confidence interval [CI], 12.2%, 73.8%) for detecting invasive ovarian cancer. The specificity was 99.9% (95% CI, 99.7%, 100%). All four women with invasive ovarian cancer were enrolled in the study for at least 3 years with low-risk annual CA125 test values prior to rising CA125 levels (CA125 change point). The authors concluded that ROCA followed by TVS demonstrated excellent specificity and positive predictive value in a population of U.S. women at average risk for ovarian cancer.

■ COMMENTARY

Some may recall the children's game "Mother may I?" in which participants follow instructions from a leader (mother) trying to guess the progress of the participants (children) toward a goal (home). Granted requests, such as "baby steps" or "scissor steps," afford minor advancements toward progress. The current study, while offering hope and promise of bridging the gap between early detection and mortality from ovarian cancer, essentially represents a minor, albeit positive, step forward. It clearly demonstrates that the process will involve several key elements such as good biomarkers, good probability esti-

mate algorithms, motivated follow-up, access to secondary triage and gynecologic oncology consultation, and ultimately validation by documentation of reduction in mortality. However, to reach this zenith, studies assessing the merits of the individual steps forward are necessary and build confidence in the process.

It is clear that a screening program's best opportunity to reduce disease mortality is to identify a pre-invasive state where intervention will prevent disease.[1] Currently, we have no such marker for ovarian cancer, which likely also consists of a high proportion of fallopian tube abnormalities that form the primary site of disease.[2] Thus, the next best opportunity to affect mortality in ovarian cancer is "stage migration;" that is, diagnosing the disease at earlier stages than what is currently observed in the general population. This can measurably impact survival as early-stage disease is curable at rates two- to three-fold that of advanced disease. Since more than 70% of ovarian cancer diagnosed in 2013 is stage IIIC/IV, there is significant opportunity to vastly alter its natural history and expected disease-specific mortality under a screening program that results in significant stage migration. The performance of the two-step screening algorithm used in this trial is remarkably consistent with the initial prevalence report presented by the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)[3] group in 2009 (also reviewed in *OB/GYN Clinical Alert*).[4] Although incidence was not reported in that study, the general specificity and positive predictive value of the two-step algorithm (which is similar to current study) were very consistent and, fortunately for screening participants, required only two to three operations from "positive screens" to identify cases of ovarian cancer — all in "early-ish" stages (Stage IC-IIB).

It was also of interest that two of the four cancers identified in this study had "normal" CA-125 values but met the criteria for a significant CA125 change point while remaining within the normal range. This highlights the value of establishing a normal baseline and the power of serial investigation. In addition, nearly 85% of all participants just went on getting annual CA-125 tests, demonstrating the low overall specificity of the program. The 200,000 person UKCTOCS trial's primary endpoint is disease-specific mortality; it is hoped that the preliminary results will be confirmed, offering practice changing policies in the management of screening menopausal women. ■

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See-and-Treat for Cervical Intraepithelial Lesions

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

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

Synopsis: *In this retrospective, cohort study, a see-and-treat protocol resulted in only a 4.5% overtreatment rate, as long as the patient had both a high-grade referring pap smear and high-grade colposcopic impression.*

Source: Bosgraaf RP, et al. Overtreatment in a see-and-treat approach to cervical intraepithelial lesions. *Obstet Gynecol* 2013;121:1209-1216.

This is a large, retrospective, cohort study of 3192 women who were referred for colposcopy at one medical center in the Netherlands and underwent a see-and-treat protocol. With all subjects entered into an internal database from 1981 to 2010, the authors were able to examine the referring Pap smear result, colposcopic impression, and final histopathologic interpretation on the large loop electrical excision of the transformation zone (LLETZ) specimen for this population. The Dutch cervical cancer screening program offers Pap smears every 5 years to women aged 30-60. This study also included women who had Pap smears for "cervical complaints" or outside of the population screening program. From the study description, women with high-grade cervical squamous intraepithelial lesion (HSIL) or worse and persistent low grade with positive high-risk HPV (HPV triage started in 2008) were referred for colposcopic examination. When the Pap smear result, colposcopic impression, or both were suggestive of high-grade cervical intraepithelial neoplasia (CIN 2 or worse), immediate treatment followed. Overtreatment was defined as treatment for no

CIN or CIN 1 on final histopathology results.

The authors found that the referral Pap smear was low-grade in 20.2% (95% confidence interval [CI], 18.8-21.7) of cases and high-grade in 79.3% (CI, 77.8-80.7) of cases. Histologic examination of the 3192 specimens revealed 579 cases (18.1%; CI, 16.7-19.5) with no CIN or low-grade CIN, 2613 cases (81.9%; CI, 80.6-83.2) with CIN 2 or CIN 3, and 177 cases (5.5%; CI, 4.8-6.4) with cancer. Overall, the over-treatment rate was 18.1%. For women with a low-grade Pap smear and low-grade colposcopic impression, the rate was 73.4%. A low-grade Pap smear and high-grade colposcopic impression resulted in an overtreatment rate of 29.2%. Equally, a high-grade Pap smear with a low-grade impression resulted in an over-treatment rate of 28.6%. However, the overtreatment rate for women with both a high-grade Pap smear and high-grade colposcopic impression was only 4.5%. Older women had higher rates of overtreatment compared to women younger than 30 (odds ratio [OR], 1.77; 1.31-2.40 for age 40-49 years, and OR, 3.39: 2.31-4.99 for age 50 years and older).

■ COMMENTARY

This study took advantage of a single-institution database to report a large case series of the see-and-treat treatment protocol for CIN. Certain factors of this study are unique to the Netherlands. Namely, their cervical cancer screening program includes only women aged 30-60 years and only screens them every 5 years. This was and is different than other countries that typically screen a broader population at shorter intervals, which may result in higher over-treatment rates. In addition, the use of HPV testing for triage to colposcopy is not yet reflected in this study. The unique finding of this study was lower over-treatment rates for younger women. This likely reflects a more conservative approach by the colposcopist among women who may be at risk for preterm birth after LLETZ.

The see-and-treat approach to colposcopy has been studied before and rates vary in the literature depending on the population studied.[1] In the United States, it may be practiced less frequently due to the medico-legal climate. Indeed, in our colposcopy clinic, we usually only perform the see-and-treat approach for high-grade lesions in women who are unlikely to return for a follow-up visit. The advantage of see-and-treat protocols are patient convenience because diagnosis and treatment are combined. In addition, the diagnosis may be superior to punch biopsies that could miss a portion of the lesion or underestimate its severity. The disadvantage, of course, is the risk of overtreatment.[1] This is especially true depending on the skill of the colposcopist. However, as this study shows, overtreatment can be kept to a minimum as long as the patient has a high-grade referring pap smear and a high-grade colposcopic impression.

The American Society of Colposcopy and Cervical Pathology (ASCCP) 2012 guidelines do not recommend a see-and-treat protocol for women age 21-24 years with HSIL.[2] For women age 25 and older, immediate loop electrosurgical excision is acceptable for women with a high-grade pap smear (except in pregnancy) or colposcopy may be performed. Given that 60% of women with HSIL will have CIN 2 or worse, the ASCCP states that "this justifies immediate excision of the transformation zone for many women, especially those who are at risk for loss to follow-up or who have completed childbearing." On a humbling note, it is important to remember that studies show that the sensitivity of colposcopy for detecting CIN 2 or worse is lower than previously thought.[3] It is now recommended that multiple biopsies be performed at colposcopy rather than just taking one biopsy of the worst-appearing lesion.[4] Therefore, our motto in colposcopy clinic now is: "If it is white, take a bite." ■

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CME Objectives

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.

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CME Questions

1. Which of the following is not correct regarding to prevention of preterm birth (PTB) in twins?

a. 17 alpha-hydroxy progesterone (17P) decreases the rate of PTB in those with short cervices.
b. Bed rest has no effect on the rate of PTB.
c. Vaginal progesterone has not yet conclusively been shown to decrease the rate of PTB.
d. A recent study has shown a decrease in PTB with pessaries in twins with short cervices.

2. The pessary works to prevent PTB in twins by decreasing inflammation.

a. True
b. False

3. Which of the following is the most appropriate answer regarding various methods of prevention of PTB?

a. 17P has been shown to decrease the PTB in singleton patients with a history of PTB.
b. Vaginal progesterone does not increase PTB rate in singleton pregnancies with short cervices.
c. Cerclage has been shown to increase PTB rate in twins.
d. No studies have shown benefit of pessaries in singletons with short cervices.

4. Which of the following is true regarding the volume of breast milk consumed by and growth patterns observed in infants whose mothers were taking a combined oral contraceptive compared to those using a copper IUD?

a. Milk intake and growth patterns were the same.
b. Milk intake was reduced but the growth pattern was not affected.
c. Both milk intake and growth were reduced.
d. Milk intake was increased and growth was reduced.

5. Which of the following characteristics was a stated eligibility or exclusion of women in the ovarian cancer screening trial?

a. Age > 50 years
b. At least one intact ovary
c. Previous history of ovarian cancer
d. No evidence of another cancer within 5 years of initial screening

6. In the study by Bosgraaf et al, younger women with cervical intraepithelial lesions had higher overtreatment rates.

a. True
b. False

In Future Issues: **The Effect of Low-dose Fluoride on Osteoporosis Risk**

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

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

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Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

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preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■