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Ulipristal Acetate: Ready for Prime Time?

SPECIAL FEATURE

By Michael A. Thomas, MD

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

SINCE THE BEGINNING OF MODERN TIME, RESEARCHERS HAVE BEEN TRYING to find a hormonal agent that would confer multiple therapeutic effects. This "perfect" drug would prevent pregnancy, shrink fibroids, and lessen the effects of endometriosis thereby treating contraceptive needs, symptomatic leiomyomas, and pelvic pain. What a medicine! Well, that perfect hormonal agent may finally be available. Multiple drugs have been touted as the next best thing over the last 60 years; these contenders have included combination oral contraceptives, progestin-only pills, and intrauterine devices. But the new Swiss Army knife of gynecology that may ameliorate or cure all reproductive ills may rest in the hands of the selective progesterone receptor modulators (SPRMs).

SPRMs, like ulipristal acetate (UPA), have been studied as a treatment option for patients in need of emergency contraception and are predicted to have multiple uses in the field of reproductive medicine.[1] Although UPA is FDA-approved as an emergency contraceptive, other potential uses are as a daily oral contraceptive as well as an agent to treat endometriosis and symptomatic uterine fibroids.

UPA, otherwise known as CDB-2914 or VA 2914, is a second-generation SPRM that directly blocks progesterone action in target tissues and, unlike mifepristone (RU 486), has little glucocorticoid receptor activity.[2,3] UPA is a SPRM with mixed effects at the level of the progesterone receptor.[4] It can exhibit both antagonistic and a partial agonistic effect. When it binds to the progesterone receptor, it prevents endogenous progesterone from occupying this site, inhibiting progesterone

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receptor-mediated DNA transcription. SPRMs have been demonstrated to inhibit ovulation, decrease proliferation of the endometrium (with possible alteration of implantation potential), and result in amenorrhea.[1] UPA can exhibit different effects depending on when it is administered in the menstrual cycle.

Emergency Contraception

SPRMs are an effective form of emergency contraception that can be used up to 120 hours after intercourse.[1] When comparing levonorgestrel (LNG) to UPA, LNG acts primarily by blocking or delaying the luteinizing hormone (LH) surge. Its efficacy is limited to the time frame preceding the onset of this surge, with no subsequent effects on follicular dynamics once LH levels increase. In contrast, UPA has the potential to prevent pregnancy even in the presence of increased LH levels in the advanced follicular phase. A single dose of 30 mg of UPA administered immediately prior to ovulation (dominant follicle > 18 mm) was effective in delaying subsequent follicular rupture for 5 days in 60% of subjects, primarily through postponement of the LH peak.[5]

One group of investigators directly compared the effectiveness of a single 30 mg dose of UPA to 1.5 mg of LNG in a randomized, multicenter, single-blinded, non-inferiority trial, involving 1696 women.[6] With the primary outcome being pregnancy rate in women who received emergency contraception within 72 hours of unprotected intercourse, 15 pregnancies occurred in the UPA group (1.8%; 95% confidence interval [CI], 1.0-3.0) compared to 22 in the LNG group (2.6%; CI 1.7-3.9; odds ratio, 0.68). No significant difference in pregnancy rates (P = 0.091) between the UPA and LNG group was observed. Secondary outcome was pregnancy rate from 72-120 hours of intercourse, and in this subgroup of 203 women, a total of three pregnancies were observed, all from the LNG group. A significant number of pregnancies were prevented in the UPA group compared to the LNG group (P = 0.037). When the authors analyzed the pregnancy rates between the groups over the entire 120-hour period, there was no statistical significance (P = 0.091). A meta-analysis including data from a National Institutes of Health (NIH) multicenter study involving an additional 1546 women demonstrated a lower pregnancy rate at the timepoints of 24 (P = 0.035), 72 (P = 0.046), and 120 hours (P = 0.025).[7] Unlike LNG, UPA can be used over a 5-day period, and it does not exhibit the same magnitude of decreased efficacy the longer one administers it after intercourse.

Commonly experienced symptoms observed include headache, nausea, and abdominal pain. In the two Phase 3 studies, the rates were 18%, 12%, and 12%, respectively.[6,8] Other symptoms include dysmenorrhea, fatigue, and dizziness, as well as a delay in menses that ranged between 2.1 and 2.8 days.[1]

In 2009, the new drug review application for UPA as an emergency contraceptive agent by FDA discussed the possibility of drug-drug interactions, including agents that induce or inhibit CYP3A4 enzymes. Agents that may induce this enzyme include carbamazepine, phenytoin, barbiturates, griseofulvin, rifampin, oxcarbazepine, and St. John's wort.[3] Inhibitors of this enzyme, such as ketoconazole and itraconazole, possibly could increase blood levels of this agent, as UPA is primarily degraded by the cytochrome P450 system.

UPA is categorized as a pregnancy category X drug, and, therefore, is contraindicated for use during pregnancy.[3] In addition, the potential of drug secretion into breast milk is yet unknown, so breastfeeding is not recommended. There is animal evidence that exposure of UPA during organogenesis resulted in fetal loss; however, in the fetuses that survived, no malformations were seen in the offspring. Unlike mifepristone, UPA is not approved for use in termination of pregnancy.

Daily Contraceptive Pill

In addition to use as an emergency contraceptive agent, UPA is being investigated as a potential agent for estrogen-free, long-term contraception. The capacity of UPA to inhibit or prevent ovulation for contraception has been investigated. In a prospective, randomized, placebo-controlled trial of 46 women, 5 or 10 mg of daily UPA was shown to effectively prevent ovulation over a 3-month pe-

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riod (81.8% and 80%, respectively).[9] Other investigators have used UPA in a vaginal ring, but up to 32% of 111 treatment cycles of 4 weeks noted evidence of ovulation.[10] Though a thickened, cystic-appearing endometrium is occasionally noted with users of oral UPA, PRM-associated endometrial changes (PAEC) confers no evidence of hyperplasia or endometrial cancer when seen on biopsy. Therefore, PAEC is thought to be a benign condition. Although UPA has demonstrable effects on suppressing ovulation, estrogen levels are essentially unchanged, and, therefore, any bone density changes seen secondary to a hypoestrogenic environment are not observed.

The NIH is currently conducting a Phase 2 trial using UPA in 5 and 10 mg doses continuously as a daily administered contraceptive. The 5 mg dose will also be looked at in a 24-day and 4-day sequential pattern.

Uterine Fibroids

As of now, Phase 1, 2, and 3 clinical trials using UPA for patients with uterine fibroids have been completed.[11] Most of these studies have demonstrated a decrease in bleeding, fibroid volume, and an improvement in quality-of-life parameters without any significant side effects after 13 weeks of administration. When compared to placebo, UPA in doses of 5 mg and 10 mg showed a significant reduction in bleeding, fibroid size, and adverse effects.[12] When fibroid patients were given leuprolide acetate (LA), a GnRH agonist, or UPA at similar doses, the LA and the different UPA groups had similar effects on the control of bleeding, but complaint of hot flashes was more significant in those taking LA.[13]

Endometriosis

Although studies in humans have yet to be published, when UPA was given to a rat model with surgically induced endometriosis for 8 weeks, a regression and atrophy of the endometriotic lesions was documented.[14] There was also a reduction in cytokines associated with cellular proliferation and inflammation. Whether similar findings in the human will be demonstrated remains to be seen.

Conclusion

UPA is the first SPRM approved for emergency contraception in the United States. It is also currently undergoing Phase 3 trials as treatment for uterine leiomyomas and Phase 2 trials as a long-term contraceptive agent. It has the capability to affect both ovulation and implantation, as evidenced by its effects on progesterone and the role of this hormone in the female reproductive process. Hypothetically, if there is a uterine protective effect, UPA could be used for patients with endometrial hyperplasia or early stages of endometrial cancers. The intrauterine administration of UPA, when placed in a silastic tube, in ovariectomized rhesus macaques that were estrogenized has demonstrated an induction of endometrial atrophy and amenorrhea.[15]

Muhammad Ali was a self proclaimed G.O.A.T. (Greatest of All Time). He proved worthy of this unofficial honor by years of proven boxing prowess. Whether UPA will be the reproductive equivalent of a G.O.A.T. remains to be seen. However, initial studies have shown that UPA and other second-generation SPRMs may be the future pharmaceutical agents that will allow our patients to improve their lives by protecting them against unwanted pregnancy, the bleeding and mass effect of uterine fibroids, and the menstrual and sexual pain associated with endometriosis. ■

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What is the Impact of Pediatric Cancer Care on Future Fertility in Female Survivors?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Women undergoing pediatric cancer care are significantly more likely than their siblings to have clinical infertility (≥ 12 months of non-conception despite desired attempts) and total infertility (clinically infertile women who also reported ovarian failure defined as never initiating menstruation or no periods 5 years before baseline questionnaire). Although infertile cancer survivors were no more likely to seek professional help for conception than their siblings, they were significantly less likely to receive drugs to assist with conception. They also had an increased time to achieve pregnancy. The report provides the first large-scale, comprehensive survey of infertility in childhood cancer survivors.*

Source: Barton SE, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: A report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol* 2013;Jul 12 [Epub ahead of print].

Previous studies have shown decreased pregnancy rates and early menopause in female cancer survivors; however, infertility rates and reproductive interventions have not been studied. This study investigated infertility and time to pregnancy in female childhood cancer survivors, and analyzed treatment characteristics associated with infertility and subsequent pregnancy. The primary dataset was developed by querying the Childhood Cancer Survivor Study (CCSS), a multinational (United States and Canada) cohort study enrolling 5-year cancer survivors who were younger than 21 years at the time of diagnosis between Jan. 1, 1970, and Dec. 31, 1986, and a sibling control group. Women aged 18-39 years who had ever been sexually active provided medical and reproductive data via a baseline questionnaire and underwent quantification of alkylating agent and radiation therapy exposure. The authors analyzed self-reported infertility, medical treatment for infertility, time to first pregnancy in survivors and siblings, and the risk of infertility in survivors by demographic, disease, and treatment variables. Overall, 3531 survivors and 1366 female sibling controls were evaluated. Compared with their siblings, survivors had an increased risk of clinical infertility (relative risk [RR], 1.48; 95% confidence interval [CI], 1.23-1.78; $P < 0.0001$), which was most pronounced at early reproductive ages (e.g., age 24 years; RR, 2.92; 95% CI, 1.18-7.20; $P = 0.02$, in participants ≤ 24 years). Despite being equally likely to seek treatment for infertility, survivors were significantly less likely than were their siblings to be prescribed drugs for treatment of infertility (RR, 0.57; 95% CI, 0.46-0.70; $P < 0.0001$). Increasing doses of uterine radiation and alkylating agent chemotherapy were strongly associated with infertility. Although survivors had an increased time to pregnancy compared with their siblings ($P = 0.032$), 292 of 455 participants (64%) with self-reported clinical infertility ultimately achieved a pregnancy. These data provide more comprehensive understanding of infertility after successful pediatric cancer care and avenues for counseling and decision-making about future conception attempts and fertility preservation.

■ COMMENTARY

Successful care in pediatric cancers has been a remarkable achievement over the past several decades. Overall, long-term survivorship is now the norm and many of these patients (male and female) have interest in achieving pregnancy. The CSS is a comprehensive, multinational, cohort study that enrolled patients with pediatric cancers and their unaffected siblings (controls) to evaluate interventions and outcomes.[1] This latest report targeted reproductive history and fertility to better define expectations from treatment and significantly enhance the limited data on the topic to provide better counseling opportunities. Eligible malignancies were leukemia, CNS cancer, Hodgkin's lymphoma, non-Hodgkin lymphoma, Wilms' tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors. Many of these malignancies are treated with partial or total body radiation and/or the use of alkylating agents, both of which have been linked to reproductive failure

and infertility.[2] By using a sibling cohort, the investigators were better able to estimate relative infertility in affected individuals by providing some control of shared familial and environmental risks. Previous studies of the participants in the CSS have documented no significant clinical or demographic differences in the cohorts.

Overall, the data are in line with expectations from these types of therapy. It has been known for many years that the ovaries are sensitive to radiation and fail at a higher rate than expected, even when transposed or blocked during therapy.[2] In addition, alkylating agents are known to have a dose effect on ovarian failure, which was assessed in the current study by creating an index of total exposure based on dose, frequency, and number of courses of chemotherapy involving these agents. However, the new data demonstrate that the impact of therapy on clinical infertility is greatest early on (≤ 24 years of age) and diminishes over time, despite remaining more common in survivors compared to their siblings. This was manifested by increasing time to first pregnancy despite the similar rates of infertility specialist referral. Of some surprise was the lower use of fertility-enhancing drug therapies. The data did not address causes or reasons for the variance, but it was considered that there might be reluctance to use these agents due to subsequent cancer/medical risk or low confidence they would work. Although infertility care is much better today than during the time of exposure for the cohort (about a decade ago), these observations serve to enhance the discussions of health care providers with patients and caregivers in addressing the topic of fertility following therapy.

The topic is of increasing importance, as more and more cancer survivors are making it to the age of majority and are as interested in opportunities for childbearing as noncancer patients. For women who have already begun to ovulate and in whom preservation is still of interest ahead of planned additional therapy, many new options are available such as cryopreservation of oocytes, embryos, and even unstimulated ovarian cortical tissue. The American Society of Clinical Oncology recently updated its guidelines of fertility preservation, which will bring the discussion to the forefront of treatment planning.[3] ■

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Misoprostol Prior to IUD Insertion in Nulliparous Women: Where's the Benefit?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *In a randomized study of nulliparous women who presented for insertion of a copper IUD, the ease of insertion was increased, and subjective pain decreased in those who received vaginal misoprostol prior to the procedure. However, misoprostol did not decrease failed insertions and was associated with a trend toward more expulsions.*

Source: Scavuzzi A, et al. Misoprostol prior to inserting an intrauterine device in nulligravidas: A randomized clinical trial. *Hum Reprod* 2013;28:2118-2125.

Several groups have evaluated whether the routine use of misoprostol could improve the intrauterine device (IUD) placement experience for women. While well-intended, these efforts have failed to demonstrate that the approach results in an increase in successful insertion attempts or that benefit surpassed potential harm. Scavuzzi et al performed a randomized, double-blind, clinical trial at a single hospital-based clinic in Brazil. They recruited healthy nulligravid women and randomized them to receive 400 mg of misoprostol or an identical placebo tablet vaginally 4 hours prior to placement of a CuT380 IUD. The study drug was placed in the posterior fornix of the vagina by the principal investigator. The primary outcome was the subjective difficulty (as reported by the investigator) in inserting the IUD. Secondary endpoints included the frequency of women with cervical dilation ≤ 4 mm (measured by ease of inserting a #4 Hegar dilator), pain at insertion (as judged subjectively by the woman and the investigator using a visual analog scale), and the woman's subjective evaluation of the procedure (classified as not disagreeable, slightly disagreeable, disagreeable, or very disagreeable). The investigators also evaluated the frequency of pre-procedure side effects such as nausea and cramping.

A total of 190 women were randomized (95 in each group). Fewer placements were judged to be "difficult/very difficult" in the misoprostol group compared to the placebo group (relative risk [RR], 0.49; 95% confidence

interval [CI], 0.33-0.72), and active drug was also associated with a lower risk of dilatation < 4 mm (RR, 0.48; CI, 0.33-0.70), a reduction in moderate-to-severe pain at IUD insertion (RR, 0.56; CI, 0.41-0.76), and a lesser likelihood of experiencing a "disagreeable or very disagreeable sensation" (RR, 0.49; CI, 0.35-0.68). These beneficial findings were offset by an increased risk of preprocedure cramps in the misoprostol group (RR, 1.40; CI, 1.05-1.86), but no significant increase in nausea, vomiting, or diarrhea. Notably, treatment did not influence the overall risk of failed IUD placement (4/86 [4.1%] misoprostol, 3/93 [3.2%] in the placebo group), but was associated with a trend toward increased expulsion within 30 days (3/82 [3.7%] misoprostol, 1/90 [1.1%] placebo). In the published structured abstract for this paper, under the section "limitations, reasons for caution," the authors state that "the positive results do not imply that use of misoprostol is imperative prior to IUD insertion in nulligravidas and IUD insertion should not be canceled when the medication is unavailable," and then add under the header "wider implications of the findings" that "in view of its effect in promoting cervical dilatation, misoprostol may be used prior to IUD insertion both in nulligravidas and in any women with cervical stenosis irrespective of parity."

■ COMMENTARY

The use of misoprostol in gynecology is quickly becoming like the use of bacon in cuisine. Since it is tasty and good in some dishes, many chefs (and investigators) want to wrap it around everything. While this might appeal to teenage boys with the appetite and metabolism to withstand the dietary assault, common sense would suggest that the strategy is gratuitous and potentially harmful. So is misoprostol prior to IUD placement something special, or just ham wrapped in bacon?

First, three prior randomized studies have failed to support a direct benefit to the routine use of misoprostol prior to IUD insertion.[1-3] The bottom line from all of these papers is that misoprostol does soften the cervix, but that this does not reduce the failed placement rate. The cervical softening also comes at the expense of significant side effects of cramping, bleeding, and nausea prior to the procedure. Some studies have also shown that procedure-related pain is actually increased rather than decreased. With no real benefit and potential harm, the intervention has lost favor among family planning experts.

But if the evidence is clear, why does the Scavuzzi paper deserve scrutiny? These investigators used vaginal administration of misoprostol to reduce troublesome gastrointestinal (GI) side effects. While the overall effect of no reduction in failed IUD placement was no different than with buccal misoprostol, it is not surprising that this approach worked to reduce GI side effects. The same strategy was commonly used for medical abortion (MAB) in the United States prior to 2005, when several cases of death associated with *Clostridium sordellii* were described in otherwise healthy women treated with oral mifepristone followed by vaginal misoprostol.[4] Although it is not clear whether the vaginal route of administration of misoprostol was a causal factor in these rare infections, the absence of any reports in Europe (where MAB was common and vaginal misoprostol was not used) led to shift in practice patterns away from vaginal administration in the United States. Since the change to buccal misoprostol for MAB, no further cases of *C. sordellii* have been reported. Although the risk of serious infection following IUD placement is not likely to be influenced by misoprostol, there are other considerations. Vaginal administration produces a lower and delayed peak drug level, but a longer overall duration of effect. For this reason, the investigators needed to place misoprostol in the vagina 4 hours prior to IUD insertion. Presumably, women could self-administer the drug prior to the clinic visit to avoid the unnecessary exam and extra clinic time, but we have no evidence that self-administration would be associated with the same clinical benefit, or that this self-administration would be acceptable. Of greater concern is the trend toward more expulsions seen with misoprostol use. Although the number of events was small in both groups, almost 4% of placements following misoprostol resulted in expulsion within 30 days compared with only 1% in the placebo group. Given that the intervention did not reduce the proportion of failed IUD placements (about 5% in the misoprostol group vs 3% in the placebo group), this tendency toward harm is deeply concerning.

The study by Scavuzzi et al is a good reminder of why it is important to read more than the abstract of any manuscript prior to altering clinical practice. Although the authors state that the data were analyzed according to intention-to-treat rules, outcomes were not presented for nine women randomized to misoprostol (including one woman who dropped out after receiving misoprostol and did not receive an IUD) and for two subjects randomized to placebo. Did the women who dropped out of the study experience severe cramps that led to their decision not to proceed with placement? If so, these women left the clinic with a less-effective method of contraception that placed them at higher risk of unintended pregnancy. While GI side effects were no different in the treatment groups, preprocedure cramping pain occurred more commonly in the misoprostol-treated subjects. Finally, the fact that the scale used to report ease of insertion was dichotomized as "easy" or "difficult/very difficult" rather than continuous or ordinal suggests the possibility of post-hoc data manipulation to obtain statistical significance.

Most IUD placements are straightforward and unevent-

ful, even in nulliparous women. That said, the procedure can be uncomfortable, and we need to be both honest and supportive as we counsel our patients. Gentle technique, reassuring words, and the judicious use of paracervical block when cervical dilation is needed can help considerably. Although further research is needed to identify strategies to improve the insertion experience, the current evidence does not support the routine use of misoprostol. ■

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Clinical Validation of Risk Stratification Criteria for Peripartum Hemorrhage

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *A study from Pittsburgh testing the efficacy of the California Maternal Quality Care Collaborative method for "at risky" patients for possible blood transfusion validated this commonly used protocol and demonstrated that adding more high-risk categories did not add to its efficiency.*

Source: Dilla AJ, et al. Clinical validation of risk stratification criteria for peripartum hemorrhage. *Obstet Gynecol* 2013;122:120-126.

THREE YEARS AGO, THE CALIFORNIA MATERNAL QUALITY Care Collaborative drafted guidelines on how to identify and prepare for patients who are at varying risk for developing peripartum hemorrhage.[1] Since then, these guidelines have been adopted by many hospitals around the country. Magee Women's Hospital in Pittsburgh is one of them, and recently authors from this institution published an instructive paper that tested the real-life efficacy of putting these guidelines into practice.[2] Also, the authors addressed the concept of adding other high-risk criteria to the existing California guidelines in an effort to capture even more patients who might benefit from expanded preparation.

During 2011, 10,134 women delivered at this hospital. Data were available to assign every patient to one of the California risk categories — low, medium, high — according to the guidelines in Table 1. In addition, the authors added another nine categories to the list. One addition was a model for abnormal placentation (accreta and percreta). Their simple endpoint was all peripartum hemorrhage — defined as a significant hemorrhage requiring at least one unit of red blood cells (RBCs).

There were 7060 patients in the low-risk category, 2462 in the medium-risk category, and 412 in the high-risk category. The rate of hemorrhage requiring RBCs was 1.4% (139 patients) in the entire group, with a rate of hemorrhage of 0.8%, 2%, and 7.3% in the low-, medium-, and high-risk groups, respectively. Of the 139 patients needing blood, 22% came from a high-risk group. When the authors reclassified the groups by adding their additional nine high-risk criteria, the new modified high-risk group included 85% of those needing blood, but the chance of this happening in the expanded category was only 2.6%.

■ COMMENTARY

The authors, while being candid about the lack of benefit from their modifications to the existing guidelines, were able to put the California screening and preparation strategies into proper perspective. For example, while typing and screening patients requires about 45 minutes in most hospitals, cross-matching only takes an additional 5 minutes in those hospitals using an electronic matching system now commonly employed in larger institutions. An additional 30-40 minutes is needed in hospitals where this is not available.

We always worry about being unprepared for an unexpected hemorrhage, and this is why the authors tested the concept of adding categories to up-risk more patients into a "more likely" group. A very aggressive strategy to capture more patients needing transfusion would be to type and cross-match everyone in the medium-risk group for two units of RBCs (instead of simply typing and screening them as advocated now), but it would mean that this ritual would have to be performed in 263 patients for every patient who would actually need blood (19 of 5005

Table. California Risk Categories

Low (No Prenatal Pretransfusion Testing Required)	Medium (Prenatal Type and Screen Performed, No RBC Units Cross-Matched)	High (2 Units of RBCs Cross-Matched)
No previous uterine incision	Previous cesarean delivery or uterine surgery	Placenta previa, low-lying placenta
Singleton pregnancy	Multiple gestation	Suspected placenta accreta or percreta
4 or fewer previous vaginal deliveries	More than 4 previous vaginal deliveries	Hematocrit < 30 and other risk factor
No known bleeding disorder	Chorioamnionitis	Platelets < 100,000
No history of peripartum hemorrhage	History of peripartum hemorrhage	Active bleeding (greater than show) on admission
	Large uterine leiomyoma	
	Estimated fetal weight > 4 kg	Known coagulopathy
	Morbid obesity (BMI > 35 kg/m^2)	

RBC = red blood cell, BMI = body mass index

Adapted from: Bingham D, et al. The California Maternal Quality Care Collaborative (CMQCC). CMQCC Obstetric Hemorrhage Hospital Level Implementation Guide. Palo Alto, CA: California Maternal Quality Care Collaborative; 2010.

patients). The authors postulated that if a protocol for typing and cross-matching is to be effective, more than 5% of the high-risk group would need to be transfused, and the only group in the study falling into that category was the high-risk group (7.3%). This should validate the California protocol. Also, as the authors point out, just expanding the California protocol's high-risk category to include any of the authors' five best predictors of hemorrhage would add 10 times more patients to the high-risk group, and, even then, only 2.6% in this bloated group would need a transfusion. Last, the "adding more" concept needs to be put into perspective when one realizes that it only takes about 5 minutes to cross-match the blood in most hospitals and that uncrossed type O blood is usually immediately available with little risk of hemolysis in those clinical situations where waiting is not an option.

The obvious conclusion that can be drawn from this study is that the California protocol, drafted from expert opinion alone, has stood up to scrutiny in a single institution investigation involving large numbers of patients. ■

References

1. Bingham D, et al. The California Maternal Quality Care Collaborative (CMQCC). CMQCC obstetric hemorrhage hospital level implementation guide. Palto Alto, CA: California Maternal Quality Care Collaborative; 2010.
2. Dilla AJ, et al. Clinical validation of risk stratification criteria for peripartum hemorrhage. *Obstet Gynecol* 2013;122:120-126.

CME Questions

1. **Which of the following is FDA approved as a daily-use contraceptive agent?**
   a. Ulipristal acetate
   b. Norethindrone
   c. Desogestrel
   d. Leuprolide acetate

2. **Which of the following best describes the Childhood Cancer Survivor study results or its design?**
   a. The trial was a randomized, controlled, cohort trial.
   b. The primary study cohort were cancer patients under active treatment.
   c. Infertility was classified by two definitions — clinical and total infertility.
   d. Dosing of non-alkylating agents was indexed to measure effect on future fertility.
   e. Successful pregnancy in cancer survivors reporting infertility was less than 50%.

3. **Compared to placebo, the use of vaginal misoprostol 4 hours prior to IUD placement in nulliparous women resulted in a:**
   a. nonsignificant trend toward an increase in expulsion during the first 30 days after insertion.
   b. significant reduction in the risk of failed IUD placement.
   c. decrease in painful cramps prior to the insertion procedure.
   d. significant increase in nausea prior to the procedure.

4. **Which of the following does *not* fit the CMQCC recommendations regarding screening for peripartum hemorrhage?**
   a. Low-risk patients requiring no pre-transfusion testing.
   b. Patients with platelet counts of < 100,000 are in the medium-risk category.
   c. Those with active bleeding should be typed and crossed for two units of RBCs.
   d. Those with Hct < 30% should be in the high-risk category.

In Future Issues:

See-and-Treat for Cervical Intraepithelial Lesions

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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Once-daily Tadalafil for ED: Efficacy and Safety

Source: Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

Psychological Disorders: How to Give Patients What They Want and What They Need

Source: McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

Reducing Stroke Risk After TIA or Minor Ischemic Stroke

Source: Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

Long-term Mortality Among Adults with Asthma

Source: Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

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Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Source: The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

New Hope for Hepatitis C Patients

Source: Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■