What types of exercises are best for treatment of patellofemoral pain syndrome (PFPS)?

Evidence-based answer

For short-term relief of PFPS, hip exercises alone or combined with quadriceps exercises are superior to quadriceps exercises alone or no treatment (SOR: A, consistent RCTs).

Evidence summary

Quadriceps strengthening exercises are commonly prescribed for PFPS. Four recent small studies, however, investigated the effectiveness of hip strengthening exercises in predominantly female populations.

A recent RCT enrolled 70 sedentary women aged 20 to 40 years diagnosed with PFPS of at least 3 months’ duration and divided them into 3 groups: a knee exercise (KE) group, a knee and hip exercise (KHE) group, or a control group receiving no treatment. Outcome measures included an 11-point numerical pain rating scale (NPRS) during stair ascent and descent and 3 functional scales.

At 4 weeks, both the KE and KHE groups had significant improvement in all measures compared with both the baseline and control groups. Between-group comparisons were not reported.

Another RCT compared hip abductor and lateral rotator muscle strengthening exercises plus quadriceps strengthening exercises with quadriceps strengthening exercises alone in 14 men and women aged 17 to 40 years with PFPS. After 6 weeks, the hip plus quadriceps group had a significant reduction in pain compared with baseline for usual pain (–3.6; P=.03) and worst pain (–2.6; P=.03) as measured on a 10-cm visual analog scale (VAS). The quadriceps-only group did not change compared with baseline in usual pain (–1.5; P=.31) and worst pain (–1.3; P=.20). Between-group comparisons were not reported.

A third RCT compared hip strengthening with quadriceps strengthening for 4 weeks prior to both groups engaging in 4 weeks of functional weight-bearing exercise. Thirty-three women aged 16 to 35 years diagnosed with PFPS for more than 1 month were recruited as a convenience sample.
After 4 weeks, the hip strengthening group had a significant decrease from baseline in mean pain scores (on a 10-point VAS) from 4.6 to 2.4 (\(P = .001\)), while the quadriceps strengthening group scores did not change significantly from 4.2 to 4.1 (\(P = .88\)). The differences between groups was significant (\(P = .035\)). After the additional 4-week functional weight-bearing exercise program, the between-group difference became nonsignificant.\(^{3}\)

A final RCT compared an 8-week hip strengthening program with a control group receiving analgesics for 28 women diagnosed with PFPS of at least 6 months’ duration.\(^{4}\) Outcomes were pain assessed on a 10-cm VAS and pain, stiffness, and function assessed using the 24-item Western Ontario and McMaster University (WOMAC) questionnaire, which has a best score of 0 and worst score of 96.

At 8 weeks, the hip strengthening group had a significant difference of –6.4 (95% CI, –7.9 to –4.9) in mean pain scores compared with baseline and a significant difference of –43 (95% CI, –55 to –32) on the WOMAC score, while the control group had no significant differences. Between-group comparisons were not reported.\(^{4}\)

**TABLE**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Explanation</th>
<th>Knee and hip exercises vs controla (95% CI)</th>
<th>Knee exercises vs controlb (95% CI)</th>
<th>Knee and hip vs knee exercisesa (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Lower extremity functional scale</td>
<td>Difficulty in performing 20 tasks (80-point scale; higher scores = better function)</td>
<td>14 (6.4–22)</td>
<td>7.6 (3.2–12)</td>
<td>6.6 (–1.5 to 14)</td>
</tr>
<tr>
<td>Anterior knee pain scale</td>
<td>Rating of pain with 13 tasks (100-point scale; higher scores = better function)</td>
<td>14 (7.4–21)</td>
<td>9.5 (2.9–16)</td>
<td>4.8 (–2.9 to 13)</td>
</tr>
<tr>
<td>Single limb hop test</td>
<td>Distance in centimeters</td>
<td>16 (8.3–24)</td>
<td>11.1 (3.4–18)</td>
<td>5.2 (–4.9 to 15)</td>
</tr>
<tr>
<td>NPRS ascending stairs</td>
<td>0 = no pain, 10 = worst imaginable pain</td>
<td>–2.3 (–3.4 to –1.2)</td>
<td>–1.6 (–2.4 to –0.8)</td>
<td>–0.7 (–2.0 to 0.6)</td>
</tr>
<tr>
<td>NPRS descending stairs</td>
<td>0 = no pain, 10 = worst imaginable pain</td>
<td>–2.3 (–3.5 to –1.1)</td>
<td>–0.7 (–1.9 to 0.5)</td>
<td>–1.6 (–3.0 to –0.2)</td>
</tr>
</tbody>
</table>

\(^{a}\)Values are the differences between groups in the mean change from baseline. \(\text{NPRS=numerical pain rating scale.}\)

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Elsaid Rabie, MD
Thomas Satre, MD
U of MN/St. Cloud Hospital FMR
St. Cloud, MN

**REFERENCES**

From the Editor

Early warning systems

Dear EBP Readers,

On a recent trip to Montana, my brother and I were PUTTING around a mesa top, listening to the meadow birds and the whistles of prairie dogs standing guard over their burrows. Since my brother likes a bit of excitement, he suddenly decided that this was a good place to look for snakes. He made his way back to the truck and got out his snake stick—essentially a long mechanical claw—and went hunting.

My brother has a good eye for snake habitats and he strode directly to a jumble of boulders on the edge of the mesa. In less than five minutes, he found something scaly tucked deep into a crack. He called me over to have a look.

When I got there, my brother had sufficiently disturbed the critter with the stick. I could hear a loud, incessant buzzing sound informing everything around and the Big Sky above that my brother had ticked off a rattlesnake.

The pit vipers’ rattle is one of the great early warning systems of the natural world. In comparison, the early warning system we use in medicine—the FDA black box label—looks pretty lame.

Far from Montana’s Front Range, a group of investigators reviewed 20 top-selling medications from different drug classes—10 with black box warnings and 10 without. They then reviewed the FDA labeling of all other medications in those classes (176 agents). Turns out it took an average of 5 years for a black box warning applied to 1 of the index medications to appear on other medications of the same class. In some cases, medications were completely withdrawn from the market after receiving a black box warning; meanwhile, other members of the same class never received a black box warning at all.

This is something like the FDA issuing rattles to only some of its rattlesnakes. Sure, the prairie rattler my brother found wasn’t nearly as venomous as, say, a Mojave green. But fortunately for us, it had a RATTLE too. I like that kind of consistency, and think it dang curious that even “low down snakes” have a more consistent early warning system than we doctors do.

Regards,

Jon O. Neher, MD

Corticosteroids plus physiotherapy for lateral elbow pain


This RCT compared corticosteroid injection and placebo injection (with and without physiotherapy) for the treatment of unilateral lateral epicondylalgia. One hundred sixty-five patients were randomized into 1 of 4 groups: corticosteroid injection (CSI) alone, CSI plus physiotherapy (PT), placebo injection (PI) alone, and PI with physiotherapy. Participants were blinded to the type of injection. The physiotherapy groups received eight 30-minute standardized PT and exercise sessions. The primary outcomes measured were global rating of change at 4, 8, 12, 26, and 52 weeks using a 6-point Likert scale ranging from “complete recovery” to “much worse” and 1-year recurrence.

Corticosteroid injection had a lower proportion of improvement at 1 year versus placebo injection (83% vs 96%; RR 0.86; 99% CI, 0.75–0.99; NNT=7.5) and a higher recurrence rate (54% vs 12%; RR 0.23; 99% CI, 0.10–0.51; NNT=2.4). At 26 weeks, the CSI group demonstrated lower rates of complete recovery or much improvement compared with placebo (55% vs 85%; RR 0.79; 99% CI, 0.62–0.99; NNT=5.5). PT did not demonstrate any effects on the primary or secondary outcomes at any of the time points.

**Bottom line:** Corticosteroid injections for lateral epicondylalgia do not lead to decreased pain or decreased rate of recurrence. Adding physiotherapy to corticosteroid or placebo injections provides no additional benefit.

**Review Author and Summary Author:** Sonia Oyola, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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Use of inhaled glucocorticoids in childhood asthma reduces adult height


This is a follow-up study of the Childhood in Asthma Management Program (CAMP), which randomly assigned 1,041 children, aged 5 to 12 years, with mild to moderate asthma to 400 mcg budesonide per day, 8 mg nedocromil per day, or placebo. The initial study in 2000 found that the group who used budesonide had a mean increase in height that was 1.1 cm less than the increase in height associated with placebo. In this study, adult height was obtained in 943 of the original participants (90.6%) after a mean follow-up of 13 years.

The mean adult height in the budesonide group was 1.2 cm lower than in the placebo group (171.1 vs 172.3 cm; *P*=.001); the mean height in the nedocromil group was similar to the placebo group (172.1 cm; *P*=.61). The decrease in mean height in the budesonide group compared with the placebo group was 1.3 cm; (95% CI, −1.7 to −0.9) after the first 2 years of treatment and 1.2 cm measured at adulthood (95% CI, −1.9 to −0.5), indicating that the height deficit occurred early in treatment and persisted into adulthood and was not progressive or cumulative. In addition, the effect occurred in prepubertal participants. Finally, children who took a larger daily dose of budesonide during the first 2 years were found to have a lower adult height (−0.1 cm for each microgram per kilogram; *P*=.007 for trend).

**Bottom line:** Inhaled glucocorticoids used in prepubertal children with mild to moderate asthma will result in a 1.2-cm permanent decrease in adult height. Physicians should weigh the risks and benefits of using inhaled glucocorticoids and counsel parents about this effect on adult height. The effect on height is dose dependent and other drugs should be considered before increasing the glucocorticoid dose.

**Review Author and Summary Author:** Mari Egan, MD, The University of Chicago, Department of Family Medicine, Chicago, IL
What is the effect of breastfeeding on dental caries?

**Bottom line**

Based on the best evidence available, breastfeeding neither predisposes children to nor protects them from early childhood caries.

**Evidence summary**

The World Health Organization recommends continuing breastfeeding for at least the first year of life and beyond, as long as mutually desired by mother and child. In contrast, the American Academy of Pediatric Dentistry recommends weaning children from the bottle or breast by age 12 to 14 months due to concern about early childhood caries. However, studies have had conflicting results. An early systematic review (published in 2000) could not draw any satisfactory conclusions due to inconsistent definitions of both early childhood caries and breastfeeding.

A 2007 study analyzed data collected via cross-sectional survey in 1999–2002 from the National Health and Nutrition Examination Survey (NHANES). Data for 1,576 children ages 2 to 5 years old were reviewed, including the frequency of early childhood caries (ECC) and severe early childhood caries (S-ECC). Overall, 60% of children were reported to have ever been breastfed and these children had lower rates of ECC and S-ECC compared with those who never breastfed; however, these differences were not statistically significant when using the study’s predetermined P<.01 cutoff.

Children breastfed for 1 year or longer were more likely to have ECC than children breastfed for less than 1 year (32.8% vs 22.5%; P<.01) but not S-ECC (adjusted odds ratio [aOR] 1.18; 95% CI, 0.59–2.34). When adjusted for poverty status, maternal age at child’s birth, and maternal prenatal smoking, however, breastfeeding was associated with a 40% reduced risk for ECC and S-ECC (aOR 0.6; 95% CI, 0.4–0.9 for both ECC and S-ECC).

A much smaller study conducted in Finland (N=144) showed equal prevalence of caries at age 5 years regardless of breastfeeding duration of >12 months or <12 months.

A study (N=227) conducted in Kuwait (in the setting of low fluoride in the water supply) on children age 18 to 48 months showed that breastfed children were significantly less likely to have caries than were children who were bottle-fed from birth. Although the practice of feeding throughout the night after age 6 months was associated with “nursing caries” (P<.01), bottle-fed children were more likely than breastfed children to develop these caries.

**References**


How effective are family educational interventions at reducing emergency department (ED) utilization by children with asthma?

**Bottom line**

Family educational interventions are highly effective in reducing ED utilization by children with asthma, especially when coupled with regular follow-up by a case manager. Patients and their families can be taught to recognize asthma triggers, symptoms, and avoidance techniques (SOR: A, consistent RCTs).

**Evidence summary**

A controlled clinical trial of 78 children (2–16 years old) with asthma and frequent ED usage investigated the efficacy of educational and medical care versus medical care only in reducing ED visits. Subjects were alternately assigned to either the intervention (n=38) or control group (n=40). Children and their caretakers in the intervention group received normal medical care with 1 individual asthma education session that covered asthma triggers, environmental controls, symptoms, warning signs, medications use, and use of spacers and peak flow meters. Reinforcement of this education occurred at follow-up visits at 1, 6, and 12 months in addition to once-monthly contact by an outreach nurse to inquire about health status, review medication administration, and refill prescriptions. The control group received routine medical care.

The mean number of ED visits for the intervention group decreased from 3.6 to 1.7 visits per child (P<.05); hospitalizations decreased from 0.6 to 0.2 per child (P<.001) and average hospital days decreased from 2.4 days to 0.9 day per child (P<.001). The control group outcome measures did not change significantly. Notably, children in the control group were 1.4 (95% CI, 1.02–1.91) times more likely to have an ED visit and 2.4 (95% CI, 1.04–5.42) times more likely to be hospitalized for asthma.

In a RCT, 57 children with asthma (1–15 years old) were assigned to either an asthma education intervention (n=29) or a control group (n=28). Given to both patients and caregivers, the intensive asthma education included information about triggers, medications, and environmental control including smoking and allergens. Both groups received this single-intensive asthma education, but the control group remained in close contact with the asthma outreach program nurse throughout the year through telephone calls and visits.

Compared with baseline, the intervention group had a 73% reduction in ED visits (P=.0002), an 84% reduction in hospitalizations (P=.0012), and an 82% reduction in healthcare costs (P=.0001). The control group had a 39% reduction in ED visits, a 43% reduction in hospitalizations, and a 28% reduction in healthcare costs. Compared with the control group, the intervention group had fewer ED visits and hospitalizations (P<.05) and lower costs (P<.001).

A RCT of 87 children (3–12 years old) investigated the effectiveness of an educational intervention in decreasing environmental tobacco smoke exposure in children with asthma. The intervention group (n=44) education consisted of 3 counseling sessions by a nurse-educator over 5 weeks concerning asthma and its treatment, environmental controls, and the role of environmental smoke exposure in exacerbating and sustaining inflammation. The control group (n=43) received usual medical care that consisted of basic information about asthma and their medication regimen.

With the intervention, the asthma-related ED and urgent care visit rate decreased from 50% in the baseline year to 29.6% in the follow-up year (OR 0.32; P=.03). The control group had an increase in asthma-related ED and urgent care visits, from 37.2% to 46.5%.

Sara Sietsema, DO
Sam Teferra, MD
Research FMRP
Kansas City, MO

**REFERENCES**

What botanicals are safe and effective for the estrogen deficiency symptoms of menopause?

Evidence-Based Answer

Soy may reduce hot flash frequency (SOR: B, inconsistent RCTs). Red clover and black cohosh are not effective in treating vasomotor symptoms of estrogen deficiency (SOR: A, systematic review and RCTs). Safety has been shown with the use of some botanicals for up to 1 year (SOR: C, underpowered RCT).

Vasomotor symptoms occur in more than 50% of women going through menopause.¹

In 2006, a systematic review and meta-analysis of 43 randomized, double-blind placebo-controlled trials investigated the efficacy and adverse effects of nonhormonal therapies for menopausal hot flashes.¹ This review included treatments with isoflavone extracts from red clover and soy. Six trials (N=403) lasting 12 to 16 weeks examined the use of red clover. Patients received Promensil 40 to 160 mg/d or Rimostil 57 mg/d.

Compared with placebo, red clover use had no significant reduction of daily hot flashes (mean difference [MD] –0.44; 95% CI, –1.47 to 0.58). Out of 11 soy trials, 4 (n=404) lasting 12 to 16 weeks were able to be pooled (because they reported hot flash frequency and evaluated soy isoflavones extracts of 50–70 mg/d) and found a significant reduction of daily hot flashes when compared with placebo (MD –0.97; 95% CI, –1.8 to –0.12). However, the 11 soy trials were generally contradictory: 5 trials showed an improvement (either frequency or severity of symptoms) and 6 trials revealed no difference between soy and placebo.¹

The Herbal Alternatives for Menopause Trial (HALT) was a randomized, double-blind placebo-controlled trial evaluating the frequency of hot flashes and night sweats per day using a naturopathic approach over 1 year.² The study included 351 women and had 3 treatment arms evaluating botanical products.

Compared with placebo, no significant change was noted in hot flashes and night sweats per day with black cohosh 160 mg/d (n=80; MD –0.54; 95% CI, –1.5 to 0.38), a multibotanical product including black cohosh 200 mg/d along with 9 other botanicals (n=76; MD 0.43; 95% CI, –0.50 to 1.4), or a multibotanical product and dietary advice on increasing daily soy intake (n=79; MD 0.09; 95% CI, –0.83 to 1.0).²

In 2009, another randomized, double-blind placebo-controlled trial of 89 postmenopausal women assessed the safety and efficacy of black cohosh 128 mg/d and red clover 398 mg/d to treat vasomotor symptoms for more than a year.³ Black cohosh (n=22) and red clover (n=22) were not found to significantly reduce the episodes of hot flashes and night sweats per week compared with placebo (difference in mean change –11 episodes per week, P=.25; and –0.07 episodes per week, P=.99, respectively). Safety measurements were not significantly different between botanicals and placebo during daily administration for 1 year.

Marcie Cain, MD
Janice Frueh, PharmD
SIU Springfield FMRP
Springfield, IL

What are the indications for intrapartum amnioinfusion?

Evidence-Based Answer

In laboring patients with meconium-stained fluid, amnioinfusion does not alter the overall cesarean section rate or the incidence of meconium aspiration syndrome, although neonatal intensive care unit (NICU) admissions may be reduced. Amnioinfusions do decrease the overall C-section rate in patients with oligohydramnios (SOR: B, systematic reviews of RCTs with heterogeneity). Evidence-based guidelines recommend amnioinfusion to decrease the recurrence of variable decelerations and C-section for abnormal fetal heart rate (FHR) patterns, but not for meconium-stained amniotic fluid, preterm premature rupture of membranes (PPROM), or for prevention of pulmonary hypoplasia in very preterm PPROM (SOR: B, evidence-based guideline).

A Cochrane review of 13 RCTs examined the use of intrapartum amnioinfusion for meconium stained amniotic fluid.³ The review included 4,143 women with singleton vertex pregnancies at 34 weeks to near term/term with trace to thick meconium, and compared transcervical infusion of saline with no intervention.
In patients who received continuous fetal monitoring, amnioinfusion compared with no intervention did not reduce the overall C-section rate (11 trials, N=3,380 women; RR 0.78; 95% CI, 0.60–1.02) or the incidence of meconium aspiration syndrome (11 trials, N=3,374 women; RR 0.52; 95% CI, 0.26–1.1). There was a reduction in C-sections for fetal distress (8 trials, N=2,765 women; RR 0.40; 95% CI, 0.19–0.86) and NICU admissions (3 trials, N=472; RR 0.45; 95% CI, 0.23–0.90). However, the studies were heterogeneous, and a planned sensitivity analysis excluded all studies with high risk for bias except one. 

For patients receiving intermittent monitoring, amnioinfusion compared with no treatment decreased NICU admissions (2 trials, N=853; RR 0.52; 95% CI, 0.37–0.73) and meconium aspiration syndrome incidence (2 trials, N=852; RR 0.25; 95% CI, 0.13–0.47). While amnioinfusion reduced C-section rates for fetal distress (2 trials, N=855; RR 0.50; 95% CI, 0.30–0.84), there was no difference in overall C-section rates (2 trials, N=845; RR 0.70; 95% CI, 0.49–1.0). Limitations of the studies included lack of obstetrician blinding, various amnioinfusion rates and volumes, and small study size.

A separate Cochrane review of 19 RCTs (N=2,217) examined amnioinfusion in the context of potential or suspected umbilical cord compression in labor for 3 indications: (1) FHR decelerations (therapeutic amnioinfusion); (2) oligohydramnios without FHR decelerations (prophylactic amnioinfusion); and (3) other indications (eg, PROM, PPROM, postdate pregnancies with oligohydramnios, intrauterine growth restriction with oligohydramnios) in laboring, singleton pregnancies with >26 weeks’ gestation and otherwise uncomplicated pregnancies.

Compared with no intervention, amnioinfusion decreased overall C-section rates in the subgroup with oligohydramnios (9 trials, N=982; RR 0.6; 95% CI, 0.42–0.85) and other indications (3 trials, N=361; RR 0.48; 95% CI, 0.27–0.86), C-section rates due to fetal distress in all 3 subgroups individually (composite result: 12 trials, N=1,588; RR 0.46; 95% CI, 0.31–0.68), and mild or severe birth asphyxia in the subgroup with oligohydramnios (1 trial, N=118; RR 0.32; 95% CI, 0.15–0.70). Limitations of the studies included small size (all but 3 were <200 patients), inconsistent reporting of attrition, and unclear blinding. Most studies included heterogenous indications for amnioinfusion therapy, thereby making it difficult to isolate specific clinical indications for which amnioinfusion actually improved outcomes.

The American College of Obstetrics and Gynecology (ACOG) recommends amnioinfusion to decrease the recurrence of variable decelerations as well as the rate of C-section for abnormal FHR patterns. ACOG does not recommend amnioinfusion for meconium-stained amniotic fluid, PPROM, or for prevention of pulmonary hypoplasia in very preterm PROM (ACOG SOR: B, based on limited or inconsistent scientific evidence).

Fred Pfenniger, MD
Tacoma FMR Rural Fellowship
Tacoma, WA

Enrique Leon, MD
Janelle Guirguis-Blake, MD
Tacoma FMRP
Tacoma, WA

Evidence-Based Answer

Is increased fall risk a significant predictor of major bleeding events in patients on warfarin?

A retrospective cohort study reviewed 19,500 Medicare patients with atrial fibrillation (AF), 1,245 of whom were determined to be high risk for falls and 420 of those on warfarin therapy. After adjusting for factors (prior stroke, prior bleeding, and neuropsychiatric impairment) associated with a higher incidence of intracranial hemorrhage (ICH), warfarin use in patients at risk of falls was not associated with increased risk of ICH (HR 1.0; 95% CI, 0.8–1.4) compared with no treatment.

Moreover, using a model that controlled for bleeding risk factors, aspirin prescription, nursing home residency, and sex, the investigators showed that warfarin was significantly protective in patients with
2 or more CHADS2 points (regardless of their fall risk), for the composite outcome of hospitalization for stroke, any hemorrhage (including ICH), myocardial infarction, or out-of-hospital death (HR 0.75; 95% CI, 0.61–0.91) compared with patients not on warfarin. A key limitation of this study was the absence of clear criteria for identifying who was at risk of falls.1

A retrospective study looked at 2,633 falls in a tertiary-care hospital over a 4-year period, to compare the rate of major hemorrhagic complications (defined as any ICH, as well as bruising or cuts that required immediate attention from a physician) in patients who received anticoagulation with those who did not.2 Of the patients who suffered falls, 379 were taking warfarin. Patients taking warfarin were less likely to suffer a fall-related major hemorrhagic injury compared with persons not taking antithrombotic therapy (6% vs 11%; \( P = .01 \)). The authors acknowledged that there may have been selection bias in favor of prescribing warfarin for patients robust enough to be at lower risk of suffering a fall-related hemorrhagic injury.

Another trial used a Markov decision analysis (a model to compare risk estimates in separate disease states) to evaluate whether the risk of ICH from falls should influence choice of anticoagulation therapy (warfarin, aspirin, or no treatment) in elderly patients with AF.3 Input data for the different variables were obtained by systematic review of the literature.

Using prospective data from 7 cohort studies with a total of 2,181 patients ≥65 years of age, the authors estimated that annual fall rate was 33% in this patient population. Combining this rate with data from 5 prospective cohort studies and retrospective case series from anticoagulation clinics (5,000 patients), they calculated that the relative risk of ICH in those who fall was 1.4, compared with those who do not fall. Stroke reduction benefits from anticoagulation in AF were taken from a meta-analysis of 5 RCTs (>4,000 patients).3

Combining these estimates, the authors used their model to determine which therapeutic strategy (warfarin, aspirin, or none) in patients with AF and risk of falling produced the highest quality-adjusted life year score (QALY). For patients at risk of stroke and falling, warfarin therapy was still associated with the highest QALYs gained (13 with warfarin vs 11 with aspirin therapy vs 10 with no antithrombotic therapy). Sensitivity analysis demonstrated that the risk of falling was not an important factor in determining optimal antithrombotic therapy. The authors concluded that, based on their calculations, a patient with AF would need to fall 295 times in a year for the risk of ICH to outweigh the stroke reduction benefit of warfarin.6

Roman Zassoko, MD
Bachir Tazkarji, MD
University of Toronto
Trillium Health Partner, Mississauga Hospital
Mississauga, ON, Canada


At what age should an infant with hydrocele be referred for surgery?

Evidence-Based Answer
Most hydroceles resolve spontaneously within the first year of life. Surgery referral is usually indicated only if the hydrocele persists beyond 12 to 18 months of age. Indications for earlier referral include large hydroceles causing pain or hydroceles with an associated inguinal hernia (SOR: B, observational studies).

A hydrocele is found in about 4.7% of newborn males.1 A 5-year prospective trial evaluated the prevalence and outcomes of hydroceles in 2,715 male neonates undergoing circumcision. During the study period, 128 patients were diagnosed with 163 cases of congenital hydrocele. Of these 163 hydroceles, 75 (46%) were communicating and 88 (54%) were noncommunicating. A total of 136 of the 163 cases resolved spontaneously by 18 months of age, with peak resolution at 4 to 6 months and no spontaneous resolution occurring after 18 months. Only 27 cases in 25 patients (0.9%) had surgery after failure of resolution by 24 months. There was no statistical difference in resolution between infants with communicating and noncommunicating hydroceles.1

In a prospective cohort study involving 121 patients younger than 1 year of age at a hospital in Baghdad, Iraq followed over 4 years, 108 patients (89%) with hydroceles had spontaneous resolution or showed marked improvement during the first 12 months of life with only 11% requiring surgical repair.2

Continued
Of the patients with spontaneous improvement, 76 (63%) had complete resolution, 21 (17%) had marked improvement, and 11 (9%) had gradual improvement. Surgery in this study was only offered in the presence of an associated inguinal hernia (7%) and development of a huge hydrocele causing pain (3%).

In a retrospective cohort study, 174 male infants younger than 18 months of age with communicating hydroceles at a pediatric urology clinic were evaluated for hydrocele outcomes. Only 110 were followed until a final disposition of spontaneous resolution or surgical correction was reached.

Of the 110 who completed the study, 69 (63%) had complete spontaneous resolution, while 41 (37%) underwent surgical repair after no improvement after 6 months of follow-up. The hydroceles of the 64 patients who were lost to follow-up had shown improvement without complete resolution prior to leaving trial. The 6 (3.4%) patients who presented between 12 and 18 months of age did no worse than those initially seen before 1 year of age.

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Bridgette Coker, MD
Shobha Rao, MD
Baylor FMR
Garland, TX


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**Does omega-3 fatty acid supplementation provide cardiovascular benefits?**

**Evidence-Based Answer**

Increasing omega-3 fatty acid intake does not provide primary or secondary mortality benefit or cardiovascular protection (SOR: A, meta-analyses).

A Cochrane review that included 48 RCTs with nearly 37,000 patients and 41 cohort studies with more than 500,000 patients assessed the effect of oral omega-3 fatty acids on mortality and cardiovascular events. Omega-3 fatty acids (as a supplement and taken as food after dietary advice) had no significant effect on total mortality compared with placebo or no such dietary advice (44 trials, N=36,000; risk ratio [RR] 0.87; 95% CI, 0.73–1.0). There was still no difference when only studies with a low risk of bias were included (6 trials, N=15,000; RR 0.98; 95% CI, 0.17–1.4).

There was no significant effect on cardiovascular events in the larger data set (31 trials, N=35,000; RR 0.95; 95% CI, 0.82–1.2) or among studies with a low risk of bias (7 trials, N=15,000; RR 1.1; 95% CI, 0.87–1.4). There was no significant effect on cardiovascular death (44 trials, N=36,000; RR 0.85; 95% CI, 0.68–1.1), fatal myocardial infarction (MI) (38 trials, N=9,849; RR 0.86; 95% CI, 0.60–1.3), nonfatal MI (25 trials, N=17,000; RR 1.0; 95% CI, 0.70–1.5), sudden death (37 trials, N=19,000; RR 0.85; 95% CI, 0.49–1.5), or stroke (26 trials, N=33,000; RR 1.2 95% CI, 0.91–1.5).

There was a significant benefit on heart failure (20 trials, N=7,684; RR 0.51; 95% CI, 0.31–0.85), but the benefit was heavily dependent on 1 study with methodological problems and the benefit was lost when that study was removed. Omega-3 fatty acid use had no effect on weight, blood pressure, serum total cholesterol, or serum high-density lipoprotein cholesterol. Omega-3 fatty acid use was associated with lower triglyceride levels (14 trials, N=2,096; WMD –0.40 mmol/L; 95% CI, –0.56 to –0.23) and increased low-density lipoprotein levels (12 trials, N=1,673; WMD 0.13 mmol/L; 95% CI, 0.03–0.22).

A meta-analysis of 20 RCTs included nearly 69,000 patients to determine the association between omega-3 polyunsaturated fatty acids (PUFAs) taken as supplements or in foods and major cardiovascular outcomes. The median treatment duration was 2 years. The mean omega-3 dose was 1.5 g/d (0.77 g/d eicosapentaenoic acid [EPA], 0.60 g/d docosahexaenoic acid [DHA]).

Compared with placebo and standard diets, high omega-3 PUFA intake did not significantly reduce all-cause mortality (17 trials, N=63,000; RR 0.96; 95% CI, 0.91–1.0), sudden death (7 trials, N=42,000; RR 0.87; 95% CI, 0.75–1.0), risk of MI (13 trials, N=54,000; RR 0.89; 95% CI, 0.76–1.0), or stroke (9 trials, N=53,000; RR 1.1; 95% CI, 0.93–1.2). Another meta-analysis included 14 RCTs investigating the effect of omega-3 fatty acid supplements in more than 20,000 patients with existing cardiovascular disease. The mean follow-up period was 2 years. The mean daily dose of EPA or DHA was 1.7 g/d.
Compared with placebo, omega-3 acid supplementation did not reduce overall cardiovascular risk (14 trials, N=20,000; RR 0.99; 95% CI, 0.89–1.1), all-cause mortality (13 trials, N=20,000; RR 0.96; 95% CI, 0.90–1.0), sudden cardiac death (5 trials, N=12,000; RR 0.93; 95% CI, 0.66–1.3), MI (11 trials, N=16,000; RR 0.81; 95% CI, 0.65–1.0), fatal MI (5 trials, N=15,000; RR 0.87; 95% CI, 0.67–1.1), nonfatal MI (7 trials, N=10,000; RR 0.86; 95% CI, 0.65–1.1), angina and unstable angina (7 trials, N=1,700; RR 0.77; 95% CI, 0.50–1.2), congestive heart failure (6 trials, N=8,400; RR 0.92; 95% CI, 0.73–1.2), transient ischemic attack and stroke (7 trials, N=10,000; RR 1.1; 95% CI, 0.77–1.7), or cardiovascular death (10 trials, N=14,000; RR 0.92; 95% CI, 0.35–1.0).\(^1\)

**Is immediate IUD insertion after childbirth effective and safe?**

**Evidence-Based Answer**

Immediate intrauterine device (IUD) insertion after childbirth is generally safe and effective. The spontaneous expulsion rate, however, may be as high as 17% to 24% (SOR: B, heterogeneous RCTs).

A 2010 Cochrane review with 9 RCTs of postpartum women compared IUD insertion within 10 minutes of passage of the placenta with different devices, insertion techniques, and insertion timing.\(^1\) Only 1 of the RCTs (N=102, mean age 25 years) examined immediate postpartum versus delayed IUD insertion (inserted 6–8 weeks after delivery). The expulsion rate for a levonorgestrel-releasing IUD at 6 months was higher in the immediate insertion group than the delayed group (24% vs 4%; OR 6.8; 95% CI, 1.4–32).\(^2\) No pregnancies occurred in either group. Infrequent complications included 1 case of chlamydia pelvic inflammatory disease (PID) in the immediate group and 1 case of trichomoniasis PID in the delayed group. No uterine perforations occurred in either group.\(^3\)

A 2011 prospective, uncontrolled cohort study in Turkey of 245 pregnant woman with scheduled cesarean section delivery (age range 18–41 years, mean age 26 years) examined the efficacy and safety of immediate insertion of a TCu 380A (copper) IUD using a ring forceps within 10 minutes of removing the placenta during cesarean section delivery.\(^3\) At the 12-month follow-up, the IUD expulsion rate was 17%. The study had no serious complications (including endometritis or uterine perforations). This study was limited by a lack of a comparable control.

The American College of Obstetricians and Gynecologists (ACOG) advises that “the immediate post-partum period is a particularly favorable time for IUD insertion” and that the practice appears safe and effective (level B recommendation: “based on limited or inconsistent scientific evidence”).\(^4\) ACOG acknowledges that the expulsion rate is higher with immediate postpartum insertion compared with interval insertion.

**Are postmenopausal women taking calcium supplementation at an increased risk of myocardial infarction?**

**Evidence-Based Answer**

Calcium supplementation (with or without concurrent vitamin D supplementation) may increase the risk of myocardial infarction (MI) in healthy postmenopausal women, but the evidence is controversial because studies often included men and cardiovascular outcomes were not primary objectives of the studies (SOR: B, inconsistent systematic review and cohort studies).

A meta-analysis that included data from the Women’s Health Initiative limited access dataset plus 8 other RCTs of postmenopausal women was conducted to investigate whether calcium supplements (≥500 mg/d, average 800 mg/d) increased the risk of cardiovascular

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events in women with a mean age of 63 years who may have been taking calcium supplementation throughout the study.1 Data from the 9 studies (N=28,000), with an average duration of 5.7 years, showed an increased risk of MI in the calcium (with or without vitamin D) supplementation group of 24% (HR 1.2; 95% CI, 1.1–1.5) compared with women not taking calcium.

A 2010 systematic review of 9 prospective cohort studies and 8 RCTs included studies of men and women (total number of patients not reported) taking calcium supplementation and/or vitamin D that reported cardiovascular disease (CVD) data did not show any effect of calcium supplementation on the risk for MI; however, there was significant heterogeneity among studies and participant characteristics.2 An included meta-analysis of 4 of the RCTs (N=2,884, men and women, aged 40 to >70 years old, doses of calcium 600–1,200 mg/d) that examined the risk of calcium alone did not find an effect on the incidence of MI compared with placebo (risk ratio [RR] 1.1; 95% CI, 0.92–1.4). Only 3 RCTs overlapped between the meta-analysis above and this systematic review.

A subsequent prospective cohort study from 2012 was conducted to determine the associations of dietary calcium intake (total, dairy, or nondairy) and calcium supplementation with MI, stroke risk, and overall CVD mortality.3 Male and female patients (N=24,000) were recruited in 1994–1998; they had a mean age of 50 years (range 35–64 years), were free of major CVD events (MI, stroke, TIA), and were followed for an average of 11 years. A total of 354 MI cases, 260 stroke cases, and 267 CVD deaths were documented. Users of any calcium supplements (with or without concurrent vitamin D) had an increased risk of MI (HR 1.9; 95% CI, 1.2–3.0) in comparison with nonusers of any supplements. There was an even greater increase risk of MI in calcium-only users (no vitamin D) (HR 2.4; 95% CI, 1.1–5.1) compared with nonusers of supplements.

Another subsequent prospective cohort study included 1,460 women, with an average age of 75 years at baseline, taken from a randomized placebo-controlled trial designed to examine the efficacy of calcium carbonate 1,200 mg or placebo for preventing fractures.4 Patients were observed for 9.5 years and the group that received calcium for 5 years did not have a higher risk of death or hospitalization from atherosclerotic events (cardiac, cerebral, and peripheral vascular disease) (HR 0.92; 95% CI, 0.74–1.2) compared with patients previously randomized to placebo. Ischemic heart disease occurred in 4.7% of the calcium group patients compared with 4.9% of the placebo group, a difference that was not significant. The study may not have had enough power to detect a difference and it was unclear if patients who had taken placebo during the initial 5 years of the study were taking supplementation during the observational part of the study.

Mary Onysko, PharmD, BCPS
Mikal Rutten, PharmD
Swedish FMR
Littleton, CO


Is expectant management safe and effective for first-trimester miscarriage?

Evidence-Based Answer
Expectant management for at least 2 weeks is a safe and acceptable alternative to medical management of first-trimester pregnancy loss (SOR: A, meta-analyses of RCTs and an observational study). Waiting 6 to 8 weeks may increase successful miscarriage without risk of infection, but may increase the risk of bleeding and need for surgical intervention (SOR: A, meta-analysis of RCTs). Studies beyond 8 weeks are lacking, and therefore a firm endpoint of safety has not been demonstrated.

Up to 15% of pregnancies end in first-trimester miscarriage. Current treatment options include surgical evacuation or curettage, oral or vaginal medications (typically misoprostol), and expectant management (watchful waiting). An observational study of 1,096 consecutive patients with a suspected first-trimester pregnancy loss reported an overall success rate for completed miscarriage of 70% at 2 weeks and 81% at 4 weeks. The success rate was higher (91%) in patients with an incomplete miscarriage (heterogeneous tissues noted at ultrasonography) and lower (66%) in women with amnionic pregnancies (empty gestational sac). Eleven patients (1%) had complications.
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A Cochrane review of 15 RCTs assessed the effectiveness, safety, and acceptability of medical versus either surgical or expectant management in 2,750 women with early (before 13 weeks) pregnancy loss. Individual studies used various methods to define successful treatment, ranging from “clinical evaluation” to sonographic imaging. Only 2 trials evaluated medical versus expectant management effectiveness, measured at 7 to 14 days. Medical management in both studies was a single 400-mcg dose of vaginal misoprostol. Although 1 study (N=126) favored medical management at 7 days (81% vs 52% success; risk ratio [RR] 1.6; 95% CI, 1.2–2.1; NNT=3), the other (N=24) found no significant difference between the 2 methods at 10 to 14 days (80% for medical vs 86% for expectant management; \( P \) value not provided), and an analysis of pooled data from both trials also showed no difference (RR 1.2, 95% CI 0.7–2.1). The Cochrane analysis demonstrated no difference in unplanned surgical interventions between medical and expectant management for up to 8 weeks (2 trials, N=308), and pelvic infections (3 trials, N=333). The reviewers judged these studies to be of “good quality overall.”

In a second Cochrane meta-analysis comparing surgical versus expectant management over 6 to 8 weeks, reviewers pooled data from 7 RCTs (N=1,521). Expectant management carried a higher risk of incomplete miscarriage, need for unplanned or additional surgery, days of bleeding, and need for transfusion (TABLE). The risk of infection and anxiety were similar for both groups, and costs were lower for expectant management. Subsequent fertility data were limited; results for pain were mixed and too heterogeneous for pooled analysis. The reviewers concluded there was no clearly superior management option in first-trimester miscarriage.

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**TABLE**

Results from a systematic review of RCTs comparing expectant vs surgical management of incomplete miscarriage

<table>
<thead>
<tr>
<th>Measured outcome</th>
<th>No. of studies</th>
<th>No. of women</th>
<th>Result (95% CI)</th>
<th>Result favors</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete miscarriage (by 2 weeks)</td>
<td>4</td>
<td>1,263</td>
<td>RR 4 (2.9–5.4)</td>
<td>Surgery</td>
<td>Moderate</td>
</tr>
<tr>
<td>Incomplete miscarriage (at 6–8 weeks)</td>
<td>3</td>
<td>430</td>
<td>RR 2.6 (1.2–5.7)</td>
<td>Surgery</td>
<td>Moderate</td>
</tr>
<tr>
<td>Need for unplanned or additional surgery</td>
<td>5</td>
<td>1,454</td>
<td>RR 7.4 (5–11)</td>
<td>Surgery</td>
<td>Moderate</td>
</tr>
<tr>
<td>Days of bleeding</td>
<td>2</td>
<td>249</td>
<td>MDD 1.6 days (0.7–2.5)</td>
<td>Surgery</td>
<td>Moderate</td>
</tr>
<tr>
<td>Need for blood transfusion</td>
<td>3</td>
<td>1,205</td>
<td>RR 6.5 (1.2–34)</td>
<td>Surgery</td>
<td>High</td>
</tr>
<tr>
<td>Pelvic infection by 8 weeks</td>
<td>7</td>
<td>1,514</td>
<td>RR 0.6 (0.4–1.1)</td>
<td>Neither</td>
<td>High</td>
</tr>
<tr>
<td>Anxiety score (instrument not specified)</td>
<td>1</td>
<td>86</td>
<td>RR 0 (~6.1 to 6.1)</td>
<td>Neither</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cost at 8 weeks (2001–2002 UK pounds sterling)</td>
<td>1</td>
<td>800</td>
<td>MDC £499 (£385–£613)</td>
<td>Expectant</td>
<td>High</td>
</tr>
</tbody>
</table>

MDC=mean difference in cost between expectant and surgical management; MDD=mean difference in days of bleeding between expectant and surgical management; RR=risk ratio.

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Sonja A. K. Ronning, MD
St. Peter FMR, Providence Health Systems
Olympia, WA

Alyson L. Smith, MD
Family Medicine of Southwest Washington, PeaceHealth Medical Center
Vancouver, WA

How safe and effective is minoxidil for familial baldness in women?

**Bottom line**

Minoxidil (in a 2% solution, 5% solution, or 5% foam) is effective for the treatment of female pattern hair loss. Minoxidil is safe and generally well tolerated; however, minor dermatologic adverse effects (hypertrichosis, pruritis, and local irritation) have been reported. The foam appears to have the fewest adverse effects (SOR: B, RCTs).

**Evidence summary**

A single blind randomized trial studied the effect of once-daily 5% minoxidil foam versus twice-daily minoxidil 2% solution in 113 women with androgenic alopecia or female pattern hair loss. At baseline, participants had similar mean total area hair count and total area hair width. After 24 weeks of treatment, both groups had similar increases in the nonvellus target area hair count compared with baseline (32 vs 29 hairs/cm² in the 5% and 2% groups, respectively, P=.441). Likewise, the nonvellus target area hair width increased in both groups compared with baseline (2.5 vs 2.3 mm/cm² in the 5% and 2% groups, respectively, P=.497). The most common adverse effects—facial hypertrichosis (11% vs 26%, P=.033), scalp pruritus (16% vs 37%, P=.012), and dandruff (5% vs 18%, P=.042)—were all significantly lower using 5% minoxidil foam compared with the 2% solution.

A 2004 randomized, double-blind, placebo-controlled multicenter trial studied the effect of twice-daily 5% minoxidil solution versus twice-daily minoxidil 2% solution in 261 women aged 18 to 49 years old with androgenic alopecia. Nonvellus hair counts at baseline were similar in all groups. Between weeks 8 and 48, the nonvellus hair count increased 25 hairs/cm² in the 5% minoxidil group, 21 hairs/cm² in the 2% minoxidil group, and 9.4 hairs/cm² in the placebo group (P=.129 for 5% vs 2%; P<.001 for 5% vs placebo; and P<.001 for 2% vs placebo). The mean change from baseline in target areas was no different between the 5% and 2% groups at all time points. Scalp coverage improved in both treatment groups compared with placebo beginning at week 16. At week 48, scalp coverage was 11% in the 5% minoxidil group, 10% in the 2% minoxidil group, and 2.2% in the placebo group (P=.001 for 5% vs placebo and P=.004 for 2% vs placebo) with no difference between the treatment groups (P=.608 for 5% vs 2%). Dermatologic adverse effects (pruritus, dermatitis, hypertrichosis, and scaling) were more common in the 5% group (14%) than in the 2% (6%) and placebo (4%) groups (no P values provided).

An open-label, randomized, multicenter comparative study evaluated the effects of twice-daily 2% minoxidil solution compared with once-daily 0.025% alfatradiol solution (α-5-reductase inhibitor) in 75 adult women with androgenic alopecia. After 6 months of treatment, the minoxidil group showed significant increases of both cumulative hair thickness (1.8 mm/cm², P<.0001) and density (15 hairs/cm², P=.0025) when compared with baseline. In the alfatradiol group, both the cumulative hair thickness (–0.5 mm/cm²) and density (–7.8 hairs/cm²) remained unchanged (no P values provided). No unwanted event or side effects were reported.

Mathilde Moazazi, MD
Philipp Narciso, MD
UAMS, AHEC South Arkansas
El Dorado, AR


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**GLOSSARY**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ARR</td>
<td>absolute risk reduction</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>LOE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NNH</td>
<td>number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SOR</td>
<td>strength of recommendation</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
</tbody>
</table>
1. Evidence shows which of the following statements is true regarding patellofemoral pain syndrome?
   a. A hip strengthening exercise program results in less pain at 1 month than a quadriceps strengthening exercise program
   b. Quadriceps strengthening consistently leads to better outcomes than hip strengthening
   c. There is no difference in outcomes between hip and quadriceps strengthening
   d. The combination of hip and quadriceps strengthening leads to worse outcomes

2. Which of the following factors is not associated with a higher risk of developing hepatocellular carcinoma?
   a. Bilirubin <18 µmol/L
   b. Age >50 years
   c. Albumin <35 g/L
   d. Cirrhosis

3. Which of the following statements is correct regarding IUD placement immediately after childbirth?
   a. There is a higher pregnancy rate compared with delayed insertion
   b. It is generally considered to be safe and effective
   c. There is a lower expulsion rate compared with delayed insertion
   d. There is a higher rate of infection compared with delayed insertion

4. Omega-3 fatty acid supplementation may reduce:
   a. Myocardial infarction
   b. Cardiovascular death
   c. Low-density lipoprotein levels
   d. Triglyceride levels

5. Which of the following statements is true regarding warfarin therapy for atrial fibrillation in patients at risk for falls?
   a. Warfarin therapy is contraindicated in patients at risk for falls
   b. The benefits of warfarin therapy in stroke prevention outweigh the risk of major hemorrhage
   c. A patient would need to suffer 10 falls a year for the risk of intracranial hemorrhage to outweigh the benefits of anticoagulation
   d. Patients at risk for falls should be kept at a lower therapeutic international normalized ratio range to offset the bleeding risk

6. Which botanical has been found to be effective for reducing vasomotor symptoms of menopause?
   a. Red clover
   b. Soy isoflavones
   c. Black cohosh
   d. None of the above

7. At what age should an infant with a hydrocele be referred for surgery?
   a. Upon discharge from hospital
   b. 3 months
   c. 6 months
   d. 18 months

8. Expectant management is safe and effective for management of first-trimester pregnancy loss, but compared with surgical management it may be associated with an increased risk of which of the following effects?
   a. Infection
   b. Need for pain relief
   c. Days of bleeding
   d. Higher cost of care

For each question, please mark the single best answer by checking the appropriate box. To receive CME credit, a minimum score of 75% (6 out of 8 correct) is required.
In diabetic patients intolerant of ACE inhibitors and ARBs, what is the best therapy for reducing the risk of diabetic nephropathy?

Evidence-Based Answer

Optimizing glucose control and blood pressure in patients with type 1 or type 2 diabetes who are intolerant of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be of benefit in reducing the progression of surrogate measures (ie, microalbuminuria/macroalbuminuria) of diabetic nephropathy (SOR: C, extrapolations of studies in patients with diabetes using ACE inhibitors or ARBs).

A systematic review of 7 RCTs (N=266), including patients with type 1 diabetes, microalbuminuria, and normal serum creatinine evaluated the effectiveness of intense glucose control on late complications of diabetes. The authors did not specify if subjects were using ACE inhibitors or ARBs. The meta-analysis of these 7 trials demonstrated a reduction in progression of nephropathy (OR 0.34; 95% CI, 0.20–0.58) in subjects with intensive glycemic control (1.4% decrease in glycosylate hemoglobin [HbA1c] compared with control).

A systematic review of 7 RCTs (N=28,000) evaluated surrogate outcome measures (microalbuminuria and macroalbuminuria) and clinical outcome measures (doubling of the serum creatinine level, end-stage renal disease [ESRD], and death from renal disease) in patients with type 2 diabetes receiving intensive glucose control (HbA1c target range 6%–7.1%) versus conventional glucose control over 2 to 15 years. Only 2 of the trials indicated the percentage of patients using ACE inhibitors or ARBs (37% in 1 trial [N=153] and 53% in another trial [N=10,000]).

Intensive control resulted in a decrease risk of microalbuminuria (7 trials, N=28,000; risk reduction [RR] 0.86; 95% CI, 0.76–0.96) and macroalbuminuria (6 trials, N=27,000; RR 0.74; 95% CI, 0.65–0.85), compared with conventional treatment. Intensive control did not reduce doubling of serum creatinine level (4 trials, N=27,000; RR 1.06; 95% CI, 0.92–1.2), ESRD (5 trials, N=28,000; RR 0.69; 95% CI, 0.46–1.1) or death from renal disease (3 trials, N=16,000; RR 0.99; 95% CI, 0.55–1.8).

A single RCT, including 480 normotensive patients with type 2 diabetes and baseline blood pressures less than 140/90 mmHg, evaluated the effect of decreasing diastolic blood pressure on vascular complications. Subjects were randomized to intensive treatment (enalapril or nisoldipine) to further reduce blood pressure 10 mmHg below baseline or to no additional treatment. Subjects were followed for 5.3 years. Change in...
24-hour creatinine clearance was the primary endpoint and effect on urinary albumin excretion was the secondary endpoint.

There was no difference in change of serum creatinine for intensive treatment compared with control at 5 years (0.06 vs 0.04 mL/min/1.43m²; P=.61). Fewer subjects in the intensive treatment progressed from normoalbuminuria to microalbuminuria (P=.012; no result given) and microalbuminuria to macroalbuminuria (P=.028; no result given) than in the control group. Progression rates were not different between the 2 medications.

Sara Wormley, PharmD
Connie Kraus, PharmD
U of WI School of Pharmacy
Madison, WI


What is the best test for Lyme disease?

Evidence-Based Answer
If a patient develops erythema migrans after a tick bite in an endemic area, no testing is required. Simply treat the patient. If the diagnosis of Lyme disease is uncertain, obtain a sensitive enzyme-linked immunosorbent assay (ELISA) followed by the more specific immunoblot (Western blot) if the ELISA is positive. A negative ELISA obtained within 1 month of exposure should be repeated in 2 weeks if the patient remains symptomatic (SOR: B, diagnostic cohort and evidence-based guidelines).

In a prospective study, 237 patients from a Lyme disease clinic were followed with weekly serum samples to determine the diagnostic accuracy of IgG ELISA and immunoblot testing. Fifty-four patients with clinically diagnosed, active Lyme disease (objective evidence of joint inflammation involving oligoarticular arthritis in a few large joints) or neuroborreliosis (Lyme disease with neurologic manifestations: meningitis, chronic encephalopathy, or polyneuropathy) were compared with 44 patients with inactive Lyme disease (history consistent with Lyme disease but no current signs or symptoms) and 139 patients with other illnesses (fibromyalgia, fatigue, rheumatologic, and neurologic conditions).

When the active and inactive Lyme disease patient groups were combined, the IgG ELISA was positive in 66 of 98 patients (67%) and was indeterminate in 23. Combining positives and indeterminate results yielded a sensitivity of 89% and a specificity of 71%, yielding a positive likelihood ratio (LR+) 3.1 and a negative likelihood ratio (LR–) of 0.15. The IgG immunoblot had a lower sensitivity of 83% and higher specificity of 95% (LR+ 17, LR– 0.18).

In a case-controlled trial, the antibody responses (6 samples over 1 year) of 55 patients in a Lyme-endemic area, who had been clinically diagnosed (physician-documented erythema migrans) and treated for early Lyme disease, were analyzed by ELISA and immunoblot assays. Both tests were performed on each sample and compared with 75 asymptomatic blood donors.

At visit 1 (day of diagnosis and treatment) 45% (25 of 55) were ELISA positive for either IgM or IgG (sensitivity 45%, specificity 98%; LR+ 23 and LR– 0.56). For the immunoblot, 55% (30 of 55) were positive (sensitivity 55%, specificity 88%; LR+ 4.6 and LR– 0.51). The peak antibody response occurred at visit 2 (8–12 days into treatment) with the ELISA (IgM or IgG) positive in 76% (42 of 55; sensitivity 76%, specificity 98%; LR+ 38, LR– 0.24) and immunoblot positive in 80% (44 of 55; sensitivity 80%, specificity 89%; LR+ 7.3, LR– 0.22). Twenty percent of the clinically diagnosed patients remained seronegative throughout this study.

To evaluate the effectiveness of a 2-tiered algorithm (ELISA screening first, then immunoblot to confirm results—similar to HIV testing), IgM and IgG immunoblots were compiled for patients who were clinically diagnosed with Lyme disease, undergoing treatment, and had positive ELISA results. Using this strategy, follow-up immunoblots had a sensitivity of 84% and specificity of 92% at visit 1 (LR+ 11, LR– 0.17,) and a 97% sensitivity and 92% specificity at visit 2 (LR+ 12, LR– 0.03).

Guidelines by the Infectious Diseases Society of America, the Centers for Disease Control and Prevention, and the British Infection Association recommend that the clinical staging of Lyme disease (early localized, early disseminated, and late disease) should determine whether testing is indicated or not. In early (<1 month) disease (history of a tick bite in an endemic area and confirmatory physical findings), serologic testing may be unreliable, so treatment should...
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begin. In later disease (>1 month), these organizations recommend a 2-tiered algorithmic approach for detection of active disease or previous infection using an ELISA followed by an immunoblot. If the ELISA is negative after 1 month, no further testing is required. If the ELISA is negative in a patient who has had signs and symptoms consistent with Lyme disease for fewer than 30 days, a convalescent ELISA serum should be tested 2 weeks later.4,5

Peter Lennox, MD
Robert Persons DO, FAAFP
Eglin Air Force Base FMR, FL

The opinions and assertions contained herein are the private views of the authors and not to be construed as official, or as reflecting the views of the US Air Force Medical Service or the US Air Force at large.


What is the best surveillance for development of hepatocellular carcinoma in a patient who is a chronic carrier of hepatitis B?

Evidence-Based Answer

Screening chronic hepatitis B carriers for hepatocellular carcinoma (HCC) with ultrasound every 6 months may lead to earlier detection of resectable tumors (SOR: C, expert opinion). A clinical predication score may help determine which hepatitis B carriers would benefit most from surveillance (SOR: B, cohort study).

A Cochrane review of screening for HCC in patients with chronic hepatitis B virus (HBV) included 3 RCTs with nearly 21,000 patients that were analyzed independently.1 One RCT of 18,816 chronic hepatitis patients aged 35 to 55 years, 92% of whom were positive for hepatitis B surface antigen (HBsAg+), compared screening with alpha-fetoprotein (AFP) plus ultrasound (US) every 6 months versus no screening over 5 years. Screening detected more resectable HCC (<5 cm diameter) compared with the control group (OR 7.1; 95% CI, 3.3–14; NNS=403 to detect 1 HCC <5 cm). There was no difference in overall HCC mortality between the groups (OR 0.81; 95% CI, 0.54–1.2). A second RCT with 1,069 adult patients with chronic hepatitis B compared screening every 6 months with AFP+US versus screening with AFP alone over a mean of 26 months. There was no difference in detection of HCC with AFP+US compared with AFP (OR 0.74; 95% CI, 0.26–2.1). The third RCT of 744 patients at high risk for HCC (platelet count <150 x 10⁹, HBsAg+, or positive for hepatitis C antibody) compared screening annually versus every 4 months with AFP and US. The study was published as an abstract only. There was no significant difference in overall 4-year survival or in 3-year HCC incidence with either screening frequency.

A cohort study with 1,005 chronic HBV carriers from China, aged 40 to 70 years, performed surveillance with AFP and US over 10 years and identified 5 independent factors, using a multivariate analysis, which were significant in predicting risk for the development of HCC.2 These factors were used to construct the HCC clinical prediction score described in the TABLE to assist clinicians in determining which patients would benefit most from surveillance.

### Components of the HCC prediction score²

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>HR for developing HCC (factor comparison) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>+3</td>
<td>2.9 (&gt;50 vs ≤50) (2.0–4.3)</td>
</tr>
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<td>≤50</td>
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<tr>
<td>≤35</td>
<td>+20</td>
<td>5.5 (≤35 vs &gt;35) (3.7–8.2)</td>
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<td>&gt;35</td>
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<td>Bilirubin, µmol/L</td>
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<tr>
<td>&gt;18</td>
<td>+1.5</td>
<td>3.8 (&gt;18 vs ≤18) (2.4–6.2)</td>
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<td>≤18</td>
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<tr>
<td>4–6</td>
<td>+1</td>
<td>1.9 [4–6 vs ≤4] (1.5–2.5)</td>
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<tr>
<td>&gt;6</td>
<td>+4</td>
<td>2.1 (&gt;6 vs ≤4) (1.6–2.7)</td>
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<td>7.2 [Yes vs No] (4.5–11)</td>
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Continued
Another cohort of 424 chronic HBV carriers in a Chinese hepatology clinic received HCC surveillance over 10 years in order to validate the HCC prediction score. HCC was diagnosed either by histology or an AFP >500 mcg/L in the presence of characteristic radiological findings. Using a cutoff score of ≥5 to identify high-risk patients had a sensitivity of 81% and specificity of 76% (positive likelihood ratio 3.3 and a negative likelihood ratio 0.25) for predicting HCC at 10 years.

The 2010 American Association for the Study of Liver Disease (AASLD) practice guideline recommended that hepatitis B carriers at high risk for developing HCC (Asian men >40 years of age, Asian women >50 years of age, those with a family history of HCC, African and North American Blacks, and any person with cirrhosis) should be entered into a surveillance program using US screening at 6-month intervals.

Bibbin Philip George, MD
Gina G. Glass, MD, FAAFP
Underwood-Memorial Hospital FMRP
Woodbury, NJ


Does self-monitoring of blood glucose improve outcomes in patients with non–insulin-dependent diabetes?

Evidence-Based Answer
Self-monitoring of blood glucose (SMBG) in persons with non–insulin-dependent diabetes mellitus (NIDDM) may decrease glycosylated hemoglobin (HbA1c) slightly, but does not provide clinically meaningful improvement in glycemic control in usual practice. SMBG does not affect body mass index (BMI), cholesterol, or blood pressure levels (SOR: C, systematic review of RCTs on disease-oriented outcomes).

A Cochrane review of 12 RCTs involving 3,259 patients with NIDDM compared SMBG with no monitoring or self-monitoring with urine glucose. Seven studies had a low risk of bias. In patients having diabetes for at least a year, HbA1c decreased significantly at up to 6 months in the SMBG group compared with controls (9 trials; N=2,324; mean difference [MD] −0.3%; 95% CI, −0.4% to −0.1%). At 12 months, the decrease in HbA1c was no longer statistically significant (2 trials; N=493; MD −0.1%; 95% CI, −0.3% to 0.04%). SMBG had no significant effect on patient satisfaction, quality of life, and general well-being in 5 studies. The authors concluded that the clinical benefit from the decrease was likely to be limited.

A meta-analysis of 6 RCTs involving 2,552 patients with NIDDM compared SMBG with clinical management without self-monitoring. These 6 RCTs were also included in the Cochrane review. SMBG was associated with a mean reduction in HbA1c level at 6 months (MD −0.2%; 95% CI, −0.3% to −0.1%) and at 12 months (3 trials; N=728; MD −0.2%; 95% CI, −0.4% to −0.1%) compared with no self-monitoring. Although the HbA1c reduction was statistically significant, the authors noted that the difference was not clinically relevant because it was less than 0.5%. No changes were seen in blood pressure or total cholesterol levels.

An earlier comprehensive review and meta-analysis of the clinical effectiveness of SMBG in patients with type 2 diabetes included 11 high-quality systematic reviews containing 3 to 13 RCTs as well as observational studies. Twenty-six RCTs including 5,373 patients were also included. Five of the systematic reviews showed a statistically significant decrease in HbA1c of between 0.21% and 0.42%. The other 6 reviews showed no benefit or no conclusive evidence of benefit. The data from the systematic reviews were not combined into a single analysis.

Ten RCTs with 2,295 patients comparing “simple” SMBG with no SMBG showed a statistically significant but clinically irrelevant decrease in HbA1c (MD −0.21%; 95% CI, −0.31% to −0.10%). Four trials with 816 patients comparing SMBG with education and feedback with no monitoring and no or nonstandardized education showed a significant decrease in HbA1c (MD −0.52%; 95% CI, −0.98% to −0.06%). There was no difference between SMBG and usual-care patients in weight or BMI (13 RCTs), lipids (6 RCTs), or blood pressure (3 RCTs).

Ghazal Sinha, MBBS
Diane J. Madlon-Kay, MD, MS
U of MN School of Medicine
Minneapolis, MN

Evidence-Based Answer

In studies of adult male circumcision in Africa, circumcision decreases the risk of HIV transmission and genital ulcers (SOR: B, systematic review of RCTs). Neonatal circumcisions appear to decrease hospitalizations secondary to urinary tract infections (UTIs) during the first year of life. Male circumcision also reduces the risk of genital human papillomavirus (HPV) in men (SOR: B, meta-analysis of RCTs and cohort studies) and cervical cancer in female partners of men with high-risk sexual behavior (SOR: B, observational studies).

A 2010 systematic review of 8 RCTs evaluated a variety of outcomes after nontherapeutic circumcision in male patients of any age compared with uncircumcised controls. Six RCTs assessed adult males from Sub-Saharan Africa (N=22,000) and 2 RCTs assessed neonatal patients (N=138). The neonatal studies only reported on pain response and maternal infant bonding.

In the adult trials, the circumcision group reported a lower prevalence of genital ulcers (1 trial, N=4,996; risk ratio [RR] 0.53; 95% CI, 0.43–0.64) compared with uncircumcised adults. This review also found a lower risk of acquiring HIV/AIDS in the circumcision group compared with the uncircumcised group (3 trials, N=10,908; OR 0.44; 95% CI, 0.32–0.59).1

A 1993 retrospective study compared circumcision infant boys who had UTIs (112 of 80,000) with uncircumcised infant boys with UTIs (384 of 27,000) during the first year of life.2 Of circumcision infant boys, 0.14% were hospitalized secondary to a UTI compared with 1.4% of uncircumcised males (P=.0001; NNT=77). This same article conducted a meta-analysis of 9 prospective and retrospective trials (total patients not reported) and found that uncircumcised infant boys had a higher risk of UTIs than their circumcised counterparts (OR 12; 95% CI, 11–14).

A systematic review and meta-analysis identified 21 studies (8,046 circumcised and 6,336 uncircumcised men) evaluating the association between male circumcision and genital HPV infection.3 Meta-analysis of all 21 studies, which included cohort, cross-sectional and RCTs, found male circumcision to be associated with a significant reduction in genital HPV prevalence compared with no circumcision (OR 0.57; 95% CI, 0.4–0.8). Pooled data from the RCTs (2 trials, N=1,784) found HPV prevalence to be significantly lower in the circumcised group at 2 years (RR 0.67; 95% CI, 0.54–0.82) compared with the uncircumcised group.

Pooled data from 7 case control studies conducted from 1985 to 1993 in 5 countries evaluated cervical cancer risk factors among 1,913 stable couples.4 The male partner was uncircumcised in 1,118 couples and circumcised in 302 couples. There was no difference in the risk of cervical cancer in female partners with circumcised or uncircumcised partners (OR 0.75; 95% CI, 0.5–1.1). However, the risk of cervical cancer was significantly decreased in monogamous women partners of circumcised men with high-risk sexual behavior (26 sexual partners, contact with prostitutes, intercourse before age 17 years) (OR 0.42; 95% CI, 0.23–0.79) compared with couples in which the high-risk male was uncircumcised.

Edward Teng, MD
James Wilkerson III, MD
Robyn Wilkerson, MD
UAMS AHEC-SW
Fort Smith, AR


In patients with hiatal hernia and reflux symptoms, is proton pump inhibitor therapy more effective than surgical intervention?

Evidence-Based Answer

No, fundoplication surgery is more effective than proton pump inhibitor (PPI) therapy, resulting in better health-related quality of life and symptom control (SOR: A, systematic reviews of RCTs).

A 2010 meta-analysis included 4 RCTs comparing laparoscopic fundoplication surgery with medical management for the treatment of gastroesophageal reflux disease (GERD) in adults.1 Outcome measures included various health-related quality-of-life scales such as the SF-36, a 36-question survey (broken down into 8 scales, each scale scored 0–100) and the Psychological General Well-Being Index (PGWBI), a 22-item questionnaire (0–5 scale for each item), both with higher scores indicating better quality of life.
Pooled 3-month and 1-year SF-36 scores showed improved health-related quality of life with surgery compared with medical management (2 trials; N=461; mean difference [MD] 5.2; 95% CI, 3.6–6.8). Another study (271 patients) revealed an improved PGWBI score with surgery at 1 year compared with medical therapy (MD 8.2; 95% CI, 3.2–13). The fourth study (554 patients) was reported to show improved health-related quality of life with surgery compared with medical therapy, but details were not given. Two studies reported greater reduction of heartburn with surgery compared with medical treatment, although results were not pooled due to methodological differences. Numerical data were presented for 1 of the studies showing a mean heartburn score (0–6 scale, with lower scores indicating fewer symptoms) at 1 year after surgery of 0.8 versus 2.8 with medical treatment (MD –2.0; 95% CI, –2.8 to –1.1).1 Subgroup analyses of patients with hiatal hernia were not reported, but most patients had hiatal hernia.

A subsequent systematic review searched for studies comparing either open or laparoscopic fundoplication surgery with medical treatment in adults with chronic GERD symptoms.2 In addition to the laparoscopic studies found in the review above, this review found 1 additional study (N=298) using an open fundoplication technique. Most patients in this study also had hiatal hernia—92% in the medical treatment arm and 93% in the surgical arm.

Although the PGWBI was similar between groups at the 7- and 12-year follow-ups, the open surgical group had less heartburn (HR 1.7; 95% CI, 1.6–1.9) and regurgitation (HR 2.4; 95% CI, 2.1–2.7) compared with medical therapy. Remission rates at 12 years also favored surgery (53% vs 40%; P=.02). Again, subgroup analyses including only patients with hiatal hernia were not reported. The study was noted to have a large dropout rate.2

Natalya Lyadova, MD
Thomas Satre, MD
U of MN/St. Cloud Hospital FMR
St. Cloud, MN


Are probiotics effective for reducing the severity of symptoms in infants with atopic dermatitis?

Evidence-Based Answer

Giving probiotics to infants and children does not appear to be effective in reducing the severity of symptoms or preventing atopic dermatitis (SOR: B, systematic review of heterogeneous RCTs). The practice of giving probiotics to expecting mothers and then to their newborns has had mixed results.

A 2008 Cochrane review of 12 RCTs (781 children; 8 of 12 trials included children <18 months of age) compared the effectiveness of probiotics with any combination of placebo, topical treatment, or other active intervention (ie, cow’s milk elimination diet) for the reduction of eczema.1 There was no significant difference in participant or parent-rated symptom scores (severity scale of 0–20) between probiotic treatment and the control group (5 trials; N=313; mean difference [MD] 0.90; 95% CI, –1.0 to 2.8). There was also no significant difference in investigator-rated eczema severity (severity scale of 0–102) between probiotic and control groups (7 trials; N=588; MD 2.5; 95% CI, –2.5 to 7.5). Heterogeneity was noted throughout the studies, and the overall quality was mixed regarding randomization procedures, blinding, and loss to follow-up.

A RCT published after the Cochrane review examined the effectiveness of a probiotic mix of *Bifidobacterium bifidum*, *B lactis*, and *Lactobacillus acidophilus* compared with placebo in infants considered high risk based on family history of allergic diseases.2 In 112 pregnant patients, a combined supplementation with $1.6 \times 10^9$ CFU of each microbe was given daily 4 to 8 weeks before delivery and continued through 3 months postpartum, during which the infant was being breastfed. The infant received the same daily supplementation from 4 to 6 months of age, with outcomes followed to 1 year of age with 68 patients completing the study.

The prevalence of eczema at 1 year in the probiotic group compared with the placebo group was significantly lower (18% vs 40%; P=.048) and the cumulative incidence during the first year of life was also significantly reduced (36% vs 63%; P=.029).2 In 2008, a double-blind, placebo-controlled prospective study utilized *Lactobacillus rhamnosus*
compared with placebo with outcomes measured at 2 years of age. In 105 pregnant mothers, supplementation was given twice daily with $5 \times 10^9$ CFU of *L. rhamnosus* or placebo, beginning 4 to 6 weeks before delivery. If the neonate was breastfed exclusively, maternal supplementation occurred until 3 months of age, and then the infant was supplemented until 6 months of age. If the neonate was not being breastfed (treatment N=2 vs placebo N=3), the supplement was given to the neonate.

The prevalence of eczema did not differ between groups (28% vs 27%, $P=.93$) and cumulative incidence was not significantly changed (38% vs 32%; $P=.53$). This study also reported increased occurrence of adverse effects (recurrent bronchitis, ≥5 episodes by age 2) in the treatment population (26% vs 9.1%; $P=.03$).

**Matt T. Muramoto, DO**
Carl R. Darnall Army Medical Center, FMRP
Fort Hood, TX

The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the US Army, Department of Defense, or the US Government. Opinions, interpretations, conclusions, and recommendations herein are those of the author and are not necessarily endorsed by the US Army.


### What are the risks and benefits of tonsillectomy and adenoidectomy in children with sleep apnea?

**Evidenced-Based Answer**

Adenotonsillectomy is an effective therapy for decreasing the severity of obstructive sleep apnea and results in improved quality of life for children (SOR: B, systematic review and cohort studies). The complication rate of the procedure is low (8%–9%), with a higher complication rate noted for children under the age of 3 (SOR: B, systematic review with cohort studies and case series).

A 2009 systematic review of 23 observational studies (1,079 pediatric patients younger than 20 years of age, mean age 6.5 years) evaluated the effectiveness of tonsillectomy and adenoidectomy (T&A) for treatment of pediatric obstructive sleep apnea/hypopnea syndrome (OSAHS) by comparing pre- and postoperative apnea hypopnea indices (AHI) and assessment of cure for OSA. The AHI is a validated index of sleep apnea severity calculated by dividing the number of events by the number of hours of sleep. T&A resulted in 66% (95% CI, 58%–74%) of patients achieving a curative AHI (range 1–5). T&A was also associated with a mean AHI decrease of 12 events per hour (95% CI, 11–14 events per hour).

A multicenter collaborative retrospective review of all polysomnograms (PSGs) completed pre- and postoperatively at 8 major sleep centers in 2010 explored the efficacy of T&A for OSAHS in children aged 8 months to 18 years. The study included data on 578 otherwise healthy children and compared pre-T&A with post-T&A PSGs via the AHI. More than 50% of the children were noted to be obese based on body mass index. Pooled results showed a reduction AHI from 18 to 4.1 events per hour of sleep ($P<.001$) and an AHI of less than 1 per hour in 27% of patients.

A Brazilian prospective study of 48 children compared pre- and postsurgical quality of life after T&A. A validated, disease-specific quality-of-life survey (OSA18) was completed by parents before and after surgery. The OSA18 correlates well with PSG findings and scores above 80 typically indicate a major negative effect on quality of life. The average OSA18 score dropped from 83 to 34 ($P<.001$), indicating a significant improvement in quality of life.

A 2006 systematic review of 16 studies (mixture of cohort, RCTs, and case series with a total of 6,698 patients) assessed the complication rate (airway compromise, hemorrhage, infections, and dehydration) for outpatient tonsillectomies in children performed for any indication, not limited to OSAHS. Pooled data analysis in the perioperative period revealed a complication rate of 8.8% (95% CI, 5.5%–12.2%) with an unplanned admission rate estimate of 8.0% (95% CI, 5.3%–11.0%). Subgroup analysis suggested that children younger than 3 years were at a higher risk for complications compared with children older than 3 years (OR 1.6; 95% CI, 1.2–2.3).

**John C. Ehrmann III, MD**
**Leah Soley, MD**
Naval Hospital FMRP
Pensacola, FL

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Navy Medical Department, the Navy at large or the Department of Defense.

How long do you continue bisphosphonate therapy for osteoporosis?

Evidence-Based Answer
At 10-year follow-up, patients who stopped bisphosphonates after 5 years have similar nonvertebral fracture rates as patients who remain on bisphosphonates for a 10 full years; however, they have greater changes in bone mineral density (BMD) and their risk of clinical vertebral fractures may be higher (SOR: B, large RCT). Patients who take bisphosphonates for 3 years will have a decrease in BMD after discontinuation for 1 year, but their mean BMD will still be higher than before bisphosphonate therapy was started (SOR: C, disease-oriented outcome).

The 2006 Fracture Intervention Trial Long-term Extension (FLEX) was a randomized double-blind trial of 1,999 postmenopausal women evaluating the effects of discontinuing alendronate after 5 or 10 years of therapy on BMD. Participants had a mean of 5 years of prior treatment with alendronate. They were randomized to alendronate 5 or 10 mg/d or placebo for an additional 5 years. Each group was also given calcium and vitamin D supplementation.

The rate of hip BMD decline after the 5 additional years for patients in the combined alendronate group (5 and 10 mg) (–1.0%) differed significantly compared with the placebo group (–3.4%) (mean difference [MD] –2.4%; 95% CI, –2.9% to –1.8%). Nonvertebral fracture risk did not differ significantly between the combined alendronate group (19%) and the placebo group (19%) (risk ratio [RR] 1.0; 95% CI, 0.76–1.3). There was a significantly lower risk of clinical vertebral fracture with the combined alendronate group (5.3%) compared with the placebo group (2.4%) (RR 0.45; 95% CI, 0.24–0.85), but not in morphometric vertebral fractures (alendronate 9.8% vs placebo 11%; RR 0.86; 95% CI, 0.60–1.2). There was no difference noted in adverse events (upper gastrointestinal track experiences or osteonecrosis of the jaw) between both groups.

A post hoc subgroup analysis of women with previous fracture and lower BMD did not show an increased incidence of fractures on placebo versus alendronate after 5 years (RR 0.47; 95% CI, 0.19–1.1). The authors concluded that for most women, discontinuing therapy for up to 5 more years after finishing 5 years of treatment with bisphosphonates is reasonable.

A 2007 clinical trial randomized 2,458 postmenopausal women to 3 years of risedronate therapy (2.5 or 5 mg daily) or placebo. Participants included women younger than 85 years with history of vertebral fractures or 1 vertebral fracture plus a T-score less than –2. Both groups had supplementation with calcium and vitamin D. By the end of the 3-year study, women were given the option to continue in the study for 1 more year after the risedronate or placebo were stopped, but calcium and vitamin D were continued. Seventy-three percent (599 of 818 original patients) completed the follow-up.

BMD decreased in the former risedronate group at the femoral neck by 1.2% (95% CI, –1.9% to –0.60%) and at the trochanter by 1.6% (95% CI, –2.2% to –0.94%) but remained higher than at the beginning of the initial study. The former treatment group had a lower vertebral fracture rate (6.5%) than the former placebo group (12%) (RR 0.54; 95% CI, 0.34–0.86). There was no difference found in nonvertebral fractures (5% in placebo vs 4.8% in treatment group; no P value provided).

What is appropriate monitoring for a man on testosterone therapy?

Evidence-Based Answer
Testosterone therapy may increase hematocrit, but there does not appear to be any significant effect on lipid results or prostate-specific antigen (PSA) levels (SOR: C, disease-oriented outcomes). However, consensus guidelines recommend measuring hematocrit, a digital rectal exam (DRE), PSA testing, and measuring testosterone at 3 and 6 months, then annually (SOR: C, consensus opinion).

A meta-analysis of 19 RCTs (651 men in the testosterone group, 433 in placebo) examined adverse events in men with low testosterone levels treated with testosterone at a variety of doses (PO, IM, and dermal: 120–160 mg/d PO; 100–250 mg IM over varying time frames; and 5 mg/d dermal).
Compared with placebo, a hematocrit >50% was 4 times more likely to occur in testosterone-treated men (OR 3.7; 95% CI, 1.8–7.5). The frequencies of cardiovascular events (OR 1.1; 95% CI, 0.59–2.2) and death (OR 0.78; 95% CI, 0.32–1.9) were not significantly different in the testosterone group versus placebo. The combined occurrence of prostate cancer, PSA >4 ng/mL, and prostate biopsies was significantly increased in the testosterone group compared with placebo (OR 1.8; 95% CI, 1.1–3.0), although taken individually, they were not statistically significant (TABLE).1

A meta-analysis of 29 RCTs (625 men randomized to testosterone therapy, 427 to placebo, and 31 to observation) examined the benefits of testosterone in men treated with testosterone to improve body composition (PO, IM, and dermal formulations at a variety of doses).2 Bone mineral density (BMD) improved at the lumbar spine in the testosterone group compared with placebo or observation (5 trials; N=264; mean increase 3.7%; 95% CI, 1.0–6.4).

A meta-analysis of 30 RCTs (808 men treated with testosterone and 834 on placebo) was performed to assess cardiovascular risk factors in men taking testosterone (using a variety of PO, IM, and dermal preparations over varying durations and doses).3 There were no significant changes in lipid values in men taking testosterone (total cholesterol standardized mean difference [MD] –0.22 nmol/L; 95% CI, –0.71 to 0.27; high-density lipoprotein [HDL] –0.04 nmol/L; 95% CI, –0.39 to 0.30; low-density lipoprotein [LDL] 0.06 nmol/L; 95% CI, –0.30 to 0.42; and triglycerides MD –0.27 nmol/L; 95% CI, –0.61 to 0.08) in the subgroup of men who started with low testosterone levels (subgroup number of patients not reported).

Currently, no evidence-based guidelines comment on if or when testosterone levels should be monitored. The...
In this review, 3 trials were reviewed that evaluated treatment with methylnaltrexone in patients where conventional laxatives failed: methylnaltrexone versus placebo (33 patients) in which a single dose (0.15 or 0.30 mg/kg) was administered; methylnaltrexone versus placebo (154 patients) in which 0.15 mg/kg was administered every other day for 2 weeks; and methylnaltrexone (33 patients) compared dosing of 1, 5, 10, and 20 mg. These studies showed 48% to 62% of the participants (vs 13%–15% for placebo) had a bowel response at 4 hours after administration of methylnaltrexone (OR 7.0; 95% CI, 3.9–13). The median time to laxation after methylnaltrexone administration was 1.3 hours for patients dosed at ≥5 mg (vs a laxation time of >48 hours in the 1-mg group; no P value provided). The Cochrane review concluded that methylnaltrexone is effective for treatment of opioid-induced constipation where conventional laxatives have failed, but more trials are needed to evaluate safety.

In 2012, the European Association of Palliative Care (EAPC) updated its guideline on the use of opioids for treatment of cancer pain. It contains an expert consensus recommendation to routinely prescribe laxatives as initial therapy for the prophylaxis of opioid-induced constipation. The EAPC guideline stated that there is no evidence to suggest choosing 1 laxative over another.
and treatment should include individual psychotherapy with or without cognitive behavioral, group, or family therapy. Oral contraceptives should be considered in an amenorrheic athlete older than 16 years with decreasing bone mineral density despite adequate nutrition and body weight. Finally, a multidisciplinary team is recommended for treatment of the female athlete triad, including a physician, a registered dietician, and, for athletes with disordered eating, a mental health provider.

Oluseun Wert, DO
Gina Glass, MD, FAAFP
Underwood-Memorial Hospital FMR
Woodbury, NJ


In boys aged 8–18, are routine inguinal hernia evaluations during sports physicals indicated?

Evidence-Based Answer
Probably not. The physical examination is less than 75% sensitive at detecting hernias and the risk of strangulation of an asymptomatic hernia is very low (SOR: C, extrapolation from cohort studies and consensus guideline).

Most literature on inguinal hernias pertains to surgical repair, with little research directed at diagnosis or prevalence in the school-age (8–18 years) population.

A systematic review published in 2012 discussed 2 RCTs that examined watchful waiting versus open surgical correction of asymptomatic inguinal hernias.

One of the trials (N=720; ages ≥18 years old) found the rate of strangulation in the watchful waiting group to be 0.27% after 1 year and 0.55% after 2 years, whereas the rates in the second trial (N=160; ages >55 years old) were 1.3% after 1 year and 2.5% after 7.5 years. There was a high rate of crossover from watchful waiting to surgery in both studies ranging from 23% to 72% depending on the period of follow-up. The reasons given for crossover in both studies were increase in size of the hernia and pain. The range of operative complications was 0% to 22% and the recurrence rate was 2.1%. Most of the patients in these trials developed symptoms over time that led them to have surgery, but emergent surgery due to strangulation was uncommon.

In 1999, a diagnostic study was conducted to compare the accuracy of detecting a hernia with physical examination, ultrasound, and MRI compared with the gold standard of laparoscopy. All 3 examinations were performed on both groins of 41 participants suspected of having at least 1 hernia, after which they all underwent laparoscopic surgery.

In this study the physical examination was only 75% sensitive and 96% specific at detecting laparoscopically proven hernias (positive likelihood ratio [LR+] 19; negative likelihood ratio [LR−] 0.26). The ultrasound was 93% sensitive and 82% specific (LR+ 5.2, LR− 0.09), and the MRI was 95% sensitive and 96% specific (LR+ 24, LR− 0.05). The average age of these patients was 58 years (range 28–77 years), so there were no patients included from the target age range. Also, as the participants all had suspected hernias, its application to asymptomatic screening is unclear.

The Preparticipation Physical Exam Monograph, a consensus opinion published jointly by several groups, including the American Academy of Family Physicians, the American Academy of Pediatrics, and the American Medical Society for Sports Medicine, states that athletes with asymptomatic inguinal hernias may participate in all sports but should be warned about red flags for strangulation. The authors stated this examination is also an opportunity to screen for cryptorchidism, which again may not exclude an athlete, but necessitates proper education prior to participation. The monograph also pointed out that testicular cancer is the leading cause of cancer death in males aged 15 to 35, and suggests this examination is a good opportunity to teach testicular self-examinations.

However, the US Preventive Services Task Force gives testicular self-examination a D rating, thus recommending against routine such screening.

Jason W. Deck, MD
Brian Potthoff, MD
James Barrett, MD

Are any iron supplement formulations better tolerated than ferrous sulfate?

Evidence-Based Answer
Iron (III) polymaltose complex (IPC) has fewer gastrointestinal adverse effects than ferrous sulfate (FeSO₄) (SOR: A, meta-analysis). Women report fewer adverse effects with iron protein succinylate (IPS) than with FeSO₄, but men report no difference (SOR: B, meta-analysis of small RCTs). Neither sustained-release FeSO₄ nor carbonyl iron is better tolerated than rapidly disintegrated FeSO₄ (SOR: B, comparison RCTs).

A 2007 meta-analysis of 557 adult patients in 6 RCTs compared IPC with FeSO₄ in equivalent doses for the treatment of iron deficiency. Hemoglobin increased equally between groups (increase across studies from 10 to 12 g/dL; weighted mean difference [WMD] 0.01; 95% CI, –0.23 to 0.21). Dropout rates were not significantly different (5 trials, N=247; 24% FeSO₄ vs 22% IPC; OR 1.1; 95% CI, 0.71–1.7).

FeSO₄ was associated with more upper digestive problems, including nausea (5 trials, N=497; 46% FeSO₄ vs 13% IPC; OR 5.6; 95% CI, 3.6–8.6) and diarrhea (4 trials, number of patients not reported; 15% FeSO₄ vs 6% IPC; OR 2.9; 95% CI, 1.6–5.4). Constipation and other less common adverse effects also occurred more frequently with FeSO₄ (3 trials, number of patients not reported; 16% FeSO₄ vs 9% IPC; OR 2.0; 90% CI, 1.1–3.5).

A meta-analysis of 1,264 adults in 3 RCTs comparing FeSO₄ with IPS reported approximately 50% fewer adverse effects (mainly gastrointestinal, specific breakdown of adverse effects not reported) with IPS in women (2 trials, N=188; 23% vs 11%; risk ratio [RR] 0.48; 95% CI, 0.36–0.64), but men reported no difference (2 trials, N=19; 16% vs 15%; RR 0.99; 95% CI, 0.43–2.3).

A randomized, double-blinded study of 1,376 adult blood donors given routine iron replacement compared 100 mg of rapidly disintegrated FeSO₄ given twice daily with the same dose of sustained-release FeSO₄. No significant difference was noted between the 2 iron groups in combined adverse effects (including constipation, diarrhea, nausea, epigastric pain, and other minor adverse effects). However, nausea occurred less often with sustained-release iron than with the rapidly disintegrated FeSO₄ (6.4% vs 3.3%, respectively; P<.05).

A randomized, double-blind trial of 75 menstruating female blood donors compared 300 mg FeSO₄, 600 mg carbonyl iron, and placebo, each taken 3 times daily for 21 doses. No significant difference was noted in total adverse effects (91% carbonyl iron vs 79% FeSO₄; P>.05). Nausea was more common with FeSO₄, but diarrhea and unpleasant taste were more common with carbonyl iron (rates not available).

Does caffeine improve cognitive function in sleep-deprived individuals?

Evidence-Based Answer
Caffeine may improve judgment and orientation in healthy sleep-deprived people when given at moderate doses. Concept formation, reasoning, verbal functioning, and language skills are not improved (SOR: B, extrapolated data from a meta-analysis).

A 2010 Cochrane review of 13 RCTs, including 331 patients, examined the effect of caffeine on sleep-deprived individuals. The studies included participants aged 16 to 65 years old, night shift workers, jet-lagged individuals, and military personnel.

In 3 of the trials, participants were sleep deprived through natural means; in the remaining 10 trials the participants were sleep deprived in simulated situations. Caffeine doses ranged between 160 and 300 mg. In 8 trials, the participants were given caffeine (or placebo) tablets and in 3 trials the participants were given caffeine (or placebo) in drink or food form. The participants completed various neuropsychological tests that measured cognitive function.

To pool the data, the trials were sorted according to the underlying cognitive construction being measured. These categories included concept formation, judgment, memory, orientation, reasoning, and verbal functioning.
A standardized mean difference was calculated for each category. Participants did better in judgment and orientation, but there were no statistically significant differences in concept formation, reasoning, verbal functioning, and language (TABLE 1).

A 2008 double-blind RCT studied the effects of caffeine, dextroamphetamine, and modafinil on executive function (concentration, memory, and planning) after induced sleep deprivation in a residence sleep lab in 54 healthy men and women aged 18–36 years. Participants were given several tests of executive function, including the Tower of Hanoi (TOH), the Tower of London (TOL), and the Wisconsin Card Sorting Test (WCST). TOH and the TOL required the participants to move a stack of rings and beads respectively in a specified order in the least amount of time and moves. The WCST required the participants to sort a stack of cards based on 4 given key cards. Both TOL and TOH helped to assess cognitive processing. The WCST helped to assess the ability of the individual to form abstract concepts, learn from feedback, and shift mental set.

Six hundred milligrams of caffeine were administered after 44 hours of sleep deprivation. This dose of caffeine is more than that consumed in common drinks (TABLE 2). Participants taking caffeine used significantly fewer moves to complete the TOH task when compared with participants taking placebo (57 vs 76, P<.05; absolute number of moves approximated from graphs presented in the article). However, participants taking caffeine did not perform better than those taking placebo on the TOL test (94 vs 102 moves, respectively, difference not significant) or WCST (52 vs 49 errors, respectively, difference not significant).


### Does vitamin D deficiency affect pregnancy outcomes?

Routine vitamin D supplementation does not alter pregnancy outcomes (SOR: A, meta-analysis). However, vitamin D deficiency (serum level <20 ng/mL) during the late second trimester is associated with an increased risk of cesarean delivery, preeclampsia, and preterm delivery (SOR: B, observational studies). Pregnant patients with an identified deficiency may be treated (SOR: C, expert opinion), but the effect of replacement on pregnancy outcomes is unknown.

A Cochrane review examining if vitamin D supplementation improved maternal and neonatal outcomes identified 6 relevant RCTs (N=1,023), all carried out in the 1980s except 1 from 2008. Five trials compared the effects of vitamin D alone versus

### Evidence-Based Answer

A standardized mean difference was calculated for each category. Participants did better in judgment and orientation, but there were no statistically significant differences in concept formation, reasoning, verbal functioning, and language (TABLE 1).

### TABLE 1

<table>
<thead>
<tr>
<th>Neuropsychiatric domain tested</th>
<th>N</th>
<th>Standardized mean difference caffeine vs placebo (negative favors caffeine)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>20</td>
<td>−1.1</td>
<td>(−2.1 to −0.09)</td>
</tr>
<tr>
<td>Orientation and attention</td>
<td>211</td>
<td>−0.55</td>
<td>(−0.83 to −0.27)</td>
</tr>
<tr>
<td>Concept formation and reasoning</td>
<td>40</td>
<td>−0.41</td>
<td>(−1.0 to 0.23)</td>
</tr>
<tr>
<td>Perception</td>
<td>20</td>
<td>−0.77</td>
<td>(−1.7 to 0.20)</td>
</tr>
<tr>
<td>Verbal functioning and language</td>
<td>33</td>
<td>0.18</td>
<td>(−0.50 to 0.87)</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>Product</th>
<th>Caffeine content, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet Coke® (12 oz)</td>
<td>39</td>
</tr>
<tr>
<td>Mountain Dew® (12.0 oz)</td>
<td>45</td>
</tr>
<tr>
<td>Red Bull® (8.2 oz)</td>
<td>67</td>
</tr>
<tr>
<td>Dunkin Donuts® coffee (16 oz)</td>
<td>143</td>
</tr>
<tr>
<td>Starbucks® drip coffee (16 oz)</td>
<td>260–565</td>
</tr>
<tr>
<td>Espresso (1 oz)</td>
<td>58</td>
</tr>
<tr>
<td>Tea, black, 3-minute steep (8 oz)</td>
<td>47</td>
</tr>
</tbody>
</table>

no supplementation/placebo (N=623 women, start of supplementation 27–28 weeks’ gestation) and the 2008 trial compared the effects of vitamin D and calcium versus no supplementation (N=400 women, start of supplementation 20–24 weeks’ gestation). The dose of vitamin D ranged from 800 to 1,200 IU/d.

No differences were noted in the incidence of birthweight of less than 2,500 g in the vitamin D group compared with placebo (3 trials; N=463; RR 0.48; 95% CI, 0.23–1.01) or risk of preeclampsia in the vitamin D plus calcium group compared with placebo (1 trial; N=400; RR 0.67; 95% CI, 0.33–1.35).

A prospective cohort study of 1,153 low-income and minority pregnant patients examined the association of vitamin D deficiency (assessed at study entry, average gestational age 13 weeks) with the risk of cesarean delivery. Overall, 290 patients (25%) were delivered by cesarean, of which 173 (15%) were a primary cesarean.

After adjusting for confounding variables (age, parity, ethnicity, pregravid body mass index, smoking, gestation at entry, and season of entry), there was an increased risk of delivery by cesarean with 25(OH)D deficiency (<12 ng/mL) compared with sufficient 25(OH)D levels (20–50 ng/mL; adjusted odds ratio [aOR] 1.7; 95% CI, 1.1–2.7) but no increased risk associated with 25(OH)D insufficiency (12–20 ng/mL; aOR 0.83; 95% CI, 0.59–1.2) compared with the deficient group. There was a 2-fold increase in the risk of primary cesarean for the specific indication of prolonged labor (aOR 2.2; 95% CI, 1.2–4.0) in the 25(OH)D deficiency group compared with the sufficient group.

A prospective cohort study of 697 pregnant patients assessed the risk of preeclampsia and vitamin D status at early gestation (12–18 weeks) and late second trimester (24–26 weeks). Thirty-two patients (4.6%) had preeclampsia during their pregnancy. Maternal 25(OH)D levels of less than 20 ng/mL at 24 to 26 weeks were associated with an increased risk of preeclampsia (aOR 3.2; 95% CI, 1.4–7.7) compared with 25(OH)D levels of more than 20 ng/mL. There was no association between 25(OH)D levels and preeclampsia at 12 to 18 weeks.

Another prospective cohort study of 266 pregnant patients, of whom 157 (59%) had 25(OH)D deficiency (<20 ng/mL), evaluated the associations of 25(OH)D deficiency with multiple pregnancy outcomes, including preterm birth and cesarean delivery. The 25(OH)D levels were drawn during 24 to 28 weeks’ gestation.

Compared with patients whose 25(OH)D levels were more than 20 ng/mL, patients with levels of less than 20 ng/mL were more likely to have a preterm (<37 weeks) delivery (23% vs 8%; OR 3.3; 95% CI, 1.5–7.2) and cesarean delivery (31% vs 12%; OR 3.9; 95% CI, 2.0–7.7).

A consensus opinion from the American College of Obstetricians and Gynecologists states evidence is insufficient to recommend vitamin D supplementation to prevent preterm birth or preeclampsia, but if vitamin D deficiency is identified (<20 ng/mL) during pregnancy, 1,000 to 2,000 IU daily of vitamin D is safe.

What treatment is most effective for tinea versicolor?

**Evidence-Based Answer**

Multiple topical and systemic azole antifungals are effective; evidence is insufficient to recommend a single best treatment (SOR: B, systematic review of low-quality randomized trials).

A 2010 meta-analysis of 93 RCTs evaluated the effectiveness of a variety of topical and oral systemic treatments for 8,327 patients with tinea versicolor. Overall quality of the included trials was judged to be low, as most trials did not adequately report methods of randomization, concealment of allocation, blinding, or use an intention-to-treat analysis. Due to design heterogeneity, most of the data could not be combined.

Several topical treatments (TABLE 1) were shown to be safe and effective. Studies comparing active treatments were underpowered and no superior treatment was identified.

The shortest duration of effective topical treatment was described in a high-quality 1998 double-blind RCT of 312 patients. Ketoconazole 2% shampoo, applied to affected areas for 5 minutes and then washed off, achieved equivalent cure rates with 1-day treatment.
Evidence-Based Answer
Screening at 24 to 28 weeks’ gestational age with a 2-hour oral glucose tolerance test (OGTT) is designed to identify patients with a 1.75 odds ratio of an adverse pregnancy-related outcome compared with patients without gestational diabetes (GDM). While this test triples the number of patients identified as having GDM compared with screening with the 1-hour glucose tolerance test (SOR: B, case-control study and evidence-based guideline), it is not yet clear that this increased rate of diagnosis will improve maternal or fetal outcomes.

Traditional GDM screening in an average-risk pregnant patient utilizes a 2-step process performed between 24 and 28 weeks’ gestation: a 1-hour glucose tolerance test followed (if the results are >130 or 140 mg/dL) with a 3-hour OGTT.1

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a 5-year multicenter, prospective, blinded, observational cohort study,
examined the association between results on a maternal 2-hour OGTT and risks of adverse pregnancy outcomes (weight >90th percentile, cord-blood serum C-peptide >90th percentile, and primary cesarean delivery). A single 2-hour 75-g OGTT was performed between 24 and 32 weeks’ gestation on more than 23,000 pregnant patients (mean age 29 years) at 15 centers in 9 countries, measuring serum glucose at fasting, 1 hour, and 2 hours after an oral 75-g glucose load. These values were retrospectively reviewed and the adjusted ORs of various outcomes were calculated for 1 standard deviation increase in fasting, 1-hour, and 2-hour glucose measurements.

A fasting plasma glucose of 88 mg/dL (vs the cohort mean of 81 mg/dL) was associated with an increase in the risk of birth weight above the 90% percentile (OR 1.4; 95% CI, 1.3–1.4), cord blood serum C-peptide level above the 90% percentile (OR 1.6; 95% CI, 1.5–1.6), and primary cesarean delivery (OR 1.1; 95% CI 0, 1.1–1.2). A 1-hour glucose of 165 mg/dL (vs the cohort mean of 134 mg/dL) was associated with an increased risk of birth weight above the 90% percentile (OR 1.5; 95% CI, 1.4–1.5), cord blood C-peptide above the 90% percentile (OR 1.5; 95% CI, 1.4–1.5), and primary cesarean delivery (OR 1.1; 95% CI, 1.1–1.2). A 2-hour glucose of 135 mg/dL (vs the cohort mean of 111 mg/dL) was associated with an increased risk of birth weight >90% (OR 1.4; CI 1.3–1.4), cord blood C-peptide >90% (OR 1.4; 95% CI, 1.3–1.4), and primary cesarean delivery (1.1; 95% CI, 1.0–1.1).2

The International Association of Diabetes and Pregnancy Study Group (IDPSG) recommended universal testing with a single 2-hour OGTT at 24 to 28 weeks’ gestation, using a diagnostic threshold at which the odds for adverse fetal outcomes in the HAPO study reached 1.75 times the estimated odds of the adverse outcomes at mean glucose values.3 This translates to the diagnosis of GDM if 1 or more of the following levels are identified: fasting glucose >92 mg/dL, 1-hour glucose >180 mg/dL, or 2-hour glucose >153 mg/dL. These new guidelines, supported by the American Diabetic Association, would increase the diagnosis of GDM from 4%–7% to 16%. No outcome data are available comparing maternal and fetal outcomes with traditional screening versus the 2-hour OGTT.

Jennifer T. Roper, MD
Lyrad K. Riley, MD
Eglin Family Medicine Residency
Eglin Air Force Base, FL

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What’s in an HDA?

We’ve asked Dr. Robert Gauer, author of numerous HDAs, What goes into writing an HDA?

I generally spend about 3 hours performing a literature search. When I get the articles I want, I go over their bibliographies and pull additional articles, spending about 8–10 hours of reading and processing.

From there, I am able to begin putting thoughts into words. This process takes about 4 hours; then I spend another 2 hours after I’ve let it sit for a few days. After the external peer review and a round or two of edits from Dr. Neher, it is usually ready for print.

My favorite part is the actual writing and seeing how I can take a mountain of information and make it into a molehill that still has relevance for the reader.

I can’t tell you the countless times I have referred to an HDA for a question asked by a student or resident. We find the answer easily, and it takes less than 5 minutes to read.

Read more at: www.fpin.org/page/Gauer