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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Do Antibiotics Reduce Hormonal Contraceptive Effectiveness?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck, and has served as a consultant for Bayer and Pharmanest.

SYNOPSIS: This is a systematic review of studies evaluating the effect of concomitant non-rifamycin antibiotic use on hormonal contraceptive effectiveness. Although data are limited, there is no evidence to support the existence of drug interactions.

SOURCE: Simmons KB, et al. Drug interactions between non-rifamycin antibiotics and hormonal contraception: A systematic review. *Am J Obstet Gynecol* 2017; July 8. pii: S0002-9378(17)30845-1. doi: 10.1016/j.ajog.2017.07.003 [Epub ahead of print].

This systematic review evaluating drug interactions between non-rifamycin antibiotics and hormonal contraception was conducted by the Centers for Disease Control and Prevention's Division of Reproductive Health. The review was conducted in support of the most recent update of the U.S. Medical Eligibility Criteria for Contraceptive Use. The review included randomized and non-randomized studies, and all trials had to have a control or comparison group. All studies that included women taking any method of hormonal contraception in combination with an oral, intramuscular, or intravenous non-rifamycin antibiotic were included. Clinical outcomes of interest included pregnancy, evidence of ovulation, antibiotic effectiveness, and adverse health effects (breakthrough bleeding, drug side effects). Pharmacokinetic outcomes also were reviewed. The quality of each study was graded with the U.S. Preventive Services Task Force grading system: good (no important limitations, results internally valid), fair (clear limitations but no fatal flaws), or poor (one or more fatal flaws). Meta-analyses could not be conducted because of the heterogeneity of the exposures and outcomes.

Out of 220 possible articles identified, 29 met criteria for inclusion in the review. Four articles were observational studies of pregnancy rates with any antibiotic use. Two of these were case crossover studies, one was a retrospective cohort, and one was a nested case control; the studies

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were rated as poor to fair in quality. None of these studies, which mostly examined oral contraceptives, showed any effect of antibiotic use on hormonal contraception failure. Next, the authors assessed the 25 trials that evaluated surrogate measures of contraceptive effectiveness (ovulation) and pharmacokinetic outcomes. Penicillins/cephalosporins, tetracyclines, fluoroquinolones, and macrolides were examined when used with oral contraceptives. No differences in ovulation by serum progesterone or ultrasound were observed with ampicillin, doxycycline, temafloxacin, ofloxacin, ciprofloxacin, clarithromycin, roxithromycin, dirithromycin, or metronidazole. Also, there were no significant decreases in any progestin or ethinyl estradiol level caused by antibiotic use in the pharmacokinetic studies. One pharmacokinetic study evaluated the contraceptive ring and found no interaction with ampicillin or doxycycline.

■ COMMENTARY

There has been persistent concern that concomitant use of antibiotics with hormonal contraception, especially combined oral contraceptives, could impair efficacy and result in pregnancy.[1] Pharmacists and providers often warn patients of this potential. Most of this concern stems from older case reports without controls and patient and provider surveys. Because the typical use failure rate of combined oral contraceptives is 9%,[2] a case report of unplanned pregnancy while taking antibiotics does not necessarily mean the antibiotics caused the contraceptive failure. Although rifampin and rifabutin are known inducers of the hepatic enzymes required for contraceptive steroid metabolism, other antibiotics are not. The authors of this study undertook to survey the known literature and assess the evidence to support the assertion that non-rifamycin antibiotics cause hormonal contraception failures.

This systematic review has several strengths including strict inclusion criteria and the evaluation of a range of clinical and pharmacokinetic outcomes. However, any systematic review is limited by the studies available. In this case, most of the literature in this area is subject to several limitations and biases. For the observational studies, most did not record pill compliance and had flaws in how exposure to antibiotics was measured, as well as tracking pregnancy rates. Furthermore, the pharmacokinetic studies were limited by small sample sizes, weakness in ovulation measurement accuracy, lack of randomization, and lack of control for confounders. Pharmacokinetic studies also are limited, as they represent only a surrogate measure of potential contraceptive failure and not a true clinical pregnancy outcome. In addition, minimum contraceptive efficacy thresholds are not yet established for ethinyl estradiol and progestins.[3] There were no studies evaluating the contraceptive patch, depot medroxyprogesterone acetate, or the etonogestrel implant. Combined oral contraceptive doses studied included only pills containing 30 or 35 mcg of ethinyl estradiol; therefore, lower-dose pills were not evaluated.

Based on this review, the U.S. Medical Eligibility Criteria for Contraceptive Use provides recommendations for contraceptive use with broad-spectrum antibiotics and other types.[4] (*See Table 1.*) Although in general, there is no evidence that broad-spectrum antibiotics interfere with hormonal contraceptive efficacy, there is always the possibility of individual variations in metabolism that could make a patient vulnerable.[5] Therefore, if a patient truly believes she had an unplanned pregnancy due

Table 1: Recommendations for Contraceptive Use With Broad-Spectrum Antibiotics

	Combined pill/ patch/ring	Implant	DMPA	Progestin-only pill
Broad-spectrum antibiotics	No restrictions	No restrictions	No restrictions	No restrictions
Antifungals	No restrictions	No restrictions	No restrictions	No restrictions
Antiparasitics	No restrictions	No restrictions	No restrictions	No restrictions
Rifampin or rifabutin therapy	Risks outweigh benefits	Benefits outweigh risks	No restrictions	Risks outweigh benefits

DMPA = depot medroxyprogesterone acetate
Adapted from: Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-104.

to concomitant antibiotic use with hormonal contraceptives, it is reasonable to advise her to use condoms for backup if she uses antibiotics in the future. Similar to other drug-contraception interactions, it is unlikely that depot medroxyprogesterone acetate or intrauterine devices are affected, and patients who have concerns could switch to these methods. ■

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ABSTRACT & COMMENTARY

Irritable Bowel Syndrome, Constipation, and Quality of Life in Women

By Chiara Ghetti, MD

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

SYNOPSIS: Irritable bowel syndrome has a negative effect on women's quality of life and affects one-third of women who present for care with fecal incontinence.

SOURCE: Markland AD, et al; Pelvic Floor Disorders Network. Irritable bowel syndrome and quality of life in women with fecal incontinence. *Female Pelvic Med Reconstr Surg* 2017;23:179-183.

The objective of this study was to determine the prevalence of irritable bowel syndrome (IBS) in women presenting for treatment of fecal incontinence and to determine the effect of IBS on quality of life. This was an ancillary analysis of the Adaptive Behaviors among women with Bowel Incontinence (ABBI) study, a multicenter, prospective cohort study designed to evaluate adaptive behaviors among women with bowel incontinence. Eligible women had fecal incontinence of liquid stool, solid stool, or mucus occurring at least monthly for three consecutive months and planned to undergo treatment for fecal incontinence. Women reporting prior rectal or colon cancer, inflammatory bowel disease, pelvic irradiation, a current or prior rectal fistula(e), removal of any portion of the colon/rectum, rectal prolapse, or severe neurological conditions were excluded.

Subjects completed validated questionnaires in person or by telephone before treatment. Questionnaires included assessment of IBS symptoms using the Rome III symptom-based diagnostic criteria, and multiple validated general health-related and condition-specific quality-of-life scales, as well as validated assessments of other pelvic floor symptoms. In this study, IBS was categorized according to the Rome III clinical criteria. In addition, subjects could self-report whether they previously were given a diagnosis of IBS.

The authors enrolled 133 women. Of these, 119 completed Rome III IBS questionnaires, and 111 reported whether they had a previous diagnosis of IBS. According to the Rome III IBS criteria, 37 women (31%) had IBS. The most common subtypes were IBS-mixed (41%) and IBS-diarrhea (35%). Twenty-four (22%) of 111 patients had a previous IBS diagnosis. Of the subjects who met Rome III IBS criteria, 23 (66%) had never had a diagnosis of IBS. There were no significant differences in baseline sociodemographic characteristics, prior treatments, and stool consistency between subjects with fecal incontinence alone compared to subjects with IBS and fecal incontinence. Women with fecal incontinence and IBS reported significantly worse quality of life compared to women without IBS, despite similar fecal incontinence severity and stool consistency. More women with fecal incontinence and IBS reported being premenopausal than women with fecal incontinence alone.

■ COMMENTARY

The findings reported in this study suggest that IBS affects one-third of women with fecal incontinence presenting for care in tertiary centers, and 76% of the women with IBS and fecal incontinence met clinical criteria for IBS-mixed and IBS-diarrhea subtypes. Two-thirds of the women who met criteria for IBS never had been told by a provider that they had IBS. Women with IBS and fecal incontinence experienced a significant negative effect on quality of life.

The strengths of this study include its prospective, multicenter cohort design and the use of validated questionnaires alongside IBS diagnostic criteria. The major limitation of this study is its small cohort size and small

number of women with IBS. The authors were limited in the analyses performed and could not perform multivariable statistical modeling, thus limiting the strength of conclusions related to the differences found between women with fecal incontinence with and without IBS. Nonetheless, this study highlights the importance of assessing IBS symptoms in women presenting for fecal incontinence treatment. From my clinical experience, I would like to further emphasize the importance of assessing IBS symptoms and constipation in all women, and especially in women presenting with any pelvic floor symptom.

IBS has been estimated to affect 10-15% of the general adult population and is the most commonly diagnosed gastrointestinal condition. IBS symptoms are more prevalent in women than in men.[1] Jelovsek et al reported 19% prevalence of IBS or one of its subtypes in subjects with pelvic floor disorders presenting for care at a tertiary urogynecologic practice.[2] IBS is divided into four subtypes: IBS-C (constipation), IBS-D (diarrhea), IBS-M (mixed, equal diarrhea and constipation types), and IBS-U (unclassified). The Rome diagnostic criteria were developed as the diagnostic criteria for IBS. Now in their third iteration, the Rome III criteria state that a patient must have recurrent abdominal pain at least three days per month over the previous three months, and the discomfort must be associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in consistency of stool.[3,4] The American College of Gastroenterology Task Force has defined IBS as abdominal pain or discomfort that occurs in association with altered bowel habits over a three-month period. Studies have shown that patients with IBS have worse quality of life, higher economic burdens, and higher healthcare utilization compared to those without IBS. IBS is heterogenous in nature and is thought to be multifactorial. Patients who meet the clinical diagnostic criteria for IBS and do not have "alarm" features, including anemia, weight loss, and a family history of colorectal cancer, inflammatory bowel disease, or celiac sprue, require little formal testing to arrive at the diagnosis of IBS.[5,6]

Constipation also is also extremely common in the general population. It is thought to affect 16% of all adults and 33% of adults older than 60 years. Heavy lifting and repetitive straining secondary to constipation long have been associated with pelvic organ prolapse and are considered risk factors.[7] Jelovsek et al reported a high prevalence of constipation in women with urinary incontinence and pelvic organ prolapse. Thirty-six percent of the 302 patients studied reported symptoms of constipation, with similar rates between women with either pelvic floor disorder.[2]

Constipation is defined as symptoms of unsatisfactory defecation characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sensation of difficulty passing stool, incomplete evacuation, hard or lumpy stools, prolonged time to pass stool, or need to perform manual maneuvers to pass stool.[4,5] Chronic idiopathic constipation refers to the presence of such symptoms for at least three months.[4,5] The American Gastroenterological Association treatment algorithm for chronic constipation recommends a trial of fiber alone or alongside a laxative. In addition, biofeedback therapy has been reported to improve symptoms more than 70% in patients with defecatory disorders.[6]

IBS and constipation are very common in the general population. This study focuses on the presence and effect on women with fecal incontinence; however, functional bowel disorders are highly prevalent in women with all pelvic floor disorders. Not only is treatment of constipation considered a possible modifiable risk factor for pelvic floor disorders, but screening for and treatment of IBS and constipation may have a significant effect on our patients' quality of life and well-being. ■

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ABSTRACT & COMMENTARY

Antenatal Steroids for Very Early PTB

By John C. Hobbins, MD

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

SYNOPSIS: A large European multicenter study has shown that antenatal corticosteroid administration in patients at risk for imminent very early preterm birth (24 to 31 weeks) will decrease perinatal mortality and morbidity substantially, even after only three hours of exposure.

SOURCE: Norman M, et al. Association of short antenatal corticosteroid administration-to-birth intervals with survival and morbidity among very preterm infants: Results from the EPICE cohort. *JAMA Pediatr* 2017;171:678-686. doi:10.1001/jamapediatrics.2017.0602.

Corticosteroids perhaps have had a greater beneficial effect on perinatal outcomes than any other in utero treatment method. Since antenatal steroids consistently have been shown to reduce the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) in preterm infants, they have become a staple in the management of patients with evidence of imminent preterm delivery. Even the dosage and timing of administration have become standard. However, it has been unclear as to when the protective effects on the fetal lung and brain kick in along the 48-hour course.

Norman and colleagues undertook an ambitious multicenter study to try to answer this question in very preterm fetuses. The authors analyzed data from 123 participating hospitals in 11 European countries (The Effect of Perinatal Intensive Care in Europe study). From 2011 through 2012, the authors identified 4,594 preterm singleton pregnancies in which mothers delivered between 24 and 31 weeks. Anomalous pregnancies and those exposed to multiple courses of steroids were excluded. The standard dose in 85% of hospitals consisted of two injections of 12 mg of betamethasone 24 hours apart. The remaining patients had an assortment of similar regimens. Dexamethasone was used in only 5% of patients.

Pregnancies were categorized according to the time between when antenatal steroids were initiated and when the patients delivered. For example, one group of 662 of infants (14.4%) received no in utero treatment; another 1,111 patients (24%) had antenatal steroids on board for less than 24 hours; another group of 1,871 patients (40%) delivered one to seven days after receiving antenatal steroids; and the last group of 950 infants (20.7%) delivered more than seven days after receiving antenatal steroids. Outcome measures most emphasized were in-hospital deaths and composite severe neonatal morbidity (grade 3 or higher IVH, cystic periventricular leukomalacia, surgical NEC, or stage III retinopathy).

The average gestational age at delivery in the entire group was 28 weeks, with a mean birth weight of 1,213 g. The greatest reduction in mortality after antenatal steroids were administered (50%) was attained with deliveries occurring within 18 to 36 hours after the first dose. Interestingly, although there was a similar trend in timeline with composite morbidity, severe brain injury appeared to occur most frequently when delivery occurred after 48 hours post first injection. Also, the benefit of antenatal steroids to diminish mortality and severe morbidity was similar after 12 hours to that noted between 18 and 48 hours. In addition, there was a reduction of 24% after only three hours.

■ COMMENTARY

The amazing story of the evolution of antenatal steroids needs re-telling. In the late 1960s, Dr. G.C. Liggins, a New Zealand obstetrician, was exploring mechanisms of labor in the readily available sheep model and noted that some lambs born before 130 days (term is 150 days) survived when they all should have succumbed to RDS. The only difference was that their mothers had been on an experimental steroid regimen to initiate labor. This led to a randomized, clinical trial (RCT), published in 1972, which suggested that antenatal steroids diminished the chances of RDS.[1] The drug, dosage, and timeline (betamethasone 12 mg q 12h x 2) were said to be chosen arbitrarily by Dr. Liggins. However, through the years this regimen appears to have been cast in stone.

Since then, antenatal steroids have been shown in many RCTs to be beneficial in pregnancies ending in preterm birth prior to 34 weeks. However, its efficacy had been in question in patients delivering at or after 34 weeks — until the Antenatal Late Preterm Steroids (ALPS) study emerged.[2] This well-designed RCT suggested significant, but modest, benefit in composite neonatal outcome in late preterm pregnancies (34/1 to 36/6 weeks), when a standard dose of betamethasone was given to patients in preterm labor with cervical dilation of > 2 cm or in whom there was a compelling reason to deliver. The control group was given a double injection of placebo 12 hours apart. Forty percent delivered within 24 hours of their first injection. The authors calculated that 35 patients would need to be treated to show benefit in the composite neonatal score and 200 would need to be treated to prevent a serious complication of prematurity. Almost immediately following this publication, the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine responded by suggesting that patients less than 37 weeks who are at risk for imminent delivery be given antenatal steroids.[3]

Now that the initial wave of antenatal steroids enthusiasm has settled, some voices of caution have surfaced. As articulated by a few authors,[4,5] the risk of neonatal hypoglycemia and later effects on insulin response should be considered, and by preventing mild RDS, antenatal steroids actually might cause preterm infants to be discharged before other insidious problems could surface. Also, although some studies have suggested no obvious neurological sequelae,[6] the possible effect on the fetal hippocampus[7] cannot be ignored.

There is ample evidence to indicate the benefit of antenatal steroids in pregnancies about to deliver prior to 35 weeks, and in late preterm births (34 to 37 weeks), antenatal steroids appear to afford some protection against RDS in those patients having cesarean delivery.[8] However, in the remainder of late preterm births, the small benefit could be outweighed by the potential long-term risks, especially in those patients at the upper end (35/1 to 36/6) of that window. Also, since the above study on very preterm birth showed a 24% reduction in mortality after only three hours post first injection and maximum (50%) benefit after about 12 hours, one injection easily could be enough in late preterm patients.

In most patients in preterm labor, there has been a tendency to delay delivery to attain the maximum benefit of antenatal steroids (thought to be about 48 hours). This new information will allow us more flexibility in making management decisions in these patients. ■

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SPECIAL FEATURE

Subclinical Hypothyroidism: What Is It and When Should We Treat It?

By Robert W. Rebar, MD

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

SYNOPSIS: The current diagnosis and treatment of subclinical hypothyroidism in women of reproductive age is controversial and may well change as new studies become available.

Overt primary hypothyroidism is common in women. The diagnosis is simple to make, and the replacement therapy is simple to institute. What is not simple is what to do with individuals with so-called subclinical hypothyroidism (SCH). Even the definition of SCH is subject to question, and whether and when to institute treatment are controversial. Yet, this disorder has potential implications for infertility and for pregnancy.

INCONSISTENT DEFINITIONS

Generally speaking, SCH is defined as a normal serum free thyroxine (fT4) level in the presence of an elevated thyroid-stimulating hormone (TSH) level.[1] The difficulty lies in determining just what is the upper limit of normal for TSH. According to the National Academy of Clinical Biochemistry, 95% of normal individuals without evidence of thyroid disease have a TSH concentration of < 2.5 mIU/L, with the normal range skewed to the right.[2] Endocrine Society guidelines[3] suggest that the reference range of a given laboratory should determine the upper limit of normal for a third-generation TSH assay. The normal TSH reference range changes with age. If there is no age-based reference range for a given assay in an iodine sufficient area, then the upper limit of normal should be considered to be 4.12 mIU/L in a nonpregnant individual. Despite this recommendation, most commercial laboratories regard 4.5 or even 5.0 mIU/L as the upper limit of the normal range. Because human chorionic gonadotropin (hCG) can bind to the TSH receptor and affect TSH levels, the Endocrine Society recommended further that the upper limit of TSH in pregnancy should change with the trimester, being 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester, and 3.5 mIU/L in third trimester. In 2017, the American Thyroid Association (with input from several societies, including the Endocrine Society and the American Congress of Obstetricians and Gynecologists) changed its recommendations from those similar to the Endocrine Society to suggest that 4.0 mIU/L be considered the upper limit of normal during pregnancy.[4] Thus, there are disagreements regarding what should be considered the normal range.

What is more problematic is determining what should be the upper limit of normal in women attempting pregnancy. Some experts advocate using the earlier lower pregnancy thresholds for women who are attempting pregnancy (2.5 mIU/L) to minimize any potential risks associated with SCH.[5] Unfortunately, the risks of SCH in pregnancy are debated and unclear. This is the case because of variability in the cutoffs for TSH used in the various studies reporting on SCH in pregnancy. These issues are particularly relevant for clinicians caring for infertile couples. Fortunately, the American Society for Reproductive Medicine (ASRM) provides some guidance here.

WHO SHOULD BE SCREENED?

After reviewing the literature, which is rife with large but poor studies with varying cutoff values for TSH, the ASRM concluded that, overall, there is good evidence against recommending universal screening of thyroid function before or during pregnancy.[6] The Endocrine Society concurred with the recommendation against universal screening before pregnancy but was unable to reach consensus about screening during pregnancy.[3] In an older document, the American College of Obstetricians and Gynecologists did not recommend routine screening for hypothyroidism in pregnancy.[7] In all cases, screening women at high risk, including those with a family or personal history of thyroid disease, symptoms or physical findings suggestive of hypothyroidism or goiter, type 1 diabetes mellitus, infertility, history of miscarriage or preterm delivery, or history of autoimmune disorders generally is warranted.

The comment about individuals with a history of autoimmune disorders being at high risk warrants further discussion. Although measurement of anti-thyroid antibodies is not needed for the diagnosis of SCH, thyroid antibodies often are measured because their presence has been associated with an increased risk of later overt hypothyroidism.[8] Although both antithyroglobulin and anti-thyroid peroxidase antibodies (anti-TPO-Abs) were present in 10-12% of the population, only anti-TPO-Abs were associated with thyroid dysfunction and thought to be of clinical importance.

WHAT ARE THE IMPLICATIONS OF NOT TREATING SCH?

Although the data are controversial, there are no consistent data documenting that failure to treat women with TSH levels between 2.5 and 4.0 mIU/L leads to any increase in adverse obstetric outcomes. In a recent large, retrospective, observational study using a U.S. administrative claims database, a cohort of 5,405 pregnant women were identified as having SCH on the basis of a TSH test result between 2.5 and 10 mIU/L (in the presence of normal fT4) within four weeks before and three months after a first pregnancy visit claim. Only 16% of these women (n = 843) with a mean baseline TSH concentration of 4.8 mIU/L were treated with thyroid hormone, while the remainder (n = 4,562) were not.[9] Treated women had 38% lower odds of pregnancy loss than did the untreated women. However, the treated women also had higher adjusted odds of preterm delivery (odds ratio [OR], 1.60), gestational diabetes (OR, 1.37), and preeclampsia (OR, 1.61). Notably, the odds of pregnancy loss were only significantly lower among those treated women with pre-treatment TSH levels between 4.1 to 10.0 mIU/L (OR, 0.45), but not among those treated women with pre-treatment TSH levels between 2.5 and 4.0 mIU/L. These findings suggest the need for counseling individuals with SCH about both the benefits and risks of replacement thyroid hormone treatment. Despite these findings, an accompanying editorial by two eminent thyroidologists noted that the early initiation of low-dose therapy with levothyroxine for SCH during pregnancy, as recommended by the American Thyroid Association, "may be of benefit, is inexpensive, and is unlikely to be harmful."[1]

One of the most important reasons cited for treating individuals with SCH during pregnancy is to prevent abnormalities in the resulting offspring. In 1999, a widely publicized study noted that 62 children of women whose serum TSH levels during pregnancy were greater than the 98th percentile had lower full-scale IQs (by 7 points) than 124 children of matched controls with normal TSH levels.[10] Subsequent studies have not all been confirmatory. In one of the largest studies to date, investigators at 15 sites in the NIH's Maternal–Fetal Medicine Network screened more than 97,000 women with a singleton pregnancy before 20 weeks' gestation to identify those with SCH, defined as a thyrotropin level of ≥ 4.00 mU/L and a normal fT4 level, and for hypothyroxemia, defined as a normal thyrotropin level (0.08 to 3.99 mU/L) and a low fT4 (< 0.86 ng/dL).[11]

In two separate trials, 677 women with SCH and 526 with hypothyroxemia randomly received either levothyroxine or placebo beginning at a mean of 16.7 and 17.8 weeks' gestation, respectively. The median IQ score of the children at 5 years of age with the use of the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) did not differ in either trial between the treated and untreated groups. In addition, there were no significant differences between groups in either trial for neurodevelopmental and behavioral outcomes in the children, and the incidence of adverse events during pregnancy did not differ and was low in all groups.

These latest results should not be viewed as surprising because the fetal thyroid axis becomes functional in utero between 12 and 16 weeks' gestation. In addition, basing SCH solely on the results of imprecise and controversial clinical testing is problematic. Still, these latest large studies do not provide us with clear evidence about any benefit of treatment of SCH during pregnancy.

FINAL THOUGHTS

Putting these thoughts together is not easy. It would seem reasonable to test women presenting for preconceptual counseling or because of infertility. It also would make sense to test women with previous miscarriages and pregnancy losses, as well as those at high risk of thyroid disease, as noted previously. Because there is fair evidence that thyroid autoimmunity is also associated with infertility and miscarriage, the ASRM further recommends levothyroxine for women with anti-TPO-Abs, especially those with TSH levels > 2.5 mIU/L.[6] Thus, it makes sense to obtain anti-TPO-Abs in any woman with TSH > 4.0 mIU/L and in infertile women with TSH levels > 2.5 mIU/L. The data also support levothyroxine therapy for women with TSH levels > 4.0 mIU/L just because the risks are low. Finally, it is clear that this is an evolving field and that future data may well lead to modifications in these recommendations — as well as in my own thoughts about SCH. ■

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CME/CE QUESTIONS

1. **In the systematic review by Simmons et al, articles were graded by which U.S. Preventive Services Task Force system?**
   a. Top-tier, middle-tier, or lower-tier
   b. Level I, II, or III
   c. Good, fair, or poor
   d. Excellent, good, or fair

2. **Irritable bowel syndrome and constipation:**
   a. are common only in women with fecal incontinence.
   b. are very prevalent in women with pelvic floor disorders.
   c. are not easily screened for.
   d. have minimal effect on women's quality of life.

3. **Norman et al found that in very preterm babies, the greatest decrease in neonatal mortality with antenatal steroids occurred:**
   a. before six hours.
   b. before 12 hours.
   c. between 12 and 48 hours.
   d. after one week.

4. **Subclinical hypothyroidism is associated with infertility and miscarriage.**
   a. Trues
   b. False

[IN FUTURE ISSUES]

The LNG IUS and Stress Reactivity:
A Mechanism for Mood Effects or a False Signal?